PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

CODE OF PRACTICE REVIEW

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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 2005

The Annual Report of the Prescription Medicines Code of Practice Authority for 2005 has now been published and copies have been sent to all who are on the mailing list for the Code of Practice Review. Further copies are available on request.

As previously reported in the Review, there were 101 complaints in 2005 as compared with 119 in 2004. There were 131 complaints in 2003.

The 101 complaints in 2005 gave rise to 107 cases, which was less than in 2004. 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, usually because no prima facie case is established.

Of the 275 rulings made by the Code of Practice Panel in 2005, 243 (88%) were accepted by the parties, 22 (8%) were unsuccessfully appealed and 10 (4%) were successfully appealed. This compares with the 4.5% of rulings which were successfully appealed in 2004.

The Code of Practice Panel met 57 times in 2005 (86 in 2004) and the Code of Practice Appeal Board met 13 times in 2005 (10 in 2004). The Appeal Board considered appeals in 17 cases as compared with 23 in 2004.

The number of complaints made by health professionals in 2005 exceeded the number made by pharmaceutical companies, there being 52 from health professionals and 28 from pharmaceutical companies. This has historically been the usual pattern but it has not been the case in three out of the last five years. Complaints made by pharmaceutical companies are usually more complex than those from outside the industry and generally raise a number of issues.

Communications Manager appointed

Niamh MacMahon was appointed to the staff of the Authority as the new Communications Manager at the beginning of July.

In this newly created role, Niamh will have responsibility for promotion of the revised ABPI Code of Practice to a wide variety of stakeholders. These will include ABPI members, non-member companies, health professionals, patients and the public, and advertising and marketing agencies.

Niamh joined the Authority from the General Social Care Council (GSCC) where she was Head of Public Affairs. Niamh had been at the GSCC for almost three years and previously worked in communications at the University of Sussex.

The Authority welcomes Niamh to its staff and believes that she will make a valuable contribution to its work.

Blogs

A blog (short for weblog) is a website that can be added to on an ongoing basis. Blogs enable people with a common interest to express their views on the Internet and hear back from and connect with others. Blogs are a popular communication tool for groups to share views and ideas. The Authority has been asked for its advice regarding the use of blogs by pharmaceutical companies. It had been suggested that such blogs could be established for use either by groups of health professionals or patients.

Clause 9.10 requires that all material sponsored by a pharmaceutical company must clearly indicate that it had been sponsored by that company and would apply to sponsorship of items on the Internet. If a company were to sponsor a blog about a medicine or a therapy area, then it would need to be careful to ensure that all of the information contributed complied with the Code. It would be unacceptable, for example, if someone contributed material to a blog about the unlicensed use of a product if that blog had been sponsored by the pharmaceutical company which marketed the product. This could be seen as the company promoting the product outside its licence as the company would in effect be distributing the information.

Given that, by their very nature, blogs are for contributors to freely and spontaneously express their personal views on a subject, the Authority considers that pharmaceutical companies should not sponsor such sites on the Internet if they were intended, or could reasonably be expected, to discuss medicines and their uses as it would be impossible to guarantee their compliance with the Code.

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:

Friday, 1 December

Seminar dates for 2007 will be arranged shortly.

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

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

How to contact the Authority

Our address is:

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

www.pmcpa.org.uk

Telephone: 020 7930 9677
Facsimile: 020 7930 4554

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

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

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

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

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

Editorial or advertisement?

Pharmaceutical companies commonly issue press releases which contain product claims and pack shots (or a statement that a pack shot is available on request). Once a press release is issued, however, neither a company nor its agent should be able to exert any control over the placement of any subsequent article and nor should any payment be made in relation to the article's publication. Whether and where articles appear in the press should be solely at the publisher's discretion and articles should be printed entirely at the publisher's expense. Any payment, such as colour separation fees and the like, will be regarded as turning the resulting article resultant into an advertisement.

Promotional stands at educational meetings

The view is expressed from time to time that it is in breach of the Code to have a promotional stand in the same room as an educational meeting. This is not so. It may be that local organizers do not want promotional stands in the same room, in which case sponsoring companies would have to respect their wishes, but there is nothing in the Code to prohibit such a practice.

CASES AUTH/1790/1/06 and AUTH/1791/1/06

MERCK SHARP & DOHME v ROCHE and GLAXOSMITHKLINE

Promotion of Bonviva

Merck Sharp & Dohme complained about the promotion of Bonviva (ibandronic acid) by Roche and GlaxoSmithKline. The material at issue, a pharmacy leavepiece, a mailer and a journal advertisement, *inter alia* compared patient preference for Bonviva vs alendronate, Merck Sharp & Dohme's product Fosamax.

Merck Sharp & Dohme noted that in the leavepiece, the question 'Faced with 52 or 12 tablets a year, what would [your] patients prefer?' introduced the claims that 'Patients prefer a monthly to a weekly bisphosphonate' (stated twice) and 'In a 6-month clinical study … [of those] patients expressing a preference' … [71%] (from a graph) 'preferred a once-monthly to a weekly bisphosphonate'. In the mailer and the advertisement, the question introduced the claim that 'It's no surprise that … 71% chose Bonviva once-monthly over alendronate once-weekly'. Merck Sharp & Dohme alleged that these claims referred to a comparison of Bonviva, prescribed one tablet monthly, and Fosamax Once Weekly, prescribed one tablet weekly, which was unfair, inaccurate and misleading.

The comparison implied that both medicines had the same clinical benefits which was not so. Fosamax Once Weekly had been shown to reduce the risk of vertebral and hip fractures in postmenopausal osteoporosis (PMO), whereas no efficacy in hip fractures had been demonstrated for Bonviva. By omitting to mention this difference the material did not present the attributes of Bonviva objectively based on an up-to-date evaluation of all the evidence and was thus incomplete and misleading. This failure to present the medicine objectively and without exaggerating its properties would amount to promotion not encouraging the rational use of a medicine and be in breach of the 2006 Code.

Merck Sharp & Dohme noted that the Bonviva summary of product characteristics (SPC) stated that the product was for 'Treatment of osteoporosis in postmenopausal women in order to reduce the risk of vertebral fractures. Efficacy on femoral neck fractures has not been established' whereas the Fosamax Once Weekly SPC stated: 'Treatment of postmenopausal osteoporosis. 'Fosamax' reduces the risk of vertebral and hip fractures'.

Merck Sharp & Dohme understood that the patient preference study, BALTO (Bonviva Alendronate Trial in Osteoporosis, Emkey *et al* 2005), upon which the 71% claim was based, was performed by physicians (mainly GPs) who were satisfied that their patients would benefit equally from either treatment. Merck Sharp & Dohme questioned the basis of such a conclusion given the differences referred to above. Similarly there was no indication that patients were aware of the comparative efficacy of the two treatments (or of the fairness and accuracy of any information given), even though this would be expected to have a major influence on their choice of preferred treatment. On currently available information, the use of this clinical trial as the basis for promotion was highly questionable, as its results did not provide a platform for a fair, accurate and unambiguous comparison.

In conclusion, these three pieces of promotional material claimed that Bonviva and Fosamax Once Weekly had a comparable clinical profile and as a result of this it was reasonable to compare convenience of dosing in isolation from any other characteristics of the two products. Licensed indications and clinical data, however, showed that the two products did not have a comparable clinical profile, and that such a comparison was therefore unfair, inaccurate and misleading. Additionally, the patient preference study might have been methodologically flawed and so unsuitable for use in promotion.

The Panel noted that Bonviva was indicated for the 'Treatment of osteoporosis in postmenopausal women in order to reduce the risk of vertebral fractures. Efficacy on femoral neck [hip] fractures has not been established'. The Panel noted, however, that the material at issue went beyond solely promoting Bonviva for its licensed indication and compared it with Fosamax Once Weekly treatment. Fosamax Once Weekly was also indicated for the treatment of PMO but its SPC included the additional statement 'Fosamax reduces the risk of vertebral and hip fracture'. The Panel noted Roche and GlaxoSmithKline's submission about recent regulatory guidance and requirements regarding the licensing of medicines for PMO and the subsequent wording of an SPC but considered that most health professionals would not appreciate the arguments involved. What mattered was that information about medicines and their uses should be conveyed clearly in a way that did not mislead either directly or by implication. The Panel considered that by directly comparing the dosage frequency and patient preference of Bonviva and Fosamax Once Weekly most readers would assume, in the absence of a statement to the contrary, that they were otherwise identical. Prescribers might be persuaded to change patients from Fosamax Once Weekly to Bonviva in the belief that the proven benefits of therapy were the same for each. This was not so; the efficacy of Bonviva on hip fractures had not been established whilst Fosamax was specifically licensed to reduce the risk of hip fracture. The Panel considered that to directly compare Bonviva and Fosamax, and not point out this difference, was misleading. Breaches of the Code were ruled.

Upon appeal by Roche and GlaxoSmithKline, the Appeal Board noted that it had previously considered another complaint about the same Bonviva campaign (Cases AUTH/1779/11/05 and AUTH/1780/11/05).

The Appeal Board noted that Bonviva 150mg was indicated for the 'Treatment of osteoporosis in postmenopausal women in order to reduce the risk

of vertebral fractures. Efficacy on femoral neck fractures has not been established'. In Cases AUTH/1779/11/05 and AUTH/1780/11/05, in relation to the complaint about a claim 'Bonviva once monthly for postmenopausal osteoporosis', the Appeal Board had considered that the statement 'Efficacy on femoral neck fractures has not been established' in the indication section of the SPC provided the evidence base for Bonviva's indication, which was the treatment of PMO. The Appeal Board saw no reason to depart from that ruling in its consideration of the cases now before it.

Cases AUTH/1779/11/05 and AUTH/1780/11/05 included a complaint about the claim 'Faced with 52 or 12 tablets a year, what would patients prefer?' and the use of the BALTO study to claim greater patient preference for a monthly bisphosphonate compared with a weekly bisphosphonate (71% vs 29% respectively). The Appeal Board had noted that the BALTO study was started before the marketing authorization for Bonviva had been granted and thus before the evidence base for the product was fully assessed. Patients could not have known that, in contrast to alendronate, efficacy on hip fractures would not be established for Bonviva. In that regard the patients did not have the full facts about Bonviva and thus, in the Appeal Board's view, would not have been able to express a genuine, well informed preference between it and alendronate. In that regard the Appeal Board had considered that the comparison was unfair and was not based on an up-to-date evaluation of all the evidence and had upheld the Panel's ruling of breaches of the Code. Roche and GlaxoSmithKline had provided the requisite undertaking and assurance in this regard.

Turning to the cases now for appeal, Cases AUTH/1790/1/06 and AUTH/1791/1/06, the Appeal Board considered that by directly comparing the dosage frequency and patient preference of Bonviva and Fosamax Once Weekly in the items at issue, most readers would assume, in the absence of a statement to the contrary, that they were otherwise identical. Prescribers might be persuaded to change patients from Fosamax Once Weekly to Bonviva in the belief that the evidence base for the indication was the same for each. This was not so; the efficacy of Bonviva on hip fractures had not been established whilst Fosamax was specifically licensed to reduce the risk of hip fracture. The Appeal Board considered that to directly compare Bonviva and Fosamax in the materials at issue, and not point out this difference, was misleading. The Appeal Board upheld the Panel's ruling of breaches of the Code.

Merck Sharp & Dohme Limited complained about the promotion of Bonviva (ibandronic acid) by Roche Products Limited and GlaxoSmithKline UK Limited. The material at issue was a pharmacy leavepiece (ref BNV/DAP/05/20703/1), a mailer (ref BNV/MLP/05/20705/1) and a journal advertisement (ref BNV/ADO/05/21553/1). The materials, *inter alia*, compared patient preference for Bonviva vs alendronate, Merck Sharp & Dohme's product Fosamax.

COMPLAINT

Merck Sharp & Dohme noted that in the leavepiece, the question 'Faced with 52 or 12 tablets a year, what would [your] patients prefer?' introduced the claims that 'Patients prefer a monthly to a weekly bisphosphonate' (stated twice) and 'In a 6-month clinical study … [of those] patients expressing a preference' … [71%] (from a graph) 'preferred a once-monthly to a weekly bisphosphonate'. In the mailer and the advertisement, the question introduced the claim that 'It's no surprise that … 71% chose Bonviva once-monthly over alendronate once-weekly'.

Merck Sharp & Dohme alleged that these claims referred to a comparison of Bonviva, prescribed one tablet monthly, and Fosamax Once Weekly, prescribed one tablet weekly, which was unfair, inaccurate and misleading, in breach of Clauses 7.2 and 7.3 of the Code.

The comparison implied that both medicines had the same clinical benefits for patients, but this was not the case. Fosamax Once Weekly had demonstrated clinical benefit in reducing the risk of vertebral and hip fractures in postmenopausal osteoporosis (PMO), whereas no efficacy in hip fractures had been demonstrated for Bonviva. By omitting to mention the differences between the two medicines, there was a failure to present the attributes of Bonviva objectively based on an up-to-date evaluation of all the evidence; the material was thus incomplete and misleading. Were this material to be judged on the basis of the 2006 Code, this failure to present the drug objectively and without exaggerating its properties, in addition to breaching Clauses 7.2 and 7.3, would amount to promotion not encouraging the rational use of a medicine in breach of Clause 7.10 of the Code.

Merck Sharp & Dohme noted that Section 4.1 (Therapeutic indications) of the Bonviva SPC stated 'Treatment of osteoporosis in postmenopausal women in order to reduce the risk of vertebral fractures. Efficacy on femoral neck fractures has not been established'. By comparison, the relevant section of the Fosamax Once Weekly SPC stated: 'Treatment of postmenopausal osteoporosis. 'Fosamax' reduces the risk of vertebral and hip fractures'.

Roche had argued that the purpose for which Bonviva should be prescribed, according to the wording of the licensed indication, was not relevant and that the regulatory authorities intended that the licensed indication be regarded as 'Treatment of osteoporosis in postmenopausal women' without further qualification. Merck Sharp & Dohme contended that the wording of a licensed indication was key to the promotion of medicines and to any comparison between two medicines. By effectively extrapolating the licensed wording to a different meaning, Roche had implied an unfair, inaccurate and misleading comparison of its product with Fosamax Once Weekly and thereby breached Clauses 7.2 and 7.3 of the Code.

Roche had based its argument largely on the Committee for Medicinal Products for Human Use (CHMP) Note for Guidance on Postmenopausal Osteoporosis in Women (2001) which it stated recognised only two indications, treatment or prevention, and that further details defining use were

not recognised as part of the indication. Roche had further stated that the guidance also clarified that any additional wording in the indication part of the SPC was intended only to elucidate the nature of the data on which the indication was granted as additional information, and did not define different types or classes of indications for specific fracture locations. However, Roche's statement was inaccurate; the guidance emphatically stated that it must be clearly specified in the indication part of the SPC those sites for which anti-fracture efficacy had been demonstrated, and that failure to demonstrate anti-fracture efficacy at a second site must also be included.

Roche had also argued that by its very nature, osteoporosis could affect any bone in the body and that it was not possible when treating the disease to predict which bone was the target of the chosen therapy, ie it was not relevant to consider whether the aim was to reduce the risk of vertebral or hip fractures. The evidence that this argument was flawed was provided in the same guidance that Roche used to support its case. The guidance stated: 'Notwithstanding osteoporosis is a single, generalised skeletal disorder, affecting both trabecular and cortical components, the timeframe for appearance of spinal (mainly trabecular) or femoral (mainly cortical) fractures is rather different. Vertebral fractures occur earlier in women, 10 to 15 years after the menopause, while hip fractures occur later in life, in both genders, mostly after 75 years …'.

Merck Sharp & Dohme therefore submitted that different fractures tended to occur at different age ranges, and the effects of Bonviva and Fosamax on these two types of fracture were extremely relevant. One was more likely to try to reduce hip fractures in older women with PMO, whilst in the younger woman the target was more likely to be vertebral fractures. Fosamax Once Weekly had demonstrated benefit at both sites, as stated in the SPC, whereas Bonviva had only demonstrated benefit in vertebral fracture, also as noted within its SPC. When determining treatment, a health professional ought to consider the fracture site targeted by a treatment. To promote Bonviva without consideration of the full wording of the indication was misleading and a comparison of the two medicines on this basis was neither valid nor fair.

Roche had informed Merck Sharp & Dohme that a reduction in risk of hip fracture had not been demonstrated with Bonviva, though 'no detriment' had been demonstrated at this site as a secondary endpoint in studies designed to investigate the product's benefit in vertebral fracture prevention. According to the CHMP Note for Guidance this was the requirement for a marketing authorization for a medicine to treat osteoporosis, the guidance stipulated that: 'The applicant will be requested to study the effect of the investigated drug on both spinal and femoral (not all non-vertebral) fractures. This should be done in properly designed and adequately powered studies'.

Merck Sharp & Dohme submitted that the failure to refer to the differences in clinical data between the two products (ie that Bonviva had not demonstrated efficacy in reducing the risk of hip fractures) compounded the misconceptions that were created by these promotional items. Furthermore, the leavepiece and mailer (but not the advertisement) contained claims of 'Proven efficacy' and 'Bonviva offers proven efficacy' followed by a graph showing reduction in vertebral fractures (leavepiece only). Although these claims were made to support the main message of the pieces, ie the comparison of the two products, they were made without clarification of the differences in demonstrated efficacy between the two products. This approach further compounded the misconceptions these materials conveyed, thus reinforcing the unfair, inaccurate and misleading comparison.

Merck Sharp & Dohme submitted that the differences between the SPCs and the lack of data to support the use of a comparison between the two products in advertising were major reasons why these items were in breach of the Code. However, the company was also extremely concerned that, from the information Roche had provided, it appeared that the BALTO study (Bonviva Alendronate Trial in Osteoporosis, Emkey *et al* 2005), upon which the claims were based might not have been conducted in a sufficiently rigorous manner to allow it to be used for advertising purposes.

Merck Sharp & Dohme understood that the study was performed by physicians (mainly GPs) who were satisfied that their patients would benefit equally from either treatment although it was unclear as to what had brought them to that conclusion. For reasons described above, Merck Sharp & Dohme was surprised that the investigators could have reached that conclusion if the data on both products had been presented to them fairly and accurately. Further, Merck Sharp & Dohme noted that Roche was unable to state how easy or difficult it was during the recruitment of investigators, to find doctors who believed the two medicines offered similar efficacy as there were no available data to indicate what proportion of doctors declined to participate in the study because they thought the comparators were not likely to provide similar efficacy.

The study outcomes were the responses of patients to questions about treatment preference and convenience. There was no indication that patients were aware of the comparative efficacy of the two treatments (or of the fairness and accuracy of any information given), even though this would be expected to have a major influence on their choice of preferred treatment.

On currently available information, the use of this clinical trial as the basis for promotion was highly questionable, as its results did not provide a platform for a fair, accurate and unambiguous comparison.

In conclusion, the claims in these three pieces of promotional material directed the reader to believe that, from a clinical viewpoint, Bonviva and Fosamax Once Weekly had a comparable clinical profile and as a result of this it was reasonable to compare convenience of dosing in isolation from any other characteristics of the two products. Licensed indications and clinical data, however, showed that

the two products did not have a comparable clinical profile, that such a comparison was therefore unfair, inaccurate and misleading and in breach of Clauses 7.2 and 7.3 of the Code. Additionally, the clinical trial, and the collection of the data from it, might have been methodologically flawed rendering it unsuitable as a reference for use in advertising material.

RESPONSE

Roche and GlaxoSmithKline submitted a joint response and noted that Merck Sharp & Dohme had argued that the licensed indications for Bonviva and Fosamax Once Weekly were dissimilar and thus did not support a comparison between the two. In rebuttal, the respondents proposed that the indication for both bisphosphonates included the treatment of PMO.

While the product licence for Bonviva provided further clarification upon the clinical dataset from which registration was obtained, this clarification neither constituted a limited licence nor hinted at narrowed clinical efficacy. This was supported by the CHMP Note for Guidance which clarified that any additional wording in the indication part of the SPC was intended only to elucidate the nature of the data on which the indication was granted as additional information and did not define different types or classes of indications for specific fracture locations. In its complaint Merck Sharp & Dohme concurred that the guidance emphatically stated that it must be clearly specified in the indication part of the SPC those sites for which anti-fracture efficacy had been demonstrated, and that failure to demonstrate anti-fracture efficacy at a second site must also be included. The respondents thus concluded that Merck Sharp & Dohme agreed with their own position: the guidelines for approval of a 'treatment of postmenopausal osteoporosis' indication only provided clarification of the clinical studies upon which registration was provided. It could not be inferred from this guidance that the EMEA intended to limit the use of Bonviva.

It was perhaps not surprising that this guidance had caused Merck Sharp & Dohme such confusion. Indeed, in its review of ibandronate, the Scottish Medicines Consortium (SMC) also sought similar clarification from the EMEA. This confirmed the EMEA's position: that the additional wording was intended solely to elucidate the nature of the data submitted to the regulatory bodies upon which the licence was granted.

The validity of distinguishing between treatment of vertebral and hip fractures was also questioned by the guideline on the licensing of products for PMO published by the EMEA. In this guideline, the Committee of Proprietary Medicinal Products stated that in PMO 'From the regulatory viewpoint, two therapeutic indications are recognised'. These indications were prevention and treatment. This was consistent with the announcement on positive opinion granted for Bonviva 'to treat osteoporosis' and with the wording in the approved Bonviva patient information leaflet. These guidelines did not indicate differential consideration of fractures in a site-specific manner, but rather alluded to treatment vs prevention of disease.

Regulatory approaches aside, it might be pertinent to consider whether distinction of fractures based upon anatomy was clinically relevant. Although osteoporosis frequently manifested in fractures of the vertebrae, wrist and hip, it was a systemic condition affecting the entire skeleton. This was in keeping with the World Health Organization (WHO) definition of osteoporosis. The respondents noted that Merck Sharp & Dohme quoted the CHMP Note for Guidance which stated that the timeframe for appearance of spinal and hip fractures was different; and therefore contended that as these fractures occurred in different age ranges, the effects of these two medicines remained pertinent to this discussion.

Vertebral and hip fractures occurred at different frequencies in disparate age groups, not because they were distinct conditions, but because the factors leading to falls and hence fracture risk differed between young and older postmenopausal subjects. The disease process leading to PMO was the same, regardless of fracture site. Preclinical studies had demonstrated that bisphosphonates were disseminated throughout the entire skeletal system. This was supported by the observation that bisphosphonates increased bone mass at all skeletal sites. Thus, the suggestion that any bisphosphonate could exert its effect in a site-specific manner was not supported by the scientific or clinical data. Support for this position might be derived from a recent German judicial review of the Bonviva promotional materials. This review upheld the position that it was not possible for any bisphosphonate to behave in a site-specific manner. Hence, isolating an effect upon vertebral from non-vertebral fractures was artificial. Notwithstanding the German provenance of this decision, the respondents noted that that marketing authorization for Bonviva was a European licence, and thus, one would expect consistency across all European markets. Details of this ruling were provided.

Hence, the differentiation between hip and vertebral fracture efficacy reflected only the design of the registration trails. It was upon this basis then, that the licence was granted for Bonviva. Therefore, the promotion of Bonviva for the treatment of PMO was entirely consistent with its licensed indication.

In summary the respondents stated that osteoporosis licences were granted for two indications alone: treatment and prevention. Both Bonviva and Fosamax had product licences for the treatment of PMO. The licence for Bonviva referred to hip fractures, but this was offered as clarification of the clinical evidence for which the licence was granted; not an attempt to restrict the licence. It was upon this basis then, that the licence was granted for Bonviva. Therefore, the promotion of Bonviva for the treatment of PMO was within its licence.

The respondents further noted that Merck Sharp & Dohme contended that there was a lack of data to support any claim towards comparable efficacy between Fosamax and Bonviva, on the basis of absence of demonstration of hip fracture efficacy. The respondents proposed that although the regulatory

authorities had granted both products a licence for the treatment of PMO, based upon efficacy data described in registration trials, no direct comparison of the relative efficacies of Fosamax and Bonviva had been made. Therefore, as (i) the indication for both medicines was for the treatment of PMO, (ii) no claims had been made about a reduction of hip fractures, and (iii) all efficacy claims had been unambiguously directed towards effectiveness in reducing the risk of vertebral fractures, the respondents were hard-pressed to understand the substantiation for Merck Sharp & Dohme's position. Thus, Roche and GlaxoSmithKline did not consider that the promotional material was misleading.

The respondents stated that whilst there were no data which directly compared the effects of Bonviva and Fosamax on bone mineral density or fracture rate, this did not suggest that one medicine was less or more effective than the other. Indeed, as both were licensed for the treatment of PMO, one might argue that the regulators had judged Bonviva as being equally worthy of a licence as Fosamax. Furthermore, the licence for Bonviva was based upon efficacy endpoints at both the hip and lumbar spine, thus, the suggestion that it exerted no effect upon hip sites was groundless.

Roche and GlaxoSmithKline submitted that the registration trials for Bonviva were performed in line with the guidelines developed by the EMEA. The respondents noted that the more recent guideline issued by the CHMP postdated the design of the seminal ibandronate (and alendronate) studies.

In summary, the respondents agreed that there was a lack of prospective data to support any efficacy comparisons between Bonviva and Fosamax. However, the relevance of this argument was questioned by the fact that, in no promotional materials, had there been an attempt to compare the relative efficacy of Bonviva and Fosamax. Furthermore, even if such an attempt had been made, it would be countered by the fact that regulatory authorities had granted both products a licence for the treatment of PMO. The respondents noted that Merck Sharp & Dohme stated that the promotional materials for Bonviva were misleading as they did not refer to the caveat relating to hip fractures. Such a stance was countered by the reference to the regulatory reason for this wording in the SPC. Furthermore, as would be evident by a perusal of the relevant materials, all claims to Bonviva's efficacy had centred upon its effectiveness in reducing vertebral fractures. As no claim about a beneficial effect on hip fractures had been made, these materials were not misleading.

The respondents noted that Merck Sharp & Dohme was concerned about the validity of the BALTO study which examined patient preference between weekly and dosing regimens, suggesting that study subjects were inadequately informed. The respondents submitted that these statements of patients preferences were the primary endpoint of a clinical trial which met Good Clinical Practice (GCP), local and national ethical guidelines.

The 'Faced with 52 or 12 tablets a year, what would [your] patients prefer?' Bonviva marketing campaign was based upon the BALTO study which assessed the dosing preferences of patients treated with both weekly Fosamax and monthly Bonviva. Postmenopausal osteoporotic women received monthly Bonviva for three months, followed by weekly Fosamax for a further three months, or vice versa. Upon completion, patients were questioned as to whether they had a preference for either dosing regime, and if so, which they might be.

The respondents noted Merck Sharp & Dohme's contention that the study was inadequately designed to support such a comparison. Roche and GlaxoSmithKline re-iterated that the study was consistent with GCP and passed ethical reviews. Furthermore, as far as was possible within the confines of a clinical study, this trial aimed to elucidate patient preferences for different dosing regimes, of treatment agents deemed appropriate by their physician. The primary endpoint of the study was to identify patient preferences for dosing regimes, not the agents themselves. Hence, the dosing frequency ie monthly v weekly was more pertinent than the clinical evidence base for either agent.

Indeed, one might argue that as dosing frequency, not clinical efficacy, was the basis of this campaign, it would be reasonable to pose the rhetorical question '52 or 12 tablets a year, what would patients prefer?', even in the absence of a clinical study documenting expressed patient preference for two tried regimes. The precedence for this might be found in Case AUTH/1563/3/04, wherein the Panel considered that drawing attention to a difference between treatments was acceptable in promotional material, and that not answering a rhetorical question was neither unbalanced nor misleading. Thus, the allusion to '52 v 12 tablets' simply referred to an undisputable difference between the two dosing regimens and could not possibly be construed as a claim.

The respondents noted that neither the publications nor the marketing tools developed from this study made any comparative efficacy claims between Bonviva and Fosamax. As no claims towards differences or similarities in efficacy between the two were made, these statements could be neither misleading nor unsubstantiated. Therapeutic choice rested with prescribing physicians, and where Bonviva was a suitable treatment option patient preference ought to be a consideration.

The respondents noted that it was neither the role of, nor appropriate for, pharmaceutical advertising to educate health professionals on all the possible benefits of, or discuss the nuances distinguishing the clinical evidence base for all products within a therapeutic field. Rather, pharmaceutical advertising had a legitimate place in highlighting the benefits of a particular medicine, in a balanced manner, where these might be substantiated. In this vein, the promotional material in question specifically and explicitly referred to vertebral fracture risk reduction. The SPC referred to generalised 'fracture risk reduction' in section 5. In this setting, the respondents contended that they had clearly promoted Bonviva within the spirit of the Code.

In conclusion the respondents stated that Bonviva was indicated for the treatment of PMO. This licence was

supported by evidence that it suppressed bone turnover, increased bone mineral density throughout the skeleton and reduced vertebral fracture risk. Although data on hip fractures were collected in the vertebral fracture study, a specific prospective hip fracture study had not been performed. This was consistent with licensing guidelines for a 'treatment of postmenopausal osteoporosis' indication. Rather, and as required by the CHMP, Bonviva showed a reduction in vertebral fractures and no detriment at other sites.

On the basis of the data presented to the CHMP, Bonviva had been granted a European Marketing Authorization. The nature of the data presented to the CHMP upon which the licence was based was reflected in the SPC. The materials promoting the use of Bonviva focused upon its efficacy in the treatment of PMO and patient preference. The former was based upon Bonviva's demonstrated efficacy at reducing vertebral fractures. No claims were made with regards to hip fractures. The latter was based upon patient preference for one of two dosing regimens, and made no reference to clinical effectiveness.

The respondents concluded that the promotional materials at issue were consistent with the licenced indications and were supported by appropriate clinical data. Therefore, the materials could not be construed to be in breach of Clauses 7.2 and 7.3 of the Code.

PANEL RULING

The Panel noted that the Bonviva SPC stated that the medicine was indicated for the 'Treatment of osteoporosis in postmenopausal women in order to reduce the risk of vertebral fractures. Efficacy on femoral neck [hip] fractures has not been established'. The Panel noted, however, that the material at issue went beyond solely promoting Bonviva for its licensed indication and compared it with Fosamax Once Weekly treatment. Fosamax Once Weekly was also indicated for the treatment of PMO but its SPC included the additional statement 'Fosamax reduces the risk of vertebral and hip fracture'. The Panel noted Roche and GlaxoSmithKline's submission that the recent CHMP guidance postdated the seminal alendronate studies. The Panel further noted the regulatory requirements regarding the licensing of medicines for PMO and the subsequent wording of an SPC but considered that most health professionals would not appreciate the arguments involved. What mattered was that information about medicines and their uses should be conveyed clearly in a way that did not mislead either directly or by implication. The Panel considered that by directly comparing the dosage frequency and patient preference of Bonviva and Fosamax Once Weekly most readers would assume, in the absence of a statement to the contrary, that they were otherwise identical. Prescribers might be persuaded to change patients from Fosamax Once Weekly to Bonviva in the belief that the proven benefits of therapy were the same for each. This was not so; the efficacy of Bonviva on hip fractures had not been established whilst Fosamax was specifically licensed to reduce the risk of hip fracture. The Panel considered that to directly compare Bonviva and Fosamax, and not point out this difference, was misleading. Breaches of Clauses 7.2 and 7.3 were ruled.

The Panel noted that Merck Sharp & Dohme had also alleged a breach of Clause 7.10 of the 2006 Code with regard to a failure to encourage rational use. This was a newly introduced requirement of the 2006 Code and so the transition period set out in the Code applied ie between 1 January 2006 and 30 April 2006 no promotional material or activity would be regarded as being in breach of the Code if it failed to comply with provisions only because of requirements which the 2006 edition newly introduced. The Panel thus ruled no breach of Clause 7.10 of the Code.

APPEAL BY ROCHE AND GLAXOSMITHKLINE

Roche and GlaxoSmithKline appealed the Panel's rulings of breaches of Clauses 7.2 and 7.3 of the Code. The companies submitted that they had interpreted the European marketing authorization for Bonviva correctly and as such had a licence for the 'treatment of postmenopausal osteoporosis'. Furthermore it was not misleading to use the BALTO data to claim patient preference for once monthly ibandronic acid compared with weekly alendronate.

The companies submitted that Bonviva was indicated for the treatment of PMO. The wording in the indications section of the SPC might appear to be restrictive as it stated 'Treatment of osteoporosis in postmenopausal women, in order to reduce the risk of vertebral fractures. Efficacy on femoral neck fractures has not been established'. However, this wording was a result of the EMEA Note for Guidance on Postmenopausal Osteoporosis in Women issued in 2001 and the intention was not to restrict the licence to vertebral fractures. The additional words about vertebral fractures and hip fractures were to highlight the evidence base, but not to restrict the target population as this would be impossible in practice.

The companies were not surprised that this guidance had caused Merck Sharp & Dohme such confusion; the Scottish Medicines Consortium (SMC), in its review, also sought similar clarification from the EMEA. The EMEA had confirmed that the marketing authorization for the treatment of PMO was granted if anti-fracture efficacy had been demonstrated at one site and no deleterious effect was observed at the other site. It could not however, be inferred from this guidance that the EMEA intended to limit the use of ibandronate. This response from the EMEA to the SMC was pertinent to the SMC's recent approval of Bonviva for use by the NHS in Scotland.

The companies submitted that this was further supported by EMEA published documents, including the announcement on the positive opinion granted for Bonviva 'to treat osteoporosis'. Further evidence for this indication was in the EMEA-approved patient information leaflet (PIL) which stated 'Bonviva is prescribed to you to treat osteoporosis' and 'Bonviva prevents loss of bone from osteoporosis, and helps to rebuild bone. Therefore Bonviva makes bone less likely to break'. The PIL did not state that efficacy was limited with regard to the risk for any particular

type of fracture. Furthermore under the legal framework of the centralised procedure, the labelling and leaflets formed part of the community decision. Article 59 of 2001/83/EC stated that 'the package leaflet shall be drawn up in accordance with the Summary of Product Characteristics'. Since the package leaflet was reviewed by the CPMP and indeed was annexed within the committee's opinion this confirmed that the licensed indication was for use in PMO without qualification.

The companies stated that by its very nature, PMO was a systemic condition, affecting both vertebral and non-vertebral sites. Treatments for osteoporosis were licensed on the basis of their systemic activity at all skeletal sites, as had been demonstrated for Bonviva. All data showed Bonviva was an effective bisphosphonate at all sites. The beneficial effect seen in bone mineral density (BMD) and other markers of bone turnover was seen in all parts of the affected skeleton (including both the spine and hip) as described in Section 5 of the SPC. This was the case in many other disease areas where well validated surrogate markers were used for regulatory approval.

The companies submitted that a prescriber could not identify which bone a postmenopausal osteoporotic woman was going to break next and therefore it did not make clinical sense to interpret the licence wording as if there were a subgroup of patients who were only at risk of vertebral fracture and not other types of fracture. All promotional claims of fracture risk reduction were clearly and explicitly labelled as being vertebral. No claims were made for reduction of hip fracture. The fracture sites referred to within the claims made were clear even to the casual reader.

The companies submitted that courts in Germany and the Netherlands had ruled that Bonviva was indicated for the 'treatment of postmenopausal osteoporosis' and upheld the position that it was not possible for any bisphosphonate to behave in a site-specific manner. Hence, isolating an effect upon vertebral from non-vertebral fractures was artificial. The companies also noted that the marketing authorization for Bonviva was a European licence, and thus, consistency was expected across all European markets.

The companies noted that the Panel had considered that by directly comparing the dosage frequency and patient preference of Bonviva and Fosamax, most readers would assume, in the absence of a statement to the contrary, that they were otherwise identical and so it was misleading to directly compare the two. This ruling was based upon the Panel's interpretation of the licence for Bonviva. Given that Bonviva was licensed for the treatment of PMO and patients were included in the BALTO study on the basis that the clinicians considered them suitable for either treatment as part of the inclusion criteria, and given that the study was specifically and robustly designed to consider patient preference the companies submitted that the use of the BALTO study to claim preference for the monthly dosing regime compared to the weekly dosing regime was accurate, balanced, fair, objective and unambiguous and should not be ruled in breach.

The primary endpoint of the BALTO study was the percentage of patients who preferred one dosing regime over the other. Neither clinicians nor patients attempted to assess efficacy and no efficacy claims were made on the basis of this study. As in standard clinical practice, the clinicians ensured the patients were suitable for either medicine under test. Both medicines were considered by the regulatory authorities to be possible first line treatments for PMO. As was true for most medicines within a therapeutic category, there were differences in the evidence base for each. If two products were both licensed for osteoporosis in postmenopausal women, and were both possible first line treatments, then it was not unreasonable to expect some doctors to prescribe one and some the other, given the same patients in front of them. There were no definitive data to show that one medicine was significantly better than the other as no head to head comparisons had been done. It would be unreasonable to expect a clinician to discuss all clinical study outcomes with each patient before prescribing a medicine. Without a head to head comparison it was very difficult for clinicians, let alone patients, to make an informed decision on which product was likely to be more effective than the other, and both were licensed first line treatments for the disease that the patient suffered. All patients took the medicines according to their licences and thus the patients involved in the study all had true to life experience of taking either alendronate weekly or Bonviva monthly. The only claims made with regards to this study were based on patient preference for one treatment regime over another.

COMMENTS FROM MERCK SHARP & DOHME

Merck Sharp & Dohme noted that its complaint which the Panel upheld was based on three distinct strings of evidence:

- The licensed indications did not support a comparison between Bonviva and Fosamax Once Weekly in this way.
- The clinical data did not support the comparison.
- The design of the BALTO study was not adequate to support such a comparison.

Merck Sharp & Dohme strongly believed that Roche and GlaxoSmithKline had defended a different charge, namely that Bonviva could be advertised for the treatment of osteoporosis. The three areas that supported the complaint and the Panel's rulings would be discussed in turn.

Licensed indications

Merck Sharp & Dohme noted that Section 4.1 Therapeutic indications of the Bonviva SPC, read 'Treatment of osteoporosis in postmenopausal women in order to reduce the risk of vertebral fractures. Efficacy on femoral neck fractures has not been established'. By comparison, the relevant section of the Fosamax Once Weekly SPC read: 'Treatment of postmenopausal osteoporosis. 'Fosamax' reduces the risk of vertebral and hip fractures'.

Merck Sharp & Dohme noted that the statements used in the current Bonviva campaign referred to a direct

comparison between Bonviva, prescribed one tablet monthly, and Fosamax, prescribed one tablet once weekly. Fosamax Once Weekly had demonstrated clinical benefit in reducing the risk of both vertebral and hip fractures in postmenopausal women with osteoporosis, whereas no efficacy for hip fractures had been demonstrated for Bonviva.

Merck Sharp & Dohme noted that Roche and GlaxoSmithKline had contended that the PIL was a regulatory document that supported their case. Merck Sharp & Dohme submitted, however, that the definitive regulatory document was the marketing authorization, and as such, it focussed its discussion on this pivotal document. The PIL was merely an abridged adaptation of the SPC for use by non-medical individuals.

Merck Sharp & Dohme alleged that the rationale contained within the licensed indication for the treatment with Bonviva was clear – it was indicated for the treatment of osteoporosis in postmenopausal women in order to reduce the risk of vertebral fractures only – no clinical benefit had been shown in hip fracture.

Roche and GlaxoSmithKline's defence was based upon the claim that the regulators intended that Bonviva was used to reduce the risk of clinical fracture at any site in the body. They based this argument on the nature of the disease and bone marker data, but this did not detract from the clarity of the licensed indication namely that the rationale for treatment with Bonviva was to reduce the risk of vertebral fractures. This rationale was supported by clinical data for Bonviva in which efficacy on hip fractures had not been established.

Merck Sharp & Dohme noted that in contrast, Fosamax Once Weekly was licensed for the treatment of PMO. Fosamax reduced the risk of vertebral and hip fractures.

Merck Sharp & Dohme alleged that there was no doubt that these indications were different and it was not appropriate to directly compare these two medicines without referring to their different licensed indications. To make the comparison contained in these promotional materials was therefore unfair, inaccurate and misleading.

Roche and GlaxoSmithKline had provided an email from the EMEA which purported to support their claim that the licensed indication was intended to mean that Bonviva should be used for the purpose of reducing the risk of osteoporotic fractures at all susceptible sites in the body and not just vertebral fractures as stated in the indication. Merck Sharp & Dohme alleged that this was hard to believe as the indication went on to state that efficacy in hip fractures had not been demonstrated, emphasising why the medicine should be used in order to reduce the risk of vertebral fractures (only). The same email also introduced the CHMP 'Guideline on the Evaluation of New Medicinal Products in the Treatment of Primary Osteoporosis' Revision 2 which replaced the CPMP 'Note for Guidance on Postmenopausal Osteoporosis in Women' Revision 1, which Roche and GlaxoSmithKline had used as their reference. In Revision 2, section 2, the CHMP stated that '… the therapeutic indication will *generally* be the treatment of osteoporosis in postmenopausal women at high risk of fracture…' (emphasis added by Merck Sharp & Dohme) and then went on to state that 'The indication may be restricted, eg. to the effect on the axial skeleton, depending on the results of clinical trials'. These statements were not made in Revision 1.

Merck Sharp & Dohme alleged that it was apparent that the Bonviva indication had been restricted to the axial skeleton because clinical efficacy had not been established elsewhere. Although Revision 2 was not published at the time Bonviva was granted its licence, it would seem that the assessors had the same thoughts in mind when restricting the Bonviva licence as indicated above.

Merck Sharp & Dohme made two further points regarding the email:

1 The author was incorrect to state that Revision 2 of the guideline replaced Revision 1 because Revision 2 was presented as a 'draft' for consultation. As this point was incorrect in the email, the Appeal Board would surely also question the accuracy of the earlier paragraph concerning the Bonviva indication upon which Roche and GlaxoSmithKline placed undue emphasis to support their cases, especially as it ran contrary to both the wording of the indication and the provisions of Revision 2 of the guideline as demonstrated above.

2 The footnote to the email stated that it was intended 'for the addressee(s) only', in this case the Chief Pharmaceutical Adviser of the SMC and 'Any disclosure of its contents or copying of its contents, or any action taken (or not taken) in reliance on it is unauthorised and may be unlawful.'

Merck Sharp & Dohme submitted that the Appeal Board might therefore elect to disregard this email completely.

Merck Sharp & Dohme noted that Roche and GlaxoSmithKline asked for consistency in the interpretation of their licensed application across Europe and in support of this cited two court cases from Germany and the Netherlands. The questions considered by these cases, however, were totally different to that which the Appeal Board was currently being asked to adjudicate. The court proceedings dealt with how the licensed indication should be portrayed in advertising materials and did not relate to any comparison with other products for osteoporosis. Indeed in Section 3.6 of the Dutch case the specific comparison now at issue, '52 or 12 tablets per year? What would your patient prefer?', had been disregarded by the committee because Roche and GlaxoSmithKline had given an undertaking that this phrase would no longer be used and consequently this specific area of the complaint was withdrawn. Merck Sharp & Dohme would be happy for consistency across Europe because the focus of its complaint was that it considered that this statement should no longer be used in the UK.

Merck Sharp & Dohme noted that a further complaint has also been adjudicated upon in Finland where the Finnish Inspection Board ordered Roche and GlaxoSmithKline to abstain from the incorrect

marketing of Bonviva where the advertising campaign created an idea of the efficacy of Bonviva being equally as good in comparison to products with more frequent administration. This complaint was essentially similar to the matter now at issue. Again, if Roche and GlaxoSmithKline were aiming for 'consistency across all European markets' as they indicated, they would have voluntarily withdrawn this claim.

Lack of clinical data to support the comparison

Merck Sharp & Dohme noted that the beneficial clinical effect of Fosamax Once Weekly in reducing the risk of osteoporotic fracture of both vertebrae and hip was well supported by clinical data; it had been demonstrated in the Fracture Intervention Trial (FIT) which was specifically designed to assess efficacy in reducing fracture risk. FIT consisted of two placebo-controlled studies using alendronate daily (5mg daily for two years and 10mg daily for either one or two additional years). FIT I (Black *et al* 1996) was a three-year study of 2027 patients who had at least one baseline vertebral fracture. In this study alendronate daily reduced the incidence of ≥ 1 new vertebral fracture by 47% (alendronate 7.9% vs placebo 15%). In addition, a statistically significant reduction was found in the incidence of hip fractures (1.1% vs. 2.2%, a reduction of 51%).

FIT II (Cummings *et al* 1998) was a four-year study of 4432 patients with low bone mass but without a baseline vertebral fracture. In this study, a significant difference was observed in the analysis of the subgroup of osteoporotic women in the incidence of hip fractures (alendronate 1.0% vs placebo 2.2%, a reduction of 56%) and in the incidence of ≥ 1 vertebral fracture (2.9% vs 5.8%, a reduction of 50%).

Merck Sharp & Dohme noted that a meta-analysis of hip fracture reduction across all treatment studies with alendronate in postmenopausal women, with and without existing vertebral fracture, provided evidence of a consistent effect of alendronate on risk reduction of hip fracture (Papapoulos *et al* 2005).

Merck Sharp & Dohme alleged that Roche had informed it that a reduction in risk of hip fracture had not been demonstrated with Bonviva, though 'no detriment' had been demonstrated at this site as a secondary endpoint in studies designed to investigate the medicine's benefit in vertebral fracture prevention.

Merck Sharp & Dohme alleged that there was therefore no doubt that the clinical differences between the two medicines that were obvious from comparing the licensed indications in the two SPCs were borne out completely by examination of the clinical data. The medicines were not comparable.

Merck Sharp & Dohme alleged that Roche's failure to include in the material in question any reference to the differences in clinical data between the two products (ie that Bonviva had not demonstrated efficacy in reducing the risk of hip fractures) compounded the misconceptions that were created by the items. Furthermore, the leavepiece and mailer (but not the advertisement) contained claims of 'Proven efficacy' (both items) and 'Bonviva offers proven efficacy' followed by a graph showing reduction in vertebral fractures (leavepiece only). Although these claims were made to support the main message, ie the comparison of the two products, they were made without clarification of the differences in demonstrated efficacy between the two products. This approach further compounded the misconceptions these materials conveyed, thus reinforcing the unfair, inaccurate and misleading comparison which was not sustainable.

Patient preference data did not support the comparison

Merck Sharp & Dohme noted that the primary objective of the BALTO study was patient preference for either once monthly ibandronate or once weekly alendronate; the secondary objective being assessment of convenience of dosing between the two medicines. As mentioned in the discussion of the paper, there were limitations to this study and most importantly data on treatment adherence could not be captured because of the study design.

Merck Sharp & Dohme stated that the BALTO study outcomes were the responses of 342 US patients to questions about treatment preference and convenience. There was no indication that patients were aware of the comparative efficacy of the two treatments (or of the fairness and accuracy of any information given), even though this would be expected to have a major influence on their choice of preferred treatment. This fact alone could be expected to invalidate the value of the results of the comparison.

Walliser *et al* (2006) evaluated patient preference between medicines taken once weekly vs once monthly, 'Patients' Preference for Osteoporosis Medications:PREFER-International study' was presented in February 2006 at The International Society for Clinical Densitometry (ISCD) meeting in San Diego. The study evaluated 3000 patients in France, Germany, Mexico, Spain and the UK and concluded that the effectiveness in reducing the risk of fracture was most frequently ranked (72%) as the most important reason for their preference whereas only 9% of patients ranked dosing frequency as reason for their preference. This study examined the preferences of a far greater number of patients than those in the BALTO study and made it clear that efficacy data was a more potent driver of patient preference than dosing intervals. The BALTO study did not incorporate knowledge of efficacy in the patient briefing when patients were asked to state their preference.

Thus, Merck Sharp & Dohme alleged that the use of the BALTO study as the basis for promotion was highly questionable, as its results did not provide a platform for a fair, accurate and unambiguous comparison.

In conclusion, Merck Sharp & Dohme alleged that Roche and GlaxoSmithKline's defence and evidence did not address the comparison between the two products but addressed a completely different subject. Merck Sharp & Dohme supported the Panel and reiterated that the Bonviva campaign directed the reader to believe that, from a clinical viewpoint, Bonviva and Fosamax Once Weekly had a comparable

clinical profile and as a result of this it was reasonable to compare their convenience of dosing in isolation from any other characteristics. Merck Sharp & Dohme submitted that it had demonstrated, with reference to the licensed indications and using clinical data that the two products did not have a comparable clinical profile, that such a comparison was therefore unfair, inaccurate and misleading and in breach of Clauses 7.2 and 7.3 of the Code.

APPEAL BOARD RULING

The Appeal Board noted that this was the second complaint it had considered about the same Bonviva campaign. The leavepiece had been at issue both times. The previous complaint (Cases AUTH/1779/11/05 and AUTH/1780/11/05), made by Procter & Gamble and Sanofi-Aventis, was the subject of appeal at the March meeting of the Appeal Board. The Appeal Board noted that Merck Sharp & Dohme had been provided with a copy of the draft case report for Cases AUTH/1779/11/05 and AUTH/1780/11/05.

The Appeal Board noted that according to the SPC Bonviva 150mg was indicated for the 'Treatment of osteoporosis in postmenopausal women in order to reduce the risk of vertebral fractures. Efficacy on femoral neck fractures has not been established'. In Cases AUTH/1779/11/05 and AUTH/1780/11/05 in relation to the complaint about a claim 'Bonviva once monthly for postmenopausal osteoporosis', the Appeal Board had considered that the statement, 'Efficacy on femoral neck fractures has not been established' in the indication section of the SPC provided the evidence base for Bonviva's indication, which was the treatment of PMO. The Appeal Board saw no reason to depart from that ruling in its consideration of the cases now before it.

Cases AUTH/1779/11/05 and AUTH/1780/11/05 included a complaint about the claim 'Faced with 52 or 12 tablets a year, what would patients prefer?' and the use of the BALTO study to claim greater patient preference for a monthly bisphosphonate compared with a weekly bisphosphonate (71% vs 29% respectively). The Appeal Board had noted that the BALTO study was started before the marketing authorization for Bonviva had been granted and thus before the evidence base for the product was fully assessed. Patients could not have known that, in contrast to alendronate, efficacy on hip fractures would not be established for Bonviva. In that regard the patients did not have the full facts about Bonviva and thus, in the Appeal Board's view, would not have been able to express a genuine, well informed preference between it and alendronate. In that regard the Appeal Board had considered that the comparison was unfair and was not based on an up-to-date evaluation of all the evidence and had upheld the Panel's ruling of breaches of Clauses 7.2 and 7.3 of the Code. Roche and GlaxoSmithKline had provided the requisite undertaking and assurance in this regard.

Turning to the cases now for appeal, Cases AUTH/1790/1/06 and AUTH/1791/1/06, the Appeal Board considered that by directly comparing the dosage frequency and patient preference of Bonviva and Fosamax Once Weekly in the items at issue, most readers would assume, in the absence of a statement to the contrary, that they were otherwise identical. Prescribers might be persuaded to change patients from Fosamax Once Weekly to Bonviva in the belief that the evidence base for the indication was the same for each. This was not so; the efficacy of Bonviva on hip fractures had not been established whilst Fosamax was specifically licensed to reduce the risk of hip fracture. The Appeal Board considered that to directly compare Bonviva and Fosamax in the materials at issue, and not point out this difference, was misleading. The Appeal Board upheld the Panel's ruling of breaches of Clauses 7.2 and 7.3. The appeal was unsuccessful.

Complaint received **26 January 2006**

Case completed **11 May 2006**

EDITOR OF A PHARMACY JOURNAL v BAYER

Celebrity endorsement

The editor of a pharmacy journal queried the appropriateness of celebrity endorsement in relation to two online articles, one on the BBC website and one on the Saga Magazine website, which referred favourably to the merits of Levitra (vardenafil) for the treatment of erectile dysfunction. The Director decided to take the matter up as a complaint under the Code with Bayer, the suppliers of Levitra.

In the BBC article, the sporting celebrity was reported as stating: 'The impotence drug Viagra did not help me and I found an alternative called Cialis did not have very quick results, but a drug called Levitra suited my lifestyle. I took it and within 15 minutes I could be 'in action'.' The Saga Magazine article was in a similar vein and, *inter alia*, reported the celebrity as describing Levitra as 'perfect'. They noted that the celebrity was also the spokesman for the 'SortEDin10' campaign.

The Panel noted celebrity endorsement *per se* was not prohibited by the Code. The mere act of using a celebrity to endorse a product did not indicate that high standards had not been maintained. No breach of the Code was ruled. The Panel similarly did not consider that celebrity endorsement *per se* failed to recognise the special nature of medicines or would be likely to cause offence. No breach of the Code was ruled.

The editor of a pharmacy journal asked the Authority to comment upon the appropriateness of celebrity endorsement in relation to two online articles which included interviews with a sporting celebrity and which referred favourably to the merits of Levitra (vardenafil) for the treatment of erectile dysfunction.

The Director decided to take the matter up as a complaint under the Code of Practice with Bayer plc, Pharmaceutical Division, the suppliers of Levitra.

COMPLAINT

Two articles were at issue, one on the BBC website and one on the Saga Magazine website.

In the BBC article, the celebrity was reported as stating:

'The impotence drug Viagra did not help me and I found an alternative called Cialis did not have very quick results, but a drug called Levitra suited my lifestyle. I took it and within 15 minutes I could be "in action"'.

The Saga Magazine article was in a similar vein and, *inter alia*, reported the celebrity as describing Levitra as 'perfect'.

The editor of the pharmacy journal noted that the celebrity was also the spokesman for the 'SortEDin10' campaign.

When writing to Bayer, the Authority advised it that this complaint related solely to the issue of celebrity endorsement and asked it to respond in relation to Clauses 9.1 and 9.2 of the Code.

RESPONSE

Bayer strongly contested that the involvement of a celebrity to support SortEDin10 was in breach of Clauses 9.1 and 9.2, which referred to high standards, format, suitability and causing offence.

SortEDin10 was a disease awareness programme to encourage men who might be embarrassed to talk about their erectile dysfunction to come forward and discuss their condition with a medical professional. It was widely acknowledged that this was an under diagnosed and under treated disease, and importantly it often masked more serious conditions. Inevitably there would be sensitivities around such a topic, but the Department of Health and medical professionals alike recognised the wider benefits of disease awareness programmes of this kind.

Bayer approached the celebrity to be the ambassador for this programme in December 2004, aware that following his prostate cancer operation, he had suffered from erectile dysfunction.

The celebrity and his wife had always been passionate about trying to help others who might be suffering in silence, and encouraging men to seek advice. As a public figure with appeal to men of his own age, and to younger men for whom he was a hero, the celebrity used 'normal' language to talk about his condition and to appeal to sufferers with a non medical background.

The celebrity had been briefed by Bayer to behave in an entirely professional manner, and it believed that he had always done so in the context of Clauses 9.1 and 9.2.

Bayer submitted that all the briefing documents to the celebrity had respected the Code and the Medicines and Healthcare products Regulatory Agency's Blue Guide. These briefing documents were supplied, together with original press releases which triggered the BBC and Saga articles. The journalists appeared to have reported this in a factual and non-salacious manner. Neither Saga nor the BBC would wish to report factual interviews that would cause widespread offence. Both interviews were under the editorial control of those organisations.

Bayer's sponsorship of the SortEDin10 campaign had always been made clear on all press materials.

PANEL RULING

The Panel noted that celebrity endorsement *per se* was not prohibited by the Code. The mere act of using a celebrity to endorse a product did not, in the Panel's view, indicate that high standards had not been maintained. No breach of Clause 9.1 was ruled. The Panel similarly did not consider that celebrity endorsement *per se* failed to recognise the special

nature of medicines or would be likely to cause offence. No breach of Clause 9.2 was ruled.

Complaint received **13 February 2006**

Case completed **11 May 2006**

CASE AUTH/1798/2/06

MEDIA/DIRECTOR v BAYER

Levitra online articles

In Case AUTH/1797/2/06 online articles featuring interviews with a sporting celebrity were taken up with Bayer by the Director following a query from the editor of a pharmaceutical journal about the appropriateness of celebrity endorsement. The articles had referred favourably to Levitra (vardenafil), Bayer's product for erectile dysfunction. In accordance with established practice the Director also took up with Bayer a further matter arising from the articles.

The two articles at issue were published on the BBC and Saga Magazine websites respectively and included interviews with the celebrity. Each article discussed the benefits of Levitra in very favourable terms. The Authority was concerned that material briefing either the press or the celebrity might have contravened the Code.

The Panel noted that when interviewed for the BBC and asked about his treatment for erectile dysfunction, the celebrity stated 'The impotence drug Viagra did not help me and I found an alternative called Cialis did not have very quick results, but a drug called Levitra suited my lifestyle. I took it and within 15 minutes I could be in 'action'.' In the article for Saga, the celebrity stated 'The doctor prescribed Levitra, a new generation of anti-impotence pills, and they have proved to be perfect'.

The Panel acknowledged that the celebrity was expressing his own opinions about his treatment with Levitra but considered that those opinions would have been known to Bayer; the company knew that he took Levitra and by briefing him to talk about his treatment and facilitating his interviews with the BBC and Saga it was responsible for the remarks he made. The Panel considered that Bayer had in effect encouraged the celebrity to make statements encouraging members of the public to ask their doctor to prescribe Levitra. A breach of the Code was ruled. The Panel considered that the online interviews advertised Levitra to the general public and thus ruled a breach of the Code.

In Case AUTH/1797/2/06 online articles featuring interviews with a sporting celebrity were taken up with Bayer plc, Pharmaceutical Division, by the Director following a query from the editor of a pharmaceutical journal about the appropriateness of celebrity endorsement. The articles referred favourably to Levitra (vardenafil), Bayer's product for erectile dysfunction. In accordance with established practice, the Director also took up with Bayer a further matter arising from the articles.

COMPLAINT

The two articles at issue were on the BBC and Saga Magazine websites respectively and included interviews with the celebrity.

Each article discussed the benefits of Levitra in very favourable items. The Authority was concerned that material provided by Bayer to the BBC, Saga, journalists or the named celebrity might have contravened Clauses 20.1 or 20.2 of the Code.

RESPONSE

Bayer noted the Authority's concern that there might have been a breach of Clause 20.1 or 20.2 of the Code. Bayer took both the Code and the Medicines and Healthcare products Regulatory Agency's (MHRA) (Blue Guide) guidance very seriously, particularly in the context of promotion of prescription medicines, and strongly contested that its action had breached the Code.

In January 2005, at the launch of SortEDin10, Bayer provided all briefing documents to the MHRA, together with relevant press articles. The MHRA had had no further queries on this campaign.

Bayer believed that information it had supplied to both the celebrity and journalists dating back to the launch of SortEDin10 in December 2004 had complied with the Code. Specific references were made to the prohibition of promotion of prescription medicines to the public in all briefing documents to the celebrity.

The said briefings to the celebrity and the press releases which generated the articles that appeared on the BBC news site and the Saga magazine, dated as appropriate, together with hard copies of email correspondence between Bayer's PR agency and the editor of Saga magazine were provided. Neither Bayer nor its agencies were provided with transcripts of any interviews by the organisations or the journalists, and had no input to the editorial copy.

The celebrity and his wife had always been particularly passionate about trying to help others who might be suffering in silence, and encouraging men to seek advice.

SortEDin10 was a disease awareness programme to encourage men who might be embarrassed to talk about their erectile dysfunction to come forward and discuss their condition with a medical professional. It was widely acknowledged that this was an under diagnosed and under treated disease, and importantly it often masked more serious conditions. Inevitably there would be sensitivities around such a topic, but

the Department of Health and medical professionals alike recognised the wider benefits of disease awareness programmes of this kind.

PANEL RULING

The Panel noted that when interviewed for the BBC and asked about his treatment for erectile dysfunction, the celebrity stated 'The impotence drug Viagra did not help me and I found an alternative called Cialis did not have very quick results, but a drug called Levitra suited my lifestyle. I took it and within 15 minutes I could be in 'action'.' In the article for Saga the celebrity stated 'The doctor prescribed Levitra, a new generation of anti-impotence pills, and they have proved to be perfect'.

As with all complaints about articles in the press the Panel examined the briefing materials which prompted the articles on the BBC and Saga websites and not the articles *per se*. The briefing for the celebrity noted that he was a Levitra patient; it was stated that he could respond truthfully, in a factual and descriptive way, to any questions regarding his treatment choice as he felt appropriate. In a section headed 'Treatment', in a statement which appeared to have been written by him it was stated that '… the winning formula is to be fast and effective, so what I wanted was a treatment that worked fast & I could rely on – a treatment in fact, a bit like me!'. In a briefing from the communications agency it was stated that the celebrity would not be encouraged to endorse or recommend Levitra although it was later stated that he would explain about his personal experience of erectile dysfunction.

The Panel considered that as the celebrity had been briefed to talk about his treatment for, and personal experience of, erectile dysfunction, Bayer was responsible for the remarks that he made to the journalists from the BBC and Saga. The celebrity had been briefed by Bayer and the company had facilitated his interviews with the BBC and Saga. It was therefore not possible for Bayer to dissociate itself from what he had said in the interview; if it were otherwise then the effect would be for companies to use patients as a means of avoiding the restrictions in the Code.

The Panel acknowledged that the celebrity was expressing his own opinions about his treatment with Levitra but considered that those opinions would have been known to Bayer; the company knew that he took Levitra and had encouraged him to talk about his treatment. The Panel considered that Bayer had in effect encouraged the celebrity to make statements encouraging members of the public to ask their doctor to prescribe Levitra. A breach of Clause 20.2 was ruled. The Panel considered that the BBC and Saga interviews advertised Levitra to the general public and thus ruled a breach of Clause 20.1.

Proceedings commenced **16 February 2006**

Case completed **3 May 2006**

MEDIA/DIRECTOR v ABBOTT

Arrangements for a meeting

An article in The Sun newspaper about an ex-employee of Abbott referred to the fact that representatives of the company had attended a gay club in Glasgow together with at least one hospital consultant. The article referred to a claim for unfair dismissal in employment tribunal proceedings. The Director considered that from the information given, Abbott might have contravened the Code. The matter was thus taken up as a complaint under the Code.

The Panel noted, with regard to the visit to the club, that Abbott representatives had claimed £40.90 for drinks. It appeared that the visit was a social event. The venue was a bar with music and dancing. The company had not provided any information about who had attended. The published article referred to the presence of a hospital consultant. This was not disputed by Abbott.

On the evidence before it, the Panel decided that the arrangements had not complied with the requirements of the Code regarding meetings and hospitality. It was probably unacceptable to take health professionals to such a venue in any circumstances and was certainly unacceptable for purely social reasons. A breach of the Code was ruled. High standards had not been maintained. Breaches of the Code were ruled. The Panel considered that irrespective of whether company money had been used to fund the visit to the bar, the arrangements in question brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

The Appeal Board noted that in its appeal Abbott had provided further and better particulars than those submitted to the Panel. Abbott had now unequivocally stated that it had not provided the consultant mentioned in The Sun article with any hospitality. There was an anonymised supporting statement from the consultant signed by Abbott's solicitors as a true and accurate copy of the original. Abbott stated that the payment of £40.90 had been claimed by the representative as part of routine expenses and not part of customer support as this would have necessitated using a different procedure. The company assumed that the payment was in respect of a manager buying drinks for Abbott staff. There was no evidence provided by the journalist that inappropriate hospitality had been provided. On the basis of the information before it the Appeal Board ruled no breach of the Code, including Clause 2.

An article in The Sun on 8 February criticised the activities of Abbott Laboratories Limited. In accordance with established practice as regards media criticism, the matter was taken up by the Director as a complaint under the Code.

COMPLAINT

The article concerned a sales force employee dismissed by Abbott who had taken her case to an employment tribunal. The article referred, *inter alia*, to the fact that Abbott representatives had attended a gay bar in Glasgow with at least one hospital consultant.

Abbott was asked to respond in relation to Clauses 2, 9.1, 15.2 and 19.1 of the 2003 Code. The Authority informed the journalist that the article was being used as the basis of a complaint under the Code and noted that other matters referred to in the article had already been dealt with in Case AUTH/1745/7/05. A copy of the case report for that case was sent to the journalist.

RESPONSE

Abbott noted that these allegations were made in connection with an employment tribunal proceeding involving a former member of its HIV sales force and that the tribunal rejected entirely the claims brought by the former employee.

The gathering at the club in question occurred during the attendance by Abbott staff at the Seventh International Congress on Drug Therapy in HIV Infection which was held in Glasgow in November 2004. Attendance at the club did not form part of Abbott's official presence at the conference. A review of the expenses of Abbott employees attending the conference did not reveal the provision of any excessive or inappropriate hospitality; only one receipt for £40.90 relating to drinks purchased there was identified. Accordingly, Abbott did not consider that the attendance at the club constituted a breach of Clauses 2, 9.1, 15.2 or 19.1 of the Code.

PANEL RULING

The Panel noted that Abbott representatives had claimed £40.90 for drinks at the club. It appeared that the visit was a social event. The venue was a bar with music and dancing. The company had not provided any information about who had attended. The published article referred to the presence of a hospital consultant. This was not disputed by Abbott.

On the evidence before it, the Panel decided that the arrangements had not complied with the requirements of Clause 19.1 of the Code regarding meetings and hospitality. It was probably unacceptable to take health professionals to such a venue in any circumstances and was certainly unacceptable for purely social reasons. A breach of Clause 19.1 was ruled. High standards had not been maintained. Breaches of Clauses 9.1 and 15.2 were ruled. The Panel considered that irrespective of whether company money had been used to fund the visit to the bar, the arrangements in question brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

APPEAL BY ABBOTT

Abbott appealed all of the Panel's rulings.

Abbott submitted that in terms of evidence a review of the circumstances in question clearly showed that on the night of the alleged inappropriate hospitality, Abbott did not invite the hospital consultant to the club. Furthermore, Abbott did not provide the consultant with any hospitality at the bar. The consultant in question had provided a written statement to this effect and an anonymised copy, signed by Abbott's solicitors as a true and accurate copy of the original, was provided.

Abbott stated that at least one other ABPI member company that had been at the club on the evening in question had provided Abbott with a letter setting out the appropriateness of the venue and the events which took place there. An anonymised copy of the letter, signed by Abbott's solicitors as a true and accurate copy of the original, was provided.

Abbott submitted that the above evidence alone was sufficient to cause the Appeal Board to reconsider the ruling of a breach and to find instead no *prima facie* case.

Abbott stated that, as a result of the provisions in Paragraph 5.2 of the 2006 Constitution and Procedure relating to a complaint which concerned 'a matter closely similar to one which has been the subject of a previous adjudication', the Panel lacked authority to proceed with this purported complaint. The subject of Case AUTH/1745/7/05, which led to Abbott's suspension from the ABPI, was the subject of a review by the Appeal Board and dealt with what constituted an inappropriate venue and hospitality, ie identical issues to the subject matter now at issue. The two cases involved similar individuals, similar allegations relating to inappropriate hospitality and occurred in roughly the same time period as the visit to the club. As such, the Director abused her discretion in proceeding with this purported complaint. As a result of Case AUTH/1745/7/05, Abbott was suspended from the ABPI for six months and had given undertakings as to its future conduct. Bringing subsequent proceedings, on such closely similar allegations, whilst a company was already suspended and subject to undertakings, was an oppressive and disproportionate measure which could have no practical benefit or consequence other than to subject Abbott to further negative publicity.

Abbott submitted that The Sun newspaper article in question had not, and could not, constitute a complaint that was subject to the jurisdiction of the Panel. The Constitution and Procedure stated in Paragraph 1.2 that 'the Authority also administers the complaints procedure by which complaints made under the Code are considered by the Code of Practice Panel and, where required, by the Code of Practice Appeal Board' (emphasis added). There were numerous other references throughout the Code to 'complaints made under the Code', such as in Clause 2.1 and the first box of the flowchart on page 38 of the Code of Practice booklet. The Sun newspaper article could not constitute a complaint 'made under the Code', since it did not refer to either the Code or any of its provisions and was not submitted to the Director in the manner set forth in the introduction to the Constitution and Procedure. Furthermore, the article could not be considered a complaint since it did not have a 'complainant'. The newspaper had reported on evidence given in an employment tribunal hearing by a former Abbott employee and was not making a complaint under the Code. There were no facts to support the view that the journalist was making a complaint. Further, the Code did not provide any basis for assuming the existence of a 'complainant'. The article did not contain any allegation of infringement of a provision of the Code. The part of the article relevant to the matters referred to a personal incident between the representative and the hospital consultant. The article had not alleged that Abbott provided hospitality to the hospital consultant at the club, a matter that would be covered by the Code.

Furthermore, Abbott submitted that it was highly inappropriate to suggest the description of the club as a 'gay club' constituted an allegation of infringement by Abbott and its representatives of the obligations to maintain high standards set out in Clauses 9.1 and 15.2 of the Code. Moreover, the supplementary information provided in the Code regarding Clause 2 stated that: 'A ruling of breach of this clause is a sign of particular censure and is reserved for such circumstances'. There was nothing about this venue, other than its description as a 'gay club', which the Panel surely could not intend to imply had any significance that would suggest an issue with this location.

Abbott submitted that even if, despite ample evidence to the contrary, the Panel was correct to conclude that The Sun article had constituted a complaint made under the Code, there was not a shred of evidence to support such a complaint. To find Abbott in breach of the Code without any evidence to support such a finding, and in spite of the denial of a breach provided by Abbott in its response, was a deviation from the requirements of fundamental fairness and due process.

Abbott stated that in providing the case report for Case AUTH/1745/7/05 to the Sun reporter, without first consulting Abbott, the Panel had effectively pre-determined the outcome of the case by increasing the likelihood of further adverse publicity for Abbott. As explained above, given that Abbott was already suspended and subject to undertakings given as a result of Case AUTH/1745/7/05, the only effective consequence of ruling a breach of the Code in the case now at issue would be further adverse publicity. The act of handing over the documents to the reporter, notwithstanding any request by the Panel that the reporter treated these documents as private and confidential, clearly increased the risk of further publicity against Abbott.

Finally, Abbott submitted that it was not it but the Panel in its ruling, its characterization of The Sun newspaper article as a complaint made under the Code and the reporter as a 'complainant'; and in sending the reporter a copy of its ruling along with the previous case report, that had engaged in activities to bring discredit upon, or reduce confidence in the pharmaceutical industry. This inappropriate contact with the media should be stopped immediately and the Constitution and Procedure revised to avoid recurrence of this unfortunate incident.

For the reasons stated above, Abbott submitted that the Panel's rulings of a breach of the Code was erroneous and unreasonable and should be set aside.

COMMENTS FROM THE JOURNALIST

The journalist stated that he had merely been reporting on an industrial tribunal for his newspaper and that he had no further interest in this case.

APPEAL BOARD RULING

The Appeal Board noted that in its appeal Abbott had provided further and better particulars than those submitted to the Panel. Abbott had now unequivocally stated that it had not provided the consultant mentioned in the Sun article with any hospitality. There was an anonymised supporting statement from the consultant signed by Abbott's solicitors as a true and accurate copy of the original. At the appeal hearing Abbott stated that the payment of £40.90 had been claimed by the representative as part of routine expenses and not part of customer support as this would have necessitated using a different procedure. The company assumed that the payment was in respect of a manager buying drinks for Abbott staff. There was no evidence provided by the journalist that inappropriate hospitality had been provided. On the basis of the information before it the Appeal Board ruled no breach of Clauses 2, 9.1, 15.2 and 19.1 of the Code. The appeal was successful.

During its consideration of this case the Appeal Board noted Abbott's concerns regarding the process by which the newspaper article was taken up and dealt with as a complaint but considered that the Director had acted in accordance with the Constitution and Procedure in that regard. Paragraph 5.1 of the Constitution and Procedure stated that when the Director received information from which it appears that a company may have contravened the Code, the company concerned is invited to comment on the matters of complaint. Public criticism of the industry was taken up and dealt with as a complaint under the Code. Established custom and practice was to give the rights of the complainant to someone and in the case of articles in the press it was usually the author of the article. As to whether the matter should have proceeded, Paragraph 5.1 stated that if a complaint concerns a matter closely similar to one which has been the subject of a previous adjudication it may be allowed to proceed in certain specified circumstances. Further the Director should normally allow a complaint to proceed if it covered matters similar to those in a decision of the Code of Practice Panel which was not the subject of appeal to the Appeal Board. The Appeal Board considered that the matters taken up by the Director were not closely similar to those the subject of Case AUTH/1745/7/05 and in any event that case was not the subject of an appeal to the Appeal Board; the matter had come before the Appeal Board as a result of a report made to it by the Panel. Further the Appeal Board thus considered that the Director had correctly followed the Constitution and Procedure in this regard. The Appeal Board fully supported the Director's decision to send the journalist the published report for the previous case, Case AUTH/1745/7/05; it was relevant to the matter at issue and already in the public domain.

Proceedings commenced **15 February 2006**

Case completed **11 May 2006**

CASE AUTH/1800/2/06

PRIMARY CARE TRUST HEAD OF PRESCRIBING v ASTRAZENECA

Invitation to a meeting

The head of prescribing at a primary care trust stated that several members of his team were invited to an educational meeting, 'Burning Issues in Gastroenterology', sponsored by AstraZeneca. The invitation had been emailed from two different sources.

The invitation referred to an indication for Nexium (esomeprazole) without providing prescribing information for this product. Additionally, one of the emails to which the invitation was attached also referred to Nexium, again without any prescribing information. In both of these cases the non-proprietary name did not appear adjacent to the brand name.

The Panel noted that the email invitation included the product name, Nexium, and thus triggered the requirement to provide prescribing information; the email should also have included the non-proprietary name immediately adjacent to the brand name. The Panel noted that neither requirement had been met and so ruled breaches of the Code. The Panel did not consider that the email constituted disguised promotion. Recipients would be aware of the nature of the meeting. The Panel ruled no breach of the Code in that regard.

The head of prescribing at a primary care trust (PCT) complained about an invitation to a meeting which he had received from a representative of AstraZeneca UK Limited.

COMPLAINT

The complainant stated that several members of his PCT team were invited to an educational meeting, 'Burning Issues in Gastroenterology', sponsored by AstraZeneca. The invitation had been emailed from two different sources.

Firstly, the invitation referred to an indication for Nexium (esomeprazole) without providing prescribing information for this product. As the meeting purported to be educational in content the complainant was surprised that a brand name was included in the programme; however, as Nexium was made and marketed by AstraZeneca he alleged that the invitation could be construed as promotional and therefore it should have included relevant prescribing information.

Additionally, one of the emails to which the invitation was attached also referred to Nexium, again without any prescribing information.

In both of these cases the non-proprietary name did not appear adjacent to the brand name.

When writing to AstraZeneca, the Authority asked it to respond in relation to Clauses 4.1, 4.3 and 10.1 of the Code.

RESPONSE

AstraZeneca confirmed that one of its representatives emailed a member of the PCT in question on 31 January. The company accepted that this communication was in breach of the Code.

AstraZeneca explained that the agenda attached to the email dated 31 January was in fact an earlier draft, which was identified as non-compliant with the Code because Nexium was mentioned in the title of one of the educational sessions with no subsequent use of the generic name and no prescribing information. This was duly corrected prior to printing the invitations for circulation.

However, in December AstraZeneca's computer system underwent a significant upgrade, which necessitated the reloading of historical data. Unfortunately, the earlier non-compliant draft version of this particular agenda was loaded in error, instead of the final version that had been corrected and approved in December 2005.

When the representative sent the email on 31 January, he accessed the computer records in the proper way according to AstraZeneca's processes and attached what he believed to be the final and approved version (unfortunately without double-checking it). Regrettably, his email also mentioned Nexium without the non-proprietary name, which was an oversight on his part. Appropriate action would be taken with the individual.

Whilst AstraZeneca was very disappointed with what it believed to be a one-off technical failure, it was pleased that its existing approval systems originally identified the issues in the draft agenda prior to printing. As a consequence of its investigation, AstraZeneca was confident that this was the only electronic invitation sent and that the vast majority of health professionals received the correct final agenda and not the incorrect draft.

The actual meeting was educational in content and this was clearly stated on the invitation. However, whilst the final agenda was correct and the content of the talk was appropriate for the title, AstraZeneca accepted that the draft title of the talk was inappropriate.

AstraZeneca concluded that while the meeting as held complied with the current Code, the specific email noted by the PCT did not. AstraZeneca apologised for its error. Despite its belief that this was a one-off technical error, AstraZeneca had initiated steps to eliminate the risk of this ever happening again in future computer upgrades. In addition, the representative involved had been re-educated on his responsibilities under the Code.

PANEL RULING

The Panel noted that the invitation, sent by email on 31 January, included the product name, Nexium, and thus triggered the requirement to provide prescribing information; the email should also have included the non-proprietary name immediately adjacent to the brand name. The Panel noted that neither requirement had been met and so it ruled breaches of Clauses 4.1 and 4.3 of the Code as acknowledged by AstraZeneca.

The Panel did not consider that the email constituted disguised promotion. Recipients would be aware of the nature of the meeting. The Panel ruled no breach of Clause 10.1 of the Code.

Complaint received	**15 February 2006**
Case completed	**6 April 2006**

CASE AUTH/1801/2/06

GENERAL PRACTITIONER v GLAXOSMITHKLINE

Reference to a patient website

A general practitioner complained about GlaxoSmithKline's involvement with the Ekbom Support Group (ESG), a support group for patients with restless leg syndrome (RLS). The complainant noted that GlaxoSmithKline had placed advertisements in the GP press drawing the reader's attention to RLS as a condition and advising that patients might like to know about the ESG website. The complainant understood that GlaxoSmithKline's product, ropinirole, would soon be licensed for the treatment of RLS.

The complainant noted that a newsletter on the ESG website referred to the use of ropinirole for RLS in Germany and the US and alleged that GlaxoSmithKline's advertisement might thus indirectly promote the product for use in a condition for which it had no UK licence. This seemed a cynical attempt, by a company with huge financial conflicts of interest, to exploit a patient support group.

The Panel noted that the advertisement in question was used from September 2004 until November 2005; it had only appeared in medical journals. GlaxoSmithKline had not informed patients or the public of the availability of the ESG website. In the UK ropinirole (GlaxoSmithKline's product Requip) was indicated for use in the treatment of Parkinson's disease.

The Panel noted that the ESG newsletter, October 2005, referred to ropinirole which was only licensed for RLS in Germany and the US. The newsletter predated the advertisement. The Panel noted that the ESG website included information about approaches for helping patients with RLS including medicines. There was no product licensed in the UK for RLS but it was anticipated that ropinirole would be so licensed by April 2006.

The Panel noted that it would have been a breach of the Code to include the information about the use of ropinirole in RLS in the advertisement as this would have constituted promotion of an unlicensed indication. On that basis, the Panel considered that referring health professionals to a website that included a newsletter giving information about an unlicensed indication in effect promoted that unlicensed indication. If that were not the case then companies would be able to refer to independent websites as a means of avoiding the restrictions in the Code. A breach of the Code was ruled which was appealed by GlaxoSmithKline.

The Panel considered that health professionals were encouraged to refer patients to the website. The Panel did not consider that this was unacceptable *per se*. The Panel did not consider that the material on the website was an advertisement for ropinirole *per se* and so no breach of the Code was ruled. The Panel noted, however, that the news section of the website referred to an article, published in December 2004, which reported that ropinirole was 'safe and effective for the treatment of RLS'. On that basis the Panel considered that GlaxoSmithKline was, in effect, directing patients to a site that contained misleading messages about the safety of ropinirole in an unlicensed indication which might indirectly encourage patients to ask their doctors to prescribe it. As above, if this were not the case then companies would be able to use independent websites as a means of avoiding the restrictions in the Code. A breach of the Code was ruled which was appealed by GlaxoSmithKline.

The Appeal Board noted that the advertisement which appeared in medical journals suggested that '… patients might appreciate being made aware of the Ekbom Support Group, which can be accessed via the internet at [website address given]'. GlaxoSmithKline was thus effectively directing both health professionals and members of the public to the website. Patient groups were not covered by the Code and thus material on their websites was a matter for the relevant patient group. Directing people to such sites, in pharmaceutical company advertising meant that the company became inextricably linked with the content of those sites whether or not they had had any input, control etc. If this were not the case then companies would be able to refer to independent websites as a means of avoiding the restrictions in the Code.

The Appeal Board noted from GlaxoSmithKline that when the advertisement was approved in August 2004, GlaxoSmithKline had checked the ESG website to ensure that directing health professionals to it did not lead to a breach of the Code. GlaxoSmithKline stated that it knew that the

newsletter on the website would be updated approximately every six months. The advertisement ran for 15 months – September 2004 until November 2005 – but GlaxoSmithKline did not recheck the website throughout that time. The Appeal Board considered that companies referring to patient group websites in their advertising needed to ensure that whenever they did so the website content was acceptable as far as the Code was concerned.

The Appeal Board noted that the ESG newsletter, October 2005, referred to ropinirole which was only licensed for RLS in Germany and the US. Although the product was not so licensed in the UK it was available, and licensed, for use in the treatment of Parkinson's Disease. GlaxoSmithKline's representatives confirmed that patients with RLS were often treated off-label.

The Appeal Board noted that it would have been a breach of the Code to include the information about the use of ropinirole in RLS in the advertisement at issue as this would have constituted promotion of an unlicensed indication. On that basis, the Appeal Board considered that referring health professionals to a website that included a newsletter giving information about an unlicensed indication in effect promoted that unlicensed indication. The Appeal Board thus upheld the Panel's ruling of a breach of the Code. Similarly, by encouraging health professionals to refer patients to the website the Appeal Board considered that GlaxoSmithKline was in effect directing members of the public to a site which contained statements which might encourage them to ask their doctors for ropinirole. The Panel's ruling of a breach of the Code was upheld.

A general practitioner complained about the involvement of GlaxoSmithKline UK Limited with the Ekbom Support Group (ESG), a patient support group for patients with restless leg syndrome (RLS). The complainant noted that GlaxoSmithKline had placed advertisements (ref RLS/DPS/04/14400/1) in the GP press which drew attention to RLS, focussing in particular on the associated sleep disturbance. The advertisement stated there was currently no licensed treatment for RLS but that patients might like to know about the ESG; the website address for the group was given.

COMPLAINT

The complainant was concerned about GlaxoSmithKline's involvement with the ESG. The Ekbom website, which GlaxoSmithKline had promoted in the GP press, offered advice on RLS. GlaxoSmithKline had a treatment, ropinirole, which was unlicensed for RLS in the UK but which the complainant understood might be licensed soon.

Ekbom was clearly a genuine patient group which was very well intentioned. A newsletter on its website, however, stated 'I know many members are now able to have ropinirole, but it is only licensed in Germany and the USA at present'. Ekbom also had a forum that members used.

The complainant was concerned about GlaxoSmithKline's involvement and that the advertisements in the GP press might indirectly be construed as promoting ropinirole for an unlicensed indication in the UK. This also seemed a cynical attempt to exploit a patient support group from a company which had huge financial conflicts of interest.

When writing to GlaxoSmithKline, the Authority asked it to respond in relation to Clauses 3.2, 20.1 and 20.2 of the Code.

RESPONSE

GlaxoSmithKline submitted that the ESG was an entirely independent group which managed and produced its own website without any influence or input from GlaxoSmithKline apart from the RLS patient information leaflet which provided information on RLS but did not refer to any medicines; GlaxoSmithKline's involvement with the leaflet was clearly stated on the website copy and on the hard copy available from the ESG. The ESG collated information from various sources on a wide range of issues that affected sufferers of RLS and made it available via its website and other media to its members.

As the ESG was not a registered charity, no money had ever been given to it, its co-ordinator or other members by GlaxoSmithKline. Since 2004, GlaxoSmithKline had however provided:

- administrative support to transfer a handwritten database onto Microsoft Excel;
- installation of broadband internet connection;
- ESG headed stationery.

GlaxoSmithKline strongly refuted the allegation of a breach of Clause 3.2. The advertisement at issue was only published in professional journals between September 2004 and November 2005. The advertisement was strictly non-promotional and certified as such; it mentioned no product names and made no product related claims. The advertisement was intended to raise awareness among health professionals of RLS as a disease. A large (n=23,052) multinational investigation of primary care patients showed that 11.1% (n=2,564) had RLS and 3.4% (n=787) had significant disease (Hening *et al* 2004). 65% of RLS sufferers consulted for their illness but only 8-13% received a diagnosis of RLS. This clearly demonstrated that awareness of the condition was low and that it was in the interest of the public, as well as the whole healthcare sector, to raise awareness of the diagnosis of RLS. The advertisement informed health professionals that there was an alternative source of information available, ie the ESG. Written permission was provided by the founder and co-ordinator of the ESG to refer to the website.

This ESG was the only support group for patients with RLS in the UK and was a completely independent organisation. The website provided further information on diagnosis and a wide range of management options including non-pharmacological treatment. This website did not, in GlaxoSmithKline's view, promote any one treatment over another, and as mentioned above, the content did not receive any input from GlaxoSmithKline.

With reference to Clauses 20.1 and 20.2 the disease awareness advertisement was only ever placed in medical publications and therefore not aimed at patients. GlaxoSmithKline therefore refuted any allegations of a breach of either Clause 20.1 or 20.2.

Health professionals were informed about the ESG website so that they could find additional information, and if the need arose, patients could be directed to it, should the doctor concerned so choose. As detailed above GlaxoSmithKline considered that this was an important source of independent, balanced information.

Whilst there was information available on the website regarding the management of RLS, this covered a plethora of different remedies for RLS from lifestyle advice, herbal, dietary remedies and alternative medicine to a wide variety of prescription medicines. In addition, the advertisement clearly stated that there were currently no licensed treatments for RLS in the UK. This website provided balanced and accurate information to patients and its content was the responsibility of the ESG. The website received no input from GlaxoSmithKline (with the exception declared above) and did not preferentially favour one treatment over another.

In summary, GlaxoSmithKline denied any breach of the Code with regard to the relationship between it and the ESG and the use of non-promotional disease awareness advertisements. Ropinirole currently had a marketing authorization for use in RLS in the US, France, Switzerland and Australia.

Ropinirole, under the brand name Adartrel, received a positive recommendation from the European Medicines Agency (EMEA) Committee for Medicinal Products for Human Use (CHMP) in September 2005 under the mutual recognition procedure. The European Commission had now indicated its intention to ratify this positive decision by the end of March 2006 and it was anticipated that the Medicines and Healthcare products Regulatory Agency (MHRA) would grant a marketing authorization in the UK around the end of April 2006.

PANEL RULING

The Panel noted that the advertisement in question was used from September 2004 until November 2005.

This case was considered under the requirements of the 2003 Code using the Constitution and Procedure in the 2006 Code of Practice booklet.

In the UK ropinirole (GlaxoSmithKline's product Requip) was indicated for use alone in the treatment of idiopathic Parkinson's disease. It could also be used with levodopa to control 'on off' fluctuations and permit a reduction in the total daily dose of levodopa.

The Panel noted that the advertisement only appeared in medical journals.

GlaxoSmithKline had not informed patients or the public of the availability of the ESG website. The advertisement to health professionals suggested that '… patients might appreciate being made aware of the Ekbom Support Group'.

The Panel noted that the ESG newsletter, October 2005, referred to GlaxoSmithKline's product, ropinirole, which was only licensed for RLS in Germany and the US. The newsletter predated the advertisement.

The Panel considered that companies referring to information on websites in their advertising needed to ensure that the website content was reasonable as far as the Code was concerned.

The ESG website included information about approaches for helping patients with RLS including medicines.

There was no product licensed in the UK for RLS but GlaxoSmithKline's product, Requip, was licensed elsewhere for RLS and it was anticipated that ropinirole would be so licensed in the UK by April 2006.

The Panel noted that it would have been a breach of the Code to include the information about the use of ropinirole in RLS in the advertisement to health professionals as this would have constituted promotion of an unlicensed indication. On that basis, the Panel considered that referring health professionals to a website that included a newsletter giving information about an unlicensed indication in effect promoted that unlicensed indication. If that were not the case then companies would be able to refer to independent websites as a means of avoiding the restrictions in the Code. Thus a breach of Clause 3.2 of the Code was ruled.

The Panel considered that health professionals were encouraged to refer patients to the website. The Panel did not consider that this was unacceptable *per se*. The Panel did not consider that the material on the website was an advertisement for ropinirole *per se* and so no breach of Clause 20.1 was ruled. The Panel noted, however, that the news section of the website referred to an article, published in December 2004, which reported that ropinirole was 'safe and effective for the treatment of RLS'. On that basis the Panel considered that GlaxoSmithKline was, in effect, directing patients to a site that contained misleading messages about the safety of ropinirole in an unlicensed indication which might indirectly encourage patients to ask their doctors to prescribe it. As in the matter considered above, if this were not the case then companies would be able to use independent websites as a means of avoiding the restrictions in the Code. A breach of Clause 20.2 was ruled.

APPEAL BY GLAXOSMITHKLINE

GlaxoSmithKline appealed the Panel's rulings of breaches of Clauses 3.2 and 20.2 of the Code.

GlaxoSmithKline noted that this case concerned a disease awareness advertisement that it had run in the medical press to raise awareness among health professionals of RLS as a disease. The advertisement informed health professionals of the ESG as the only support group for patients with RLS in the UK, and referred to the ESG website.

GlaxoSmithKline noted that the complainant was concerned about the company's involvement with the

ESG and that advertisements in the medical press 'might be indirectly construed' as promoting ropinirole in an unlicensed indication. GlaxoSmithKline submitted that the complainant had not accused it of promoting ropinirole in an unlicensed indication *per se*, and this certainly was not its intention. The advertisement was non-promotional and did not refer to any pharmaceutical products as treatments for RLS and contained no product-related claims. The advertisement clearly stated that there were no licensed treatments for RLS in the UK.

GlaxoSmithKline strongly refuted the complainant's allegation that it 'seemed a cynical attempt to exploit a patient support group'. As previously stated, the ESG was an entirely independent organisation to which GlaxoSmithKline had provided only very limited support and never made any monetary payment. GlaxoSmithKline had never had any input to or influence over the content of the ESG website (except for the patient information leaflet as previously stated and explicitly declared). The ESG October 2005 newsletter to which the Panel referred was entirely the independent work of the ESG co-ordinator. It was added to the website in October 2005 and was therefore not present at the time the advertisement was certified (August 2004) and for the great majority of the period during which it ran (September 2004 to November 2005). Thus, there was only an overlap of one month whilst the advertisement was still running and the newsletter was present on the ESG website. As previously described, the fact that this appeared on the ESG website in October 2005 was unknown to GlaxoSmithKline and outside of its control. The reference to the ESG website was provided in good faith with the knowledge of the ESG and in the expectation that it would be a useful source of information for health professionals and any patients so referred.

In addition, GlaxoSmithKline submitted that whilst the October 2005 newsletter referred to ropinirole as a treatment for RLS, it was quite clear in stating that ropinirole was not yet licensed in the UK and did not in any way suggest that any one treatment was better or more effective than others ('There are now several drugs that are used for RLS but, as yet, none are licensed for it here …. Some are in more use than others but it does not mean they are any better or more effective …. I know many members are now able to have ropinirole, but it is only licensed in Germany and the USA at present'). Elsewhere the ESG website (sections on 'Remedies') covered information on a plethora of different remedies for RLS from lifestyle advice, herbal and dietary remedies, and alternative medicines to a wide variety of prescription medicines. Thus, the website was well balanced and did not promote or preferentially favour any one treatment for RLS over another.

GlaxoSmithKline submitted that in view of all these facts, this was clearly not an attempt to promote ropinirole in an unlicensed indication, either directly or indirectly. However, the ruling implied that GlaxoSmithKline had deliberately subverted the system to direct health professionals to the website to receive this information. GlaxoSmithKline accepted that had it directed health professionals to a website containing information on ropinirole in RLS, it would have been in breach of the Code, it had not done this and it was not its intent.

GlaxoSmithKline noted that its advertisement had been ruled in breach, not for its content but only for its reference to the ESG website. However, this was made in good faith in the interests of education and information provision. The changes to the website were totally outside GlaxoSmithKline's control and were made at the very end of the advertisement period without any knowledge of, or notification to, it. Indeed, if GlaxoSmithKline was inputting to the ESG it could have ensured that there was no mention of ropinirole on the website which it was unable to do. The ESG was not an agent of GlaxoSmithKline's, and therefore not bound by the Code. GlaxoSmithKline considered that it was unreasonable as part of disease awareness activities to be aware of changes made to such independent sites when its intent from the outset was clearly educational, and circumstances outside its control made information available on the ESG website. Moreover, in its ruling, the Panel had declared that the information on the ESG website was not an advertisement *per se*. Despite this, it had ruled a breach of the Code for promotion outside of the terms of a licence. This showed an inconsistency in the interpretation of the impact of the information on the ESG website and the ruling of a breach of Clause 3.2.

Thus, GlaxoSmithKline submitted that the Panel's ruling was overly strict when it was clear that it was not the intention of the disease awareness advertisement to direct health professionals or patients to ropinirole information in an unlicensed indication. GlaxoSmithKline therefore appealed the Panel's ruling of a breach of Clause 3.2 of the Code.

GlaxoSmithKline reiterated that the disease awareness advertisement was only ever placed in medical publications and therefore not aimed at patients. Health professionals were told about the ESG website, so that they could find additional information, and if they so chose, direct patients to it. As detailed above, this was an important source of independent, balanced and accurate information on RLS, including a range of different treatment options.

GlaxoSmithKline noted that the 'News' section had referred to Walters *et al* (2004); a large, multinational, double-blind, placebo-controlled study, which reported that ropinirole was 'safe and effective for the treatment of RLS'. This statement summarised the findings of this pivotal trial which showed that ropinirole significantly improved RLS symptoms, sleep, quality of life and was well tolerated.

GlaxoSmithKline repeated that the website content was the responsibility of the ESG (with the exception declared above), and it had no input, influence or knowledge of the placement of the reference to Walters *et al*. The paragraph was added on the 30 October 2005 which post-dated the great majority of the period during which the advertisement ran. In addition, the paragraph explicitly stated 'This information is intended for primary care physicians, neurologists, sleep disorder specialists, and other

specialists who care for patients with RLS', and therefore it was clearly not aimed at patients.

For these reasons, GlaxoSmithKline strongly refuted the allegation that it was, in effect, directing patients to a website that contained misleading messages about the safety of ropinirole in an unlicensed indication which might indirectly encourage patients to ask their doctors to prescribe it. The advertisement was never directed at patients but merely advised health professionals of the only support group (the ESG) for RLS patients in the UK. Overall, GlaxoSmithKline submitted that the content of the ESG's website was fair, balanced and broad and did not preferentially favour one treatment over another; and hence, did not encourage patients to ask for a specific medicine. GlaxoSmithKline therefore also appealed the Panel's ruling of a breach of Clause 20.2 of the Code.

COMMENTS FROM THE COMPLAINANT

The complainant considered that the motivation of GlaxoSmithKline with this patient group could be in little doubt. The promotion of RLS went hand in hand with the promotion of ropinirole. This was standard marketing/sales activity seeking to generate new markets and was known as 'disease mongering'. Whether this activity was legitimate remained an ongoing debate.

The complainant accepted that although GlaxoSmithKline made no direct financial support to ESG, as a small patient group the provision of a broadband link, administrative support and stationery represented a large contribution overall. Furthermore, the publicity and profile afforded by GlaxoSmithKline's advertisements represented many thousands of pounds and was clearly beyond the reach any small interest group. This did not fit with GlaxoSmithKline's submission of 'very limited support'.

The complainant alleged that GlaxoSmithKline had used ESG to promote RLS and indirectly ropinirole (unlicensed at the time). The website referred to ropinirole and the complainant alleged that the discussion forums (which were not reviewed) were to refer to ropinirole as the quote from the newsletter highlighted 'I know many members are now able to have ropinirole'. GlaxoSmithKline had a responsibility not to promote ropinirole off-licence irrespective of the independence of ESG, even if the company alleged that it acted 'in good faith'. This argument could and would be used by other companies to defend similar activity in the future.

The complainant submitted that acceptance of the appeal would set a precedent that other companies could exploit using third party websites and the internet to side step regulations on the promotion of medicines. To restore public trust the Code must be vigorously enforced or the perception of Astro-Turfing would continue in regard to involvement with patient groups.

APPEAL BOARD RULING

The Appeal Board noted that the advertisement which appeared in medical journals suggested that '… patients might appreciate being made aware of the Ekbom Support Group, which can be accessed via the internet at [website address given]'. GlaxoSmithKline was thus effectively directing both health professionals and members of the public to the website. Patient groups were not covered by the Code and thus material on their websites was a matter for the relevant patient group. Directing people to such sites, in pharmaceutical company advertising meant that the company became inextricably linked with the content of those sites whether or not they had had any input, control etc. If this were not the case then companies would be able to refer to independent websites as a means of avoiding the restrictions in the Code.

The Appeal Board noted from GlaxoSmithKline that when the advertisement was approved in August 2004, GlaxoSmithKline had checked the ESG website to ensure that directing health professionals to it did not lead to a breach of the Code. GlaxoSmithKline stated that it knew that the newsletter on the website would be updated approximately every six months. The advertisement ran for 15 months – September 2004 until November 2005 – but GlaxoSmithKline did not recheck the website throughout that time. The Appeal Board considered that companies referring to patient group websites in their advertising needed to ensure that whenever they did so the website content was acceptable as far as the Code was concerned.

The Appeal Board noted that the ESG newsletter, October 2005, referred to GlaxoSmithKline's product, ropinirole, which was only licensed for RLS in Germany and the US. Although the product was not so licensed in the UK it was available, and licensed, for use in the treatment of Parkinson's Disease. GlaxoSmithKline's representatives confirmed that patients with RLS were often treated off-label.

The Appeal Board noted that it would have been a breach of the Code to include the information about the use of ropinirole in RLS in the advertisement at issue as this would have constituted promotion of an unlicensed indication. On that basis, the Appeal Board considered that referring health professionals to a website that included a newsletter giving information about an unlicensed indication in effect promoted that unlicensed indication. The Appeal Board thus upheld the Panel's ruling of a breach of Clause 3.2. The appeal on this point was unsuccessful.

The Appeal Board considered that the Panel's ruling of no breach of Clause 20.1, ie that the ESG website did not constitute an advertisement for a prescription only medicine to the public, was not inconsistent with the ruling that the advertisement promoted an unlicensed indication to health professionals.

The Appeal Board considered that health professionals were encouraged to refer patients to the website. The news section of the website referred to an article, published in December 2004, which reported that ropinirole was 'safe and effective for the treatment of RLS'. On that basis the Appeal Board considered that GlaxoSmithKline was, in effect, directing members of the public to a site that contained misleading messages about the safety of ropinirole in an unlicensed indication which might indirectly encourage them to ask their doctors to

prescribe it. The Appeal Board thus upheld the Panel's ruling of a breach of Clause 20.2. The appeal on this point was unsuccessful.

Complaint received **20 February 2006**

Case completed **26 May 2006**

CASES AUTH/1803/2/06 and AUTH/1804/2/06

PROCTER & GAMBLE and SANOFI-AVENTIS v ROCHE and GLAXOSMITHKLINE

Bonviva Once Monthly slide kits

Procter & Gamble and Sanofi-Aventis complained jointly about two Bonviva Once Monthly (ibandronate) slide kits issued by Roche and GlaxoSmithKline. Procter & Gamble and Sanofi-Aventis supplied Actonel (risedronate).

Procter & Gamble and Sanofi-Aventis noted that slide 6 in the slide kit entitled 'Osteoporosis, bisphosphonates and Bonviva (ibandronic acid)' correctly described ibandronate as a bisphosphonate. Slide 11 stated that the National Institute for Health and Clinical Excellence (NICE) recommended bisphosphonates as first-line therapy in the secondary prevention of osteoporotic fragility fractures. Only alendronate, etidronate and risedronate, and not ibandronate, had been evaluated by NICE. By not excluding ibandronate, slide 11 misled the health professional to believe that NICE had recommended ibandronate as well. The NICE recommendation was based on an analysis of the cost effectiveness of medicines. Ibandronate was not licensed, nor had it demonstrated efficacy, in preventing hip fractures, the key cost driver in osteoporosis health economic evaluations. Efficacy of ibandronate in preventing non-vertebral fractures, another costly treatment, had also not been demonstrated. It should therefore not be implied that NICE would group ibandronate with the other bisphosphonates. Indeed during the evaluation of the available evidence the Scottish Medicines Consortium concluded that a grouping of ibandronate with other bisphosphonates in terms of hip and non-vertebral fractures was not appropriate. The omissions made in this slide kit were alleged to be in breach of the Code.

Slide 11 also claimed that bisphosphonates in clinical trials had demonstrated vertebral and non-vertebral fracture reduction efficacy. The slide inferred this was also true for Bonviva, which was not the case, as specifically and unambiguously noted in the Bonviva Once Monthly summary of product characteristics (SPC). These claims were alleged to be in breach of the Code.

The Panel noted that according to the SPC, Bonviva was indicated for the treatment of osteoporosis in postmenopausal women in order to reduce the risk of vertebral fractures. Efficacy on femoral neck fractures had not been established. Bonviva was first authorised in September 2005 ie eight months after the NICE guidance was published.

The NICE Technology Appraisal 87, dated January 2005, was titled 'Bisphosphonates (alendronate, etidronate, risedronate), selective oestrogen receptor modulators (raloxifene) and parathyroid hormone (teriparatide) for the secondary prevention of osteoporotic fragility fractures in postmenopausal women. Page 47 of the document defined certain terms and it was stated that bisphosphonates included alendronate, etidronate and risedronate. In the Panel's view it was thus clear that even when the NICE document referred to 'bisphosphonates' it referred only to those three medicines.

The Panel noted that slide 11 referred to bisphosphonates and that they had '… been recommended by NICE as first-line therapy in the secondary prevention of osteoporotic fragility fractures'. This statement was referenced to the NICE Technology Appraisal 87. Section 1.1 of that document, however, stated: 'Bisphosphonates (alendronate, etidronate and risedronate) are recommended as treatment options for the secondary prevention of osteoporotic fragility fractures [in certain groups of women].'

The Panel considered that in a presentation entitled 'Osteoporosis, bisphosphonates and Bonviva' which cited the NICE guidance it was misleading not to state clearly which bisphosphonates the guidance covered. Bonviva had not been assessed by NICE. The Panel considered that slide 11 implied that ibandronate had been included in the NICE guidance which was not so. Slide 11 was misleading in this regard and not capable of substantiation. Breaches of the Code were ruled.

The Panel noted that slide 11 stated that vertebral and non-vertebral efficacy with bisphosphonates had been demonstrated in clinical trials. The Panel that the statement implied that all bisphosphonates, including Bonviva, had demonstrated *both* vertebral and non-vertebral efficacy; given the licensed indication for Bonviva this was not so. Breaches of the Code were ruled.

Procter & Gamble and Sanofi-Aventis noted that slides 29-43 of the slide kit entitled 'Slides for hospital sales force Bonviva (ibandronic acid) monthly for postmenopausal osteoporosis' presented data from the Monthly Oral iBandronate In LadiEs (MOBILE) study which had compared daily and monthly ibandronate. The main conclusion was that 'Once-monthly ibandronate can provide an effective, well-tolerated and practical alternative to daily and weekly oral

bisphosphonates' (slide 43). This suggested that a comparison to other once weekly bisphosphonates was made which was not the case and was thus grossly misleading. It further suggested that the study demonstrated similar efficacy between all bisphosphonates, which was clearly not the case as there were no head-to-head fracture studies between Bonviva and the other bisphosphonates. On the contrary all the data so far published on ibandronate differed from alendronate and risedronate by having failed to show fracture risk reduction efficacy at both the hip and non-vertebral sites. Roche and GlaxoSmithKline argued that despite this lack of head-to-head evidence the claim was still justified, but they failed to provide any scientific rationale or support. The claim was alleged to be in breach of the Code.

The Panel noted that slide 44, headed 'MOBILE Study: Conclusions', stated that 'Once-monthly ibandronate can provide an effective, well-tolerated and practical alternative to daily and weekly oral bisphosphonates'. The MOBILE study compared once monthly ibandronate with once daily ibandronate not daily or weekly bisphosphonates. It was thus misleading to make a statement comparing once a month ibandronate with daily and weekly bisphosphonates under the heading 'MOBILE Study: conclusions'. The statement was inaccurate in the context of the heading. Breaches of the Code were ruled. The Panel did not consider that the statement *per se* was outside the Bonviva marketing authorization or inconsistent with the SPC and thus in this regard no breach of the Code was ruled.

Procter & Gamble Pharmaceuticals UK Ltd and Sanofi-Aventis, writing as The Alliance for Better Bone Health, complained jointly about two Bonviva Once Monthly slide kits. Slide Kit P117414 was entitled 'Osteoporosis, bisphosphonates and Bonviva (ibandronic acid)' and was used by clinicians, and available upon specific request. The second slide kit, P117413, was entitled 'Slides for hospital sales force Bonviva (ibandronic acid) monthly for postmenopausal osteoporosis'. This slide kit was used by hospital representatives to support formulary submission to Drugs and Therapeutics Committees. Bonviva Once Monthly (ibandronate) was promoted by Roche Products Ltd (Case AUTH/1803/2/06) and GlaxoSmithKline UK Limited (Case AUTH/1804/2/06).

Procter & Gamble and Sanofi-Aventis supplied Actonel (risedronate).

Since Roche and GlaxoSmithKline were intent on persisting with making claims outside their licensed indication, were grouping the bisphosphonates together suggesting a class effect on fracture efficacy (including hip and non-vertebral fracture risk reduction), as raised in Cases AUTH/1779/11/05 and AUTH/1780/11/05, and were claiming interchangeability between bisphosphonates without any supporting data, Procter & Gamble and Sanofi-Aventis requested that the Authority urgently provided a clear ruling so that there were no future breaches of either the letter or spirit of the Code on these matters. The companies urged the Authority to instruct Roche and GlaxoSmithKline to immediately withdraw this material and issue a corrective statement amending these erroneous claims.

1 NICE guidelines

COMPLAINT

Procter & Gamble and Sanofi-Aventis noted that slide 6 in slide kit P117414 correctly described ibandronate as a bisphosphonate. Slide 11 stated that the National Institute for Health and Clinical Excellence (NICE) recommended bisphosphonates as first-line therapy in the secondary prevention of osteoporotic fragility fractures. Only alendronate, etidronate and risedronate, and not ibandronate, had been evaluated by NICE. By not excluding ibandronate, slide 11 misled the health professional to believe that NICE had recommended ibandronate as well. The NICE recommendation was based on an analysis of the cost effectiveness of medicines. Ibandronate was not licensed, nor had it demonstrated efficacy, in preventing hip fractures, the key cost driver in osteoporosis health economic evaluations. Efficacy of ibandronate in preventing non-vertebral fractures, another costly treatment, had also not been demonstrated. It should therefore not be implied that NICE would group ibandronate with the other bisphosphonates. Indeed during the evaluation of the available evidence the Scottish Medicines Consortium concluded that a grouping of ibandronate with other bisphosphonates in terms of hip and non-vertebral fractures was not appropriate. The omissions made in this slide kit were alleged to be in breach of Clauses 7.2 and 7.4 of the Code.

Slide 11 also claimed that bisphosphonates in clinical trials had demonstrated vertebral and non-vertebral fracture reduction efficacy. The slide inferred this was also true for Bonviva, which was not the case, as specifically and unambiguously noted in the Bonviva Once Monthly summary of product characteristics (SPC). These claims were alleged to be in breach of Clauses 7.2 and 7.4 of the Code.

RESPONSE

Roche and GlaxoSmithKline submitted that the data presented in the slides outlined current guidelines and issues in the management of osteoporosis. No attempt was made to imply that NICE had grouped ibandronate with other bisphosphonates. The clinical evidence base supporting the licensing of ibandronate justified the positioning of Bonviva as an alternative to current bisphosphonates.

Roche and GlaxoSmithKline stated that the three points raised by Procter & Gamble and Sanofi-Aventis were:

a) that the slide sets purported to 'claim that NICE recommended bisphosphonates as first-line therapy in the secondary prevention of osteoporotic fragility fractures';

b) the same slide sets implied that NICE recommended the use of ibandronate; and

c) the slide sets overstated the anti-fracture efficacy of ibandronate at non-vertebral sites.

The companies submitted that the slides only represented accurate and widely accepted thinking of the role of bisphosphonates in osteoporosis care and all allusions to ibandronate's clinical profile were based upon firm and published clinical evidence.

Roche and GlaxoSmithKline were certain that Procter & Gamble and Sanofi-Aventis knew that the NICE, Health Technology Appraisal published in January 2005, proposed that bisphosphonates were used as first-line therapy in the secondary prevention of osteoporotic fragility fractures. Therefore, reference to this guidance constituted a statement of fact.

Roche and GlaxoSmithKline failed to understand the contention that the positioning of slides 6 and 11 could mislead clinicians to believe that NICE recommended ibandronate for the prevention of secondary osteoporotic fragility fractures. Slides 6 and 11 were part of a presentation which flowed through the following sequence: (i) a discussion of osteoporosis: its definition, clinical sequelae, therapeutic options and issues in management (slides 2-10), (ii) a discussion of bisphosphonates: their mechanism of action and place in therapy (slides 11-13) and (iii) a discussion of the clinical evidence base of ibandronate. Within the discussion of osteoporosis, slide 6 outlined all available pharmacological interventions licensed for osteoporosis. Within the bisphosphonate class, all oral options (etidronate, alendronate, risedronate and ibandronate) were listed. In the next section which specifically discussed bisphosphonate therapy, a reference to the NICE guidelines recommending bisphosphonates as first-line agents in the secondary prevention of osteoporotic fractures was described as a single bullet point on slide 11.

Furthermore, these slides represented true and accurate information. Additionally, slides 6 and 11 were separated by a discussion regarding issues in osteoporosis management. With the exception of the inclusion of ibandronate (a single word) amongst the list of currently licensed bisphosphonates, no further mention was made of Bonviva during this discussion of osteoporosis and bisphosphonates (though, subsequent discussions of the key ibandronate clinical studies followed in slides 14-46). Likewise, there was a single bullet point which referred to the NICE guidelines on a slide which described characteristics of bisphosphonates. Roche and GlaxoSmithKline thus failed to comprehend why Procter & Gamble and Sanofi-Aventis believed that there was an attempt to suggest that NICE had reviewed and recommended ibandronate for the secondary prevention of osteoporotic fractures. The respondents noted that NICE, not having reviewed ibandronate, had not indicated any necessity to do so.

Roche and GlaxoSmithKline did not understand Procter & Gamble and Sanofi-Aventis' allegation regarding overstating of the anti-fracture efficacy of ibandronate at vertebral and non-vertebral sites. The statement referring to the vertebral and non-vertebral fracture efficacy was contained within a slide describing the characteristics of bisphosphonates. No allusion to ibandronate was made at this point. Whilst these slides referred to the vertebral fracture efficacy of ibandronate, this was consistent with the SPC for Bonviva. Furthermore, no non-vertebral fracture efficacy of this compound was discussed throughout this slide series.

In summary, the suggestion that Roche and GlaxoSmithKline wilfully intended to mislead clinicians regarding ibandronate's status with NICE was unfounded. At no point, did these slides allude to ibandronate in relation to NICE's recommendations. Likewise, in rebuttal to the suggestion by Procter & Gamble and Sanofi-Aventis that Roche and GlaxoSmithKline attempted to exaggerate the non-vertebral or hip fracture efficacy data for ibandronate, the discussion of ibandronate's evidence base did not cite this data. Any mention of ibandronate was solely as a bisphosphonate, and chronologically separated from any discussion of NICE's recommendations. The inclusion of ibandronate within this slide series was justified on the basis of its marketing authorization.

PANEL RULING

The Panel noted that the indication section of the Bonviva SPC stated that it was for the treatment of osteoporosis in postmenopausal women in order to reduce the risk of vertebral fractures. Efficacy on femoral neck fractures had not been established. Bonviva was first authorized in September 2005 ie eight months after the NICE guidance was published.

The NICE Technology Appraisal 87, dated January 2005, was titled 'Bisphosphonates (alendronate, etidronate, risedronate), selective oestrogen receptor modulators (raloxifene) and parathyroid hormone (teriparatide) for the secondary prevention of osteoporotic fragility fractures in postmenopausal women. Page 47 of the document defined certain terms and it was stated that bisphosphonates included alendronate, etidronate and risedronate. In the Panel's view it was thus clear that even when the NICE document referred to 'bisphosphonates' it referred only to those three medicines.

The Panel noted that slide 11 referred to bisphosphonates and that they had '… been recommended by NICE as first-line therapy in the secondary prevention of osteoporotic fragility fractures'. This statement was referenced to the NICE Technology Appraisal 87. Section 1.1 of that document, however, stated:

'Bisphosphonates (alendronate, etidronate and risedronate) are recommended as treatment options for the secondary prevention of osteoporotic fragility fractures:

- in women aged 75 years and older, without the need for prior dual energy X-ray absorptiometry (DEXA) scanning
- in women aged between 65 and 74 years if the presence of osteoporosis is confirmed by DEXA scanning, and
- in postmenopausal women younger than 65 years of age, if they have a very low bone mineral density (BMD), that is with a T-score of approximately –3 SD or below*, established by a DEXA scan), or if they have confirmed

osteoporosis plus one, or more, additional age-independent risk factor: [these were listed].'

The Panel considered that in a presentation entitled 'Osteoporosis, bisphosphonates and Bonviva' which cited the NICE guidance it was misleading not to state clearly which bisphosphonates the guidance covered. Bonviva had not been assessed by NICE. The Panel considered that slide 11 implied that ibandronate had been included in the NICE guidance which was not so. Slide 11 was misleading in this regard and not capable of substantiation. Breaches of Clauses 7.2 and 7.4 of the Code were ruled.

The Panel noted that slide 11 stated that vertebral and non-vertebral efficacy with bisphosphonates had been demonstrated in clinical trials. The Panel considered this was misleading as it would be assumed that the statement implied that all bisphosphonates, including Bonviva, had demonstrated both vertebral and non-vertebral efficacy; given the licensed indication for Bonviva this was not so. Breaches of Clauses 7.2 and 7.4 of the Code were ruled.

2 MOBILE Study

COMPLAINT

Procter & Gamble and Sanofi-Aventis noted that slides 29-43 of slide kit P117414 presented data from the Monthly Oral iBandronate In LadiEs (MOBILE) study. The MOBILE study compared daily and monthly ibandronate. The primary endpoint of the study was bone mineral density (BMD) change at the lumbar spine; secondary endpoints only included BMD changes and changes in bone turnover markers. The main conclusion was that 'Once-monthly ibandronate can provide an effective, well-tolerated and practical alternative to daily and weekly oral bisphosphonates' (slide 43). This suggested that a comparison to other once weekly bisphosphonates was made which was not the case and was thus grossly misleading. It further suggested that the study demonstrated similar efficacy between all bisphosphonates, which was clearly not the case as there were no head-to-head fracture studies between Bonviva and the other bisphosphonates. On the contrary all the data so far published on ibandronate differed from alendronate and risedronate by having failed to show fracture risk reduction efficacy at both the hip and non-vertebral sites. Roche and GlaxoSmithKline argued that despite this lack of head-to-head evidence the claim was still justified, but they failed to provide any scientific rationale or support demonstrating an unwillingness to resolve this issue. The claim was alleged to be in breach of Clauses 3.2, 7.2 and 7.4 of the Code.

Similar claims, relating to the MOBILE study, had also come to the companies' attention, slide kit (P117413) (slide 21). Procter & Gamble and Sanofi-Aventis were very concerned about the way in which Roche and GlaxoSmithKline miscommunicated their licensed indication and associated data. The above concerns had been raised with Roche and GlaxoSmithKline as required by the Code, but they insisted on continuing with these misleading communications without compromise, despite the potential patient safety concerns.

RESPONSE

With regard to the claim 'once-monthly ibandronate may provide an effective, well-tolerated and practical alternative to daily and weekly oral bisphosphonates', Roche and GlaxoSmithKline acknowledged that there were no published head-to-head clinical studies directly comparing ibandronate with other bisphosphonates. The companies submitted that ibandronate was a valid alternative to current oral bisphosphonates. This was amply supported by the clinical evidence and the marketing authorization. The efficacy of ibandronate had been established by seminal registration trials which had met the standards imposed by the regulatory bodies. Ibandronate administered daily effectively reduced bone turnover, increased lumbar and hip BMD and reduced fracture risk. Monthly ibandronate was shown to be superior to daily ibandronate in increasing lumbar and hip BMD. On this basis, ibandronate had been granted a licence. Thus, Roche and GlaxoSmithKline were justified in offering ibandronate as an alternative to other oral bisphosphonates.

Procter & Gamble and Sanofi-Aventis also contended that a statement proffering ibandronate as an alternative to currently available oral bisphosphonates might only be made after demonstration of comparable anti-fracture efficacy. Whilst demonstration of fracture risk reduction within a head-to-head study would indeed be ideal, this required the recruitment of substantial patients numbers which was prohibitive. For this reason, surrogate markets were accepted for fracture endpoints; for osteoporosis these included bone markers and BMD. The evidence base for ibandronate strongly suggested that Bonviva induced suppression of bone turnover and gains in lumbar and hip BMD as would be expected of a bisphosphonate. For these reasons, Roche and GlaxoSmithKline were justified in suggesting that ibandronate represented an alternative to other available oral bisphosphonates.

PANEL RULING

The Panel noted that slide 44, headed 'MOBILE Study: Conclusions', stated that 'Once-monthly ibandronate can provide an effective, well-tolerated and practical alternative to daily and weekly oral bisphosphonates'. The MOBILE study compared once monthly ibandronate with once daily ibandronate not daily or weekly bisphosphonates. It was thus misleading to make a statement comparing once a month ibandronate with daily and weekly bisphosphonates under the heading 'MOBILE Study: conclusions'. The statement was inaccurate in the context of the heading. Breaches of Clauses 7.2 and 7.4 of the Code were ruled.

The Panel did not consider that the statement *per se* was outside the Bonviva marketing authorization or inconsistent with the SPC and thus in this regard no breach of Clause 3.2 of the Code was ruled.

* * * * *

During its consideration of this case, the Panel noted Procter & Gamble and Sanofi-Aventis' request that Roche and GlaxoSmithKline be required to issue a corrective statement. This was a sanction available to the Appeal Board but not to the Panel.

Complaint received	**23 February 2006**
Case completed	**21 April 2006**

CASES AUTH/1806/3/06 and AUTH/1809/3/06 *NO BREACH OF THE CODE*

THE SUNDAY TIMES/DIRECTOR AND A GENERAL PRACTITIONER v GLAXOSMITHKLINE

Sponsored nurses

An article entitled 'Nurses earn bonuses for use of latest drugs', which appeared in The Sunday Times, criticized the activities of, *inter alia*, GlaxoSmithKline. In accordance with established practice the matter was taken up by the Director as a complaint under the Code (Case AUTH/1806/3/06).

The article stated that GlaxoSmithKline had paid nurses through an agency to conduct free audits in GP surgeries to identify patients with conditions such as asthma or diabetes who might benefit from a new medicine. The nurses were paid a salary and usually a bonus; nurses were said to be rewarded for the number of surgeries they visited or the number of patients or records they saw. The article also stated that the nurses were described in promotional literature as being able to 'influence' new prescriptions for the benefit of their pharmaceutical companies. The nurses were routinely backed up by sales teams.

A general practitioner subsequently complained about the involvement of GlaxoSmithKline in providing nursing advisors as detailed in The Sunday Times (Case AUTH/1809/3/06). The complainant was greatly concerned about the nurse advisors because they had a conflict of interest to promote a particular product. The Sunday Times had assured the complainant that the story was correct. The GP alleged that it was a clear admission that the nurse advisors were not independent but were involved in the marketing of medicines. A breach of the Code was alleged.

The Panel noted that the documentation for the schemes offered by GlaxoSmithKline ensured that the practice agreed to the arrangements including identifying the search criteria, the inclusion and exclusion criteria to define patients appropriate for review and the treatment options from the full range of therapeutic options. Further each change of treatment had to be authorized and implemented by a GP and the reasons for changes documented.

The Panel considered that the roles of the GlaxoSmithKline promotional staff and non promotional staff appeared to be clearly separated. Where the representatives both promoted medicines and provided detailed information about the service it appeared that this was clearly separated in that the representatives could not carry out both functions at the same visit. This point was covered by the briefing material.

The Panel noted that the remuneration of the nurse advisors was linked to the number of patients seen, the number of clinics run and customer satisfaction; it was not linked to the prescription, supply, administration, recommendation or purchase of any medicine.

The Panel considered that some of the arrangements might be of concern, much would depend on the practice which had control of every step of the process. Provided the nurse advisors complied with their professional codes, and there was no evidence that they had not, it did not appear to the Panel that the arrangements were in general necessarily unacceptable. There was no complaint about any specific arrangements, the complaints concerned the generality of the review services.

Overall the Panel considered that the services offered by GlaxoSmithKline were not unacceptable. The services would enhance patient care. The provision of the services was not linked to the prescription of any specific medicine. The decision of what to prescribe lay with the patient's doctor. The Panel did not consider that the services were an inducement to prescribe, supply, administer, recommend or buy any medicine. No breaches of the Code were ruled including no breach Clause 2.

An article entitled 'Nurses earn bonuses for use of latest drugs', which appeared in The Sunday Times, criticized the activities of, *inter alia*, GlaxoSmithKline UK Limited. In accordance with established practice the matter was taken up by the Director as a complaint under the Code (Case AUTH/1806/3/06).

A general practitioner subsequently complained about the involvement of GlaxoSmithKline in providing nursing advisors as detailed in The Sunday Times (Case AUTH/1809/3/06).

COMPLAINT

The article stated that GlaxoSmithKline had paid nurses through an agency to conduct free audits in GP surgeries to identify patients with conditions such as asthma or diabetes who might benefit from a new medicine. The nurses were paid a salary and usually a bonus; nurses were said to be rewarded for the number of surgeries they visited or the number of patients or records they saw.

The article also stated that the nurses were described in promotional literature as being able to 'influence' new prescriptions for the benefit of their pharmaceutical companies. The nurses were routinely backed up by sales teams.

A recruitment consultant had told an undercover reporter that the job of the nurses was to identify patients with a specific condition '[it] opens the doors to a medical representative. They come in and close the business'.

The complainant (Case AUTH/1809/3/06) was greatly concerned by the involvement of these nurse advisors because they had a conflict of interest to promote a particular company product. The complainant stated that he had contacted The Sunday Times which had transcripts of conversations between a reporter and an agency representative. The Sunday Times had assured the GP that the story was correct. The GP alleged that it was a clear admission that the nurse advisors were not independent but were involved in the marketing of medicines. The complainant alleged that this was in breach of the Code. The complainant requested that the Panel considered halting any current nurse advisor activity until this case had completed.

GlaxoSmithKline was asked to respond in relation to Clauses 2, 9.1 and 18.1 of the Code.

RESPONSE

GlaxoSmithKline noted that The Sunday Times article included the following relevant information: that nurses were provided free to GP surgeries and were given access to patients' medical records to check whether they were on the most up-to-date medicines; that, although barred from promoting the pharmaceutical company's products, 15% of their pay was linked to the number of patients or records they saw; that the nurses were routinely backed up by sales teams; that nurses were described in promotional literature as being able to 'influence' new prescriptions for the benefit of the pharmaceutical companies; that nurse advisors were paid a salary and usually a bonus, with nurses being rewarded for the number of surgeries that they visited and the nurse agency being quoted as paying performance bonuses; that an 'undercover reporter' had been told by a recruitment agency that the nurse's role was to identify patients with a specific condition and this 'opens the doors to a medical representative who come in and close the business'.

GlaxoSmithKline noted that the article provided no evidence to support the headline 'Nurses earn bonuses for use of the latest drugs'. All of the information in the article related to nurses being incentivised according to the number of surgeries they attended or the number of patients or records they reviewed, and not the number of prescriptions dispensed for any particular medicine.

GlaxoSmithKline stated that it engaged nurses in patient review services across the following therapy areas to benefit health practitioners, patients and the NHS: asthma; chronic obstructive pulmonary disease (COPD); Diabetes; Osteoporosis; Parkinson's Disease and travel health.

GlaxoSmithKline was extremely confident that the patient review services that were carried out across all these areas complied with the Code and copies of the relevant documentation for all the review services were provided. GlaxoSmithKline also provided details of the objectives and operation of each service.

GlaxoSmithKline submitted that its asthma patient review service was an appropriate example of the principles applied by it regarding the use of nurses in these programs and the compliance of these programs with the Code.

GlaxoSmithKline submitted that in any instance where particular therapeutic options might be discussed, information was presented on all other medicines within the class, and was not limited to medicines supplied by GlaxoSmithKline.

GlaxoSmithKline submitted that there were no individual key performance indicators for the travel medicine service that linked bonus levels to promotion, prescription or recommendation of any medicine.

GlaxoSmithKline noted that Clause 18.4 of the Code allowed for the provision of medical and educational goods and services which enhanced patient care, or benefited the NHS and maintained patient care, to be provided as long as such goods and services did not bear the name of any medicine and did not act as an inducement to prescribe, supply, administer, recommend, buy or sell any medicine.

GlaxoSmithKline contended that its review and audit services complied with Clause 18.4 of the Code since it was clear from the protocols and agreements on which these services were strictly based that the services enhanced patient care in terms of identifying and reviewing appropriate patients as determined by pre-defined criteria and strict protocols agreed with clinicians prior to implementation of the services, and these services were not an inducement to prescribe, supply, administer, recommend, buy or sell any medicine. The service agreements for all therapy areas set out which treatment recommendations clinicians would endorse according to the patient's current clinical regimen from a complete list of appropriate therapeutic options for those patients that included, but was not exclusive to, medicines supplied by GlaxoSmithKline. The services were not therefore an inducement to prescribe any particular medicine, or indeed solely GlaxoSmithKline medicines. In addition, the review service for Parkinson's Disease did not involve nurse advisors in presenting recommendations for, or alterations to, therapeutic, management of patients.

GlaxoSmithKline noted that The Sunday Times article stated: 'nurses are provided free to GP surgeries and are given access to patients' medical records to check whether they are on the most up-to-date drugs' and 'are earning bonuses of £3,500 by identifying NHS patients who can be put on costly new drug regimes'. GlaxoSmithKline submitted that whilst nurses were provided free to GP surgeries and given access to patients' medical records this was not in breach of Clause 18.4 since pharmaceutical companies were allowed to provide services that would enhance patient care or benefit the NHS, and GlaxoSmithKline's review and audit services would clearly deliver these benefits. In addition, whilst the nurses were given access to patients' medical records this was strictly controlled by health professionals

and, by seeking their signed consent to the search and the search criteria, allowed access to only those records of patients identified as being appropriate for review as agreed between the health professional and the nurse advisor. Furthermore, the nurse advisors were independent, and acted as a third party to ensure that no GlaxoSmithKline employees could access individual patient records.

GlaxoSmithKline submitted that it was clear from the details provided of its review and audit services that nurses were not given free access to patient records to 'check whether they are on the latest drugs'. The audit and review service protocols as agreed with the practice/clinic clearly set out the criteria for selection of patients that would be identified and reviewed through the services, and detailed the information that would be collected during the clinic reviews with the nurse advisor, which included personal history, medical history, clinical status and compliance in addition to current therapy. The nurse advisor, as a health professional, bound by a professional code of conduct, would only make treatment recommendations when the patient's current therapy was not consistent with their clinical status as required by the health professionals in the practice/clinic for that patient and as defined in the service agreements.

GlaxoSmithKline submitted that it was clear from the principles of remuneration of both individuals and the companies undertaking the review and audit services on behalf of GlaxoSmithKline that no scheme was in place to incentivise individuals for identifying patients that were suitable for new medicines. Indeed, the protocol in place as part of the review and audit services did not allow for the specific identification of patients that were suitable for new medicines, rather they identified patients that suffered from a particular condition as defined by criteria agreed with the health professional in the practice/clinic who could potentially benefit from a detailed review of their condition. During the review a number of factors were considered such as diagnosis, clinical condition, current therapy, compliance and side effects and, as a result of the review, a number of interventions might be considered, such as advice and education, as well as treatment changes. However, these changes were only recommended in accordance with the pre-defined protocols that had already been agreed with the practice/clinic.

With regard to The Sunday Times article, 'although they are barred from promoting their drugs firm's products, 15% of their pay is linked to the number of patients or records they see', 'nurse advisors are paid a salary of about £25,000 and usually a bonus of 10% to 15%', 'they [nurses] are rewarded for the number of surgeries that they visit' and 'it [agency] pays performance bonuses of up to £3,500', GlaxoSmithKline submitted that the nurse advisors involved in review and audit services were strictly prohibited from promotional activities and were subject to the Nursing & Midwifery Council (NMC) Code of Professional Conduct: standards for conduct, performance, and ethics as stated in the appropriate service authorisation agreements for each service. It was not a breach of Clause 18.4 of the Code for these nurses to be incentivised according to the number of reviews they completed or the number of surgeries that they visited, since this did not constitute an inducement to prescribe, supply, administer, recommend, buy or sell any medicine and furthermore benefited both the NHS and the practices concerned for the review and audit services to be carried out as quickly and efficiently as possible.

GlaxoSmithKline submitted that the contracts it had in place for remuneration of nurse advisors under third party arrangements took account of a number of factors which were important in delivering these review and audit services, and in measuring the overall contribution of the review service to meeting the objectives of benefiting patients, practices and the NHS. It was important to note, however, that the actual numbers of patients identified for review and the treatment changes that were implemented as a result of services were driven solely by the criteria laid out in pre-specified agreements with practices and clinicians, and not by the activity levels of a nurse in an individual practice or clinic.

With regard to The Sunday Times article that 'nurses are routinely backed up by sales teams' GlaxoSmithKline submitted that it was difficult to understand exactly what was meant by this as it had sales representatives as well as review services, but actually what was meant by 'backed up' was unclear. However, the review and audit services did not breach Clause 18.4 of the Code since non-promotional activities were strictly separated from promotional activities. Although Clause 18.1 of the Code allowed for promotional representatives to introduce a review service, wherever possible this activity was separated further by using a strictly non-promotional representative team for this purpose. Where this had not been possible, activities of the promotional representatives were in accordance with the Code through a clear separation of promotional and non-promotional activities. Consequently, the review and audit services were either introduced by a non-promotional representative or a promotional representative during a strictly non-promotional call, and when agreement was received to proceed with the service the contact was passed to the non-promotional nurse advisor. In addition, GlaxoSmithKline had given recent guidance to all representatives and review service staff that during the period when the nurse advisor was undertaking a review service in a practice and for a period of two days either side of the review service taking place all promotional activity by the sales representatives was prohibited.

With regard to The Sunday Times article that 'nurses are described in promotional literature as being able to "influence" new prescriptions of their drug companies', GlaxoSmithKline submitted that without sight of the actual documents referred to it was difficult to know exactly what was being referred to. However, the review and audit services did not breach Clause 18.4 of the Code since nurse advisors were fully briefed on, and contracted to abide by, the strictly non-promotional nature of their roles and act according to the NMC Code of Professional Conduct.

A number of materials had been designed for the nurse advisors, none of which stated that there was an expectation for nurse advisors to influence new prescriptions for their medicines. For example the materials for non-promotional representatives introducing the asthma and COPD review services, stated that:

'– the [agency] Nurse Advisors are "employed and managed by [the agency] and are completely independent of any pharmaceutical organisation; their independence is assured through the requirement to fulfil, at all times, the code of professional conduct as set out by the Nursing and Midwifery Council. This code governs their professional registration and states clearly that they must not use their registration to act in a promotional capacity".

– this [patient review service] is a non-promotional service sponsored by Allen & Hanburys as a service to medicine.'

With regard to The Sunday Times article that the nurse 'identifies patients with a specific condition'… '[it] opens the doors to a medical representative. They come in and close the business', GlaxoSmithKline noted that these comments had been attributed to a recruitment consultant acting on behalf of the agency to recruit nurses to review services run by pharmaceutical companies. GlaxoSmithKline submitted that it had clear protocols in place for the conduct of the review and audit services which predefined the actions that would occur as a result of the individual patient reviews. The non-promotional nature of the review services was clearly separated from the promotional activity, with the prohibition of representative activity before, during and after the review service such that once patients with a specific condition had been identified all necessary actions, including treatment changes, were completed according to pre-defined protocols in agreement with the practice prior to any further representative activity. Accordingly it was not feasible that a nurse advisor could identify a patient such that any treatment change would be influenced by representative activity prior to the treatment change being introduced.

However, whilst both GlaxoSmithKline and the agency were very familiar with the details of the review services in place to enhance patient care and deliver benefits to the NHS it was possible that agents of its third parties such as recruitment consultants were not. As a result GlaxoSmithKline had requested that its third party agents reviewed their own arrangements for briefing their third party agents as to the details of, and the constraints of, the GlaxoSmithKline review services.

Consequently GlaxoSmithKline did not consider that its review and audit services were in breach of Clause 18.4 since they were very strictly set up to enhance patient care in line with the general requirements of the NHS and the specific requirements of individual practices or clinics and these services were not an inducement to prescribe, supply, administer, recommend, buy or sell any particular medicine. Furthermore, none of the comment in The Sunday Times article was supported by protocols and contracts set with third party agents for the operation of these review and audit services.

GlaxoSmithKline noted that Clause 9.1 of the Code stated that high standards must be maintained at all times. GlaxoSmithKline submitted that it had endeavoured to set up beneficial services to patients and the NHS which took account of all aspects of the Code. The provision of review and audit services was based on informed consent to the service from practices or clinics and the establishment of a number of detailed agreements as to appropriate activities and actions for nurse advisors in accordance with health professional requirements and following detailed protocols and contracts. In addition, a practice satisfaction questionnaire had been incorporated as part of the review services to collate feedback from the NHS on their views of the review services. Consequently GlaxoSmithKline considered that high standards had been maintained at all times and therefore that there was no breach of Clause 9.1.

GlaxoSmithKline noted that Clause 2 of the Code stated that activities or materials associated with the promotion must never be such as to bring discredit upon, or reduce confidence in, the pharmaceutical industry. GlaxoSmithKline considered that the highest standards had been maintained across all its review and audit services programs and that all activities and materials associated with the services were fully compliant with all aspects of the Code. Consequently GlaxoSmithKline submitted that there was no breach of Clause 2.

Copies of relevant briefing material for representatives regarding service provision were provided.

PANEL RULING

The Panel noted that these cases were considered in relation to the 2003 Code using the 2006 Constitution and Procedure.

The Panel noted that the documentation for the schemes offered by GlaxoSmithKline ensured that the practice agreed to the arrangements including identifying the search criteria, the inclusion and exclusion criteria to define patients appropriate for review and the treatment options from the full range of therapeutic options. Further each change of treatment had to be authorized and implemented by a GP and the reasons for changes documented.

The Panel considered that the roles of the GlaxoSmithKline promotional staff and non promotional staff appeared to be clearly separated. Where the representatives both promoted medicines and provided detailed information about the service it appeared that this was clearly separated in that the representatives could not carry out both functions at the same visit. This point was covered by the briefing material.

The Panel noted that the remuneration of the nurse advisors was linked to the number of patients seen, the number of clinics run and customer satisfaction; it was not linked to the prescription, supply, administration, recommendation or purchase of any medicine.

The asthma service was designed to enhance each practice's management of patients whose asthma was uncontrolled. There were three inclusion criteria, two of which referred to patients who were uncontrolled. The third referred to patients who were currently prescribed an inhaled corticosteroid and a long-acting beta-2 agonist in separate inhalers but did not state that such patients had to be uncontrolled. The exclusion criteria included patients with well controlled asthma. It was not clear whether a patient on two separate inhalers who was well controlled would be included in the audit. This should be clarified particularly as the section for the GP to sign to authorize the search did not include in the list of exclusion criteria 'patients with well controlled asthma'. This inconsistency in the documentation should be corrected. The Panel did not consider that the inconsistency meant that the material was in breach of the Code. There was an inhaler which combined a corticosteroid and a long-acting beta-2 agonist other than that produced by GlaxoSmithKline.

The Panel was curious as to why the osteoporosis service outlined details of 'Osteoporosis the disease' including the cost of fracture etc and advocated the use of effective treatments and lifestyle changes. None of the documentation for the other services included such a section. One of the objectives of the osteoporosis service was to improve practice knowledge of osteoporosis; the service reviewed patients currently on or previously prescribed treatment. The aim was to optimise the management of osteoporosis. The patient review protocol set out a list of actions for the nurse advisor to discuss with the patient. This included a discussion of treatment options. This was of concern given that the inclusion criteria were for patients currently prescribed medication for osteoporosis. There could be patients attending patient review who adhered to treatment and had no problems with side effects. Was it appropriate to discuss treatment options with such patients particularly given that Roche and GlaxoSmithKline had just introduced a once monthly treatment? The point would be covered by the treatment management plan agreed with the practice which should set out first line and second line interventions for lapsed patients (those previously prescribed treatment for osteoporosis), patients on repeat medication which appeared to be non adherent and those on repeat medication that appeared adherent. Patient preference was given as a reason for the therapy recommended as per the agreed treatment management plan.

The Representative Briefing Document for the osteoporosis service (dated November 2005) included an example of how the medical representative could initially introduce the service after a promotional call. The example referred to the health professional seeing the benefit offered by Bonviva and then asking whether the practice had an osteoporosis clinic. If the health professional said that there was not a clinic the representative went on to describe the unconditional nurse run service to medicine, to recall and review patients to help provide optimal care. The representative would offer for a colleague to discuss it further if wanted. The Panel had some concerns about this but did not consider this meant that the introduction of the service was an inducement to prescribe, supply, administer, recommend or buy Bonviva. There was no implication that the health professional had to agree to use Bonviva before the service could be offered.

The diabetes service identified patients with diabetes, diabetes mellitus, type 2 diabetes, or non insulin dependent diabetes mellitus and stated that patients with an HbA_{1c} above a certain figure (determined by the practice) would be deemed as requiring additional control and would be reviewed by the practice.

The Parkinson's Disease service aimed to develop a Parkinson's Disease centre level clinical audit and review service by providing the resource to establish a clinical audit tool and process for each centre. All patients diagnosed with Parkinson's Disease would have their notes reviewed unless otherwise requested by the consultant. Patients requiring therapy would be flagged on the audit. These patients being all those who had not been reviewed within the last 12 months and all patients who required monitoring and medication review due to functionally limiting side effects. Patients were referred to the Parkinson's Disease nurse specialist at the centre and not the agency nurse advisor.

The main focus for the travel health service was to facilitate best practice and provide travel health advice and education to support health professionals in achieving the travel vaccination goals of the World Health Organisation. The service included the following components: patient search, vaccination clinic, education and materials provision. The objectives were to work with both GPs and practice nurses through education and audit to improve patient health status, patient and practice knowledge of travel related diseases and vaccination programmes and to provide practices with a comprehensive audit and review process. The Panel was unsure whether all the objectives would be met bearing in mind the overview and patient search related to booster Hepatitis A vaccination.

The objectives in the travel health service briefing material were given as 'Generating patient Hepatitis A booster vaccination opportunities', 'Proactively promoting good malaria management in line with recognised guidelines' and 'Developing practice nurse capability knowledge and confidence within the travel health arena'. The activity guidelines were 50% booster recall and 50% education. Travel health nurses would administer the booster vaccination which was supplied by the practice.

The Panel considered that some of the arrangements might be of concern as highlighted above. Much would depend on the practice which had control of every step of the process. Provided the nurse advisors complied with their professional codes, and there was no evidence that they had not, it did not appear to the Panel that the arrangements were in general necessarily unacceptable. There was no complaint about any specific arrangements, the complaints concerned the generality of the review services.

Overall the Panel considered that the services offered were not unacceptable; they would enhance patient

care. The provision of the services was not linked to the prescription of any specific medicine. The decision of what to prescribe lay with the patient's doctor. The Panel did not consider that the services were an inducement to prescribe, supply, administer, recommend or buy any medicine. No breach of Clause 18.1 of the 2003 Code was ruled. The Panel also ruled no breach of Clauses 9.1 and 2 of the 2003 Code.

Case AUTH/1806/3/06

Proceedings Commenced 10 March 2006

Case completed 21 July 2006

Case AUTH/1809/3/06

Complaint received 13 March 2006

Case completed 21 July 2006

CASES AUTH/1808/3/06 and AUTH/1811/3/06 *NO BREACH OF THE CODE*

THE SUNDAY TIMES/DIRECTOR AND A GENERAL PRACTITIONER v WYETH

Sponsored nurses

An article entitled 'Nurses earn bonuses for use of latest drugs', which appeared in The Sunday Times, criticized the activities of, *inter alia*, Wyeth. In accordance with established practice the matter was taken up by the Director as a complaint under the Code (Case AUTH/1808/3/06).

The article stated that Wyeth had paid nurses through an agency to conduct free audits in GP surgeries to identify patients with conditions such as asthma or diabetes who might benefit from a new medicine. The nurses were paid a salary and usually a bonus which was linked to the number of patients or records they saw. The article also stated that the nurses were described in promotional literature as being able to 'influence' new prescriptions for the benefit of their pharmaceutical companies. The nurses were routinely backed up by sales teams.

A general practitioner subsequently complained about the involvement of Wyeth in providing nursing advisors as detailed in The Sunday Times (Case AUTH/1811/3/06). The complainant was greatly concerned about the nurse advisors because they had a conflict of interest to promote a particular product. The Sunday Times had assured the complainant that the story was correct. The GP alleged that it was a clear admission that these nurse advisors were not independent but were involved in the marketing of medicines. A breach of the Code was alleged.

Wyeth stated that it currently offered one audit service in primary care, the GastroCare Service.

The Panel noted that the GastroCare service provided a review of patients' medication in line with the prescribing decisions of the GP. Representatives' briefing material stated that the service and the promotion of Wyeth's products must not be linked in any way. In addition the service had to be freely offered ie to all customers. Representatives could not restrict the offering or steer customers to a specific choice. The GPs must make the decision having been given full details of all options available. The detail flow for Zoton FasTab did not refer to the GastroCare service. At least 10 working days had to elapse either before or after a call to promote or discuss Wyeth's products and a call to discuss the GastroCare Service. The Panel did not consider that the service was an inducement to prescribe, supply, administer, recommend or buy any medicine. No breaches of the Code were ruled including no breach of Clause 2.

An article entitled 'Nurses earn bonuses for use of latest drugs', which appeared in The Sunday Times, criticized the activities of, *inter alia*, Wyeth Pharmaceuticals Ltd. In accordance with established practice the matter was taken up by the Director as a complaint under the Code (Case AUTH/1808/3/06).

A general practitioner in Glasgow, subsequently complained about the involvement of Wyeth in providing nursing advisors as detailed in The Sunday Times (Case AUTH/1811/3/06).

COMPLAINT

The article stated that Wyeth had paid nurses through an agency to conduct free audits in GP surgeries to identify patients with conditions such as asthma or diabetes who might benefit from a new medicine. The nurses were paid a salary and usually a bonus which was linked to the number of patients or records they saw.

The article also stated that the nurses were described in promotional literature as being able to 'influence' new prescriptions for the benefit of their pharmaceutical companies. The nurses were routinely backed up by sales teams.

A recruitment consultant had told an undercover reporter that the job of the nurses was to identify patients with a specific condition '[it] opens the doors to a medical representative. They come in and close the business'.

The complainant (Case AUTH/1811/3/06) was greatly concerned by involvement of these nurse advisors because they had a conflict of interest to promote a particular company product. The complainant stated that he had contacted The Sunday Times which had transcripts of conversations between a reporter and an agency representative. The Sunday

Times had assured the GP that the story was correct. The GP alleged that it was a clear admission that these nurse advisors were not independent but were involved in the marketing of medicines. The complainant alleged that this was in breach of the Code. The complainant requested that the Panel consider halting any current nurse advisor activity until this case had completed.

Wyeth was asked to respond in relation to Clauses 2, 9.1 and 18.1 of the Code.

RESPONSE

Wyeth submitted that it currently offered one audit service in primary care, the GastroCare Service. This service provided GP practices with the resource to implement National Institute of Health and Clinical Excellence (NICE) and Scottish Intercollegiate Guidelines Network (SIGN) dyspepsia guidelines, with a view to ensuring patients received optimal treatment following a clinical assessment by the practice. The GastroCare Service did not promote any specific product nor did it lead automatically to a Wyeth product being prescribed. The GastroCare Service was offered without any condition that a Wyeth product would be prescribed or indeed that any medicine would be prescribed at all. The practice was asked to indicate in writing its treatment plan before the audit commenced and all treatment decisions arising out of the audit rested solely with the practice. The practice might change its treatment decisions during the audit.

Wyeth submitted that the GastroCare Service consisted of three different audit options. Copies of the materials describing each option for GPs were provided (including Upper GI Audit & Review; NSAID Audit & Review; *H. pylori* Eradication Test & Treat Audit & Review). These documents clearly explained the aim of the audit service and what it involved. The documents were currently in the process of being reviewed and certified in relation to the new requirements of the 2006 Code.

Roles of sales representatives, nurses, the agency and GPs

Wyeth submitted that its GastroCare Service was offered to practices by its sales representatives. If a practice was interested in undertaking the audit, the representative arranged a date for a registered nurse to attend that practice in order to implement the GastroCare Service. If requested by a practice, the nurse would also attend an introductory meeting with the practice. The nurse would not have contact with a practice unless this arrangement was put in place by the representative. Representatives could have no further involvement in the process once the booking and consent form had been signed by the practice and were not permitted to visit the practice to promote Wyeth products whilst the nurse was implementing the GastroCare Service at that practice.

Wyeth submitted that it had a contract with an agency for it to provide nurses for the GastroCare Service. These nurses were employed by the agency and it was, therefore, responsible for matters such as remuneration.

Wyeth submitted that the representatives and nurses had been given a briefing document to set out the scope of their respective roles. The GastroCare Service briefing document was provided. The role of the representative was also governed by a Wyeth standard operating procedure. In accordance with the Code, the Nursing & Midwifery Council (NMC) Code of professional conduct and Wyeth policies and procedures, the briefing document made it clear that the nurses must not be involved in product promotion. The role of the GastroCare nurse was only to implement the GastroCare Service in accordance with the requirements of the practice. As stated above, GPs were asked to indicate in writing their treatment management plan before the audit commenced and all treatment decisions arising out of the audit rested solely with the GPs.

Wyeth submitted that the agency's literature placed considerable weight on its nurses complying with the ABPI Code and the NMC Code of professional conduct.

Nurse remuneration

Wyeth reiterated that the agency was responsible for remuneration of the GastroCare nurses. Remuneration consisted of a salary and eligibility to an incentive scheme under which the nurses might qualify for a bonus. Salary fell between bands 6 and 7 of NHS nurse salaries, which was consistent with the level and status of the nurse. The incentive scheme was designed to recognise the amount of work carried out in an audit by a nurse and was specifically based on the numbers of notes a nurse would have to review in any audit programme. The bonus was not linked in any way to either audit outcomes or to local or national sales of a specific product or products. The supplementary information to Clause 18.4 of the 2006 Code stated 'Bonus schemes linked to a company's overall national performance, or to the level of service provided, may be acceptable'. Given that the agency's incentive scheme was linked to the level of service provided, both the agency and Wyeth considered that the scheme was acceptable under the Code.

Therefore, for the reasons indicated above, Wyeth submitted that its arrangements for the current GastroCare Service complied with the requirements of Clause 18.4 of the 2006 Code (as noted, the arrangements were currently under review having regard to the requirements newly introduced by the 2006 Code and revised materials for the GastroCare Service would be introduced shortly). Further, Wyeth submitted that, in relation to the GastroCare Service, it had maintained high standards at all times and had not done anything to discredit or reduce confidence in the pharmaceutical industry. Consequently, Wyeth did not accept that it had breached Clauses 2, 9.1 or 18.4 of the Code in relation to the GastroCare Service.

Copies of relevant briefing material for representatives regarding service provision were provided.

PANEL RULING

The Panel noted that these cases were considered in

relation to the 2003 Code using the 2006 Constitution and Procedure.

With regard to therapy review services the supplementary information to Clause 18.4 of the 2006 Code provided helpful guidance. A therapeutic review which aimed to ensure that patients received optimal treatment following a clinical assessment was a legitimate activity for a pharmaceutical company to support and/or assist. The result of such clinical assessments might require, among other things, possible changes of treatment including changes of dose or medicine or cessation of treatment. A genuine therapeutic review should include a comprehensive range of relevant treatment choices, including non-medicinal choices, for the health professional and should not be limited to the medicines of the sponsoring pharmaceutical company. The arrangements for therapeutic review must enhance patient care, or benefit the NHS and maintain patient care. The decision to change or commence treatment must be made for each individual patient by the prescriber and every decision to change an individual patient's treatment must be documented with evidence that it was made on rational grounds.

The supplementary information to Clause 18.1 of the 2003 Code (and the supplementary information to Clause 18.4 of the 2006 Code) stated that if a service required patient identification or contact then the service provider should be appropriately qualified eg a sponsored registered nurse not employed as a medical representative. Sponsored health professionals should not be involved in the promotion of specific products. Nurses were required to comply with the Nursing and Midwifery Council Code of professional conduct which required that registration status was not used in the promotion of medicines.

The remuneration of service providers must not be linked to sales in any particular territory or place or to sales of a specific product or products. Bonus schemes linked to actual performance or to the level of service provided might be acceptable. The supplementary information to Clause 18.1 of the 2003 Code (and the supplementary information to Clause 18.4 of the 2006 Code) stated that companies must ensure that patient confidentiality was maintained and that data protection legislation was complied with.

The Panel noted that the GastroCare service provided a review of patients' medication in line with the prescribing decisions of the GP. Representatives' briefing material stated that the service and the promotion of Wyeth's products must not be linked in any way. In addition the service had to be freely offered ie to all customers. Representatives could not restrict the offering or steer customers to a specific choice. The GPs must make the decision having been given full details of all options available. The detail flow for a Zoton FasTab detail aid (ZZOT3979) did not refer to the GastroCare service. At least 10 working days had to separate a call to promote or discuss Wyeth's products and a call to discuss the GastroCare Service. Similarly, once a GastroCare service had been completed representatives could not promote Wyeth products at that surgery until a further 10 working days had elapsed. The Panel did not consider that the service was an inducement to prescribe, supply, administer, recommend or buy any medicine. No breach of Clause 18.1 of the 2003 Code was ruled. The Panel also ruled no breach of Clause 2 and 9.1 of the 2003 Code.

Case AUTH/1808/3/06

Proceedings Commenced 10 March 2006
Case completed 20 July 2006

Case AUTH/1811/3/06

Complaint received 13 March 2006
Case completed 20 July 2006

CASE AUTH/1812/3/06

PFIZER v BAYER

SortEDin10 campaign

Pfizer complained about an erectile dysfunction (ED) disease awareness and educational campaign, SortEDin10, sponsored by Bayer. The material at issue was an interview with a sporting celebrity which appeared on the BBC News website. Pfizer alleged that SortEDin10 targeted the public via a website and associated materials.

Pfizer noted the BBC News website published an interview with the celebrity who was the primary spokesman for the SortEDin10 campaign. Under the auspices of that campaign, the celebrity was quoted as saying 'The impotence drug Viagra did not help me and I found an alternative called Cialis did not have very quick results, but a drug called Levitra suited my lifestyle. I took it and within 15 minutes I could be in action. If you take one of these drugs you do not get an erection immediately'. Pfizer alleged that that statement promoted Levitra to the public and encouraged men with ED to ask their health professional to prescribe Levitra in breach of the Code. Pfizer further alleged that the implication of the celebrity's statement was made even more serious because of his high profile and his widely advertised association with the SortEDin10 education campaign and website.

Pfizer further alleged that the statement was disparaging; the claims made by the celebrity implied that Viagra did not work effectively and that it was an inferior choice for the treatment of ED.

The Panel noted that when interviewed for the BBC and asked about his treatment for erectile dysfunction, the celebrity stated 'The impotence drug Viagra did not help me and I found an alternative called Cialis did not have very quick results, but a drug called Levitra suited my lifestyle. I took it and within 15 minutes I could be in "action". If you take one of these drugs you do not get an erection immediately'.

The Panel acknowledged that the celebrity was expressing his own opinions about his treatment with Viagra and Levitra but considered that those opinions would have been known to Bayer; the company knew that he took Levitra and by briefing him to talk about his treatment and facilitating his interview with the BBC it had encouraged him to talk about his treatment and so it was responsible for the remarks he made to the BBC journalist. The Panel considered that Bayer was responsible under the Code for the statements made by the celebrity and that the statement about Levitra encouraged members of the public to ask their doctor to prescribe it. A breach of the Code was ruled. The Panel considered that the BBC interview in effect advertised Levitra to the public and thus ruled a breach of the Code.

With regard to the statement by the celebrity that '…Viagra did not help me…' the Panel considered that while the statement was no doubt personally true for him, it lacked balance in that there was no reference to the many men that Viagra would have helped. The Panel thus considered that the celebrity's statement disparaged Viagra. A breach of the Code was ruled.

Pfizer Limited complained about an erectile dysfunction (ED) disease awareness and educational campaign, SortEDin10, sponsored by Bayer Health Care Pharmaceutical Division of Bayer plc. The material at issue was an interview with a sporting celebrity which appeared on the BBC News website.

Intercompany correspondence had failed to resolve the issues.

COMPLAINT

Pfizer alleged that SortEDin10 targeted the public in the UK via a website and associated materials. The educational platform was championed by the sporting celebrity. Bayer had previously confirmed that the celebrity was under contractual legal obligations to adhere to the Code and UK law not to either directly or indirectly promote prescription only medicines to the public.

Pfizer noted that in a recent series on celebrities and their health, the BBC News website published an interview with the celebrity in question who was the primary spokesman for the SortEDin10 campaign. Under the auspices of that campaign, the celebrity was quoted as saying 'The impotence drug Viagra did not help me and I found an alternative called Cialis did not have very quick results, but a drug called Levitra suited my lifestyle. I took it and within 15 minutes I could be in action. If you take one of these drugs you do not get an erection immediately'.

Pfizer alleged that the quote could be construed to promote a specific medicine for ED to the public, ie Levitra (vardenafil), manufactured and promoted by Bayer. The statement also encouraged men with ED to ask their health professional to prescribe Levitra.

Pfizer alleged that the implication of the celebrity's statement was made even more serious because of his high profile and his widely advertised association with the SortEDin10 education campaign and website. Pfizer alleged that his statement was in breach of Clauses 20.1 and 20.2 of the Code.

Pfizer further alleged that the statement was disparaging, in breach of Clause 8.1 of the Code. The BBC News website interview and the claims made by the celebrity implied that Viagra did not work effectively and that it was an inferior choice for the treatment of ED.

Pfizer also alleged that there had been prior instances during the Summer of 2005 in which Bayer had been implicated in promoting Levitra to the public.

RESPONSE

Bayer noted that the BBC transcript had not appeared on its SortEDin10 website; it had only appeared on the BBC website over which Bayer had no editorial control.

Bayer submitted that in January 2005, at the launch of SortEDin10, it had provided all briefing documents to the Medicines and Healthcare products Regulatory Agency (MHRA), together with relevant press articles. The MHRA requested no further information and made no comments suggesting that further scrutiny was needed to exclude a breach of the Code.

Bayer submitted that information supplied to both the celebrity and journalists dating back to the launch of SortEDin10 in December 2004 had complied with the Code. Specific references were made to the prohibition of promotion of prescription medicines to the public in all briefing documents to the celebrity. The relevant briefings to the celebrity were provided including his responsibilities in respect of the Code.

Bayer submitted that the press release which generated the article that appeared on the BBC News site and all other press releases clearly stated Bayer's role as sponsor of the disease awareness campaign.

Bayer submitted that neither it or its agencies were provided with transcripts of any interviews by the BBC and had had no input into the editorial copy, and so did not agree that it was a breach of any of the clauses cited.

Bayer submitted that with regard to the alleged breach of Clause 8.1, the 'disparaging' remark made by the celebrity was simply a factual statement of his own personal experience in response to a direct question regarding his treatment.

Bayer submitted that it was important to look at this complaint in the context of the ED market. This was a market of exceptionally high brand awareness; the word 'Viagra' appeared in at least two English dictionaries, and was common parlance in the English language. Bayer stated that it did not intend to complain to the Authority every time the word Viagra appeared in the lay press. Some recent examples were provided.

Bayer noted that the remit of a disease awareness campaign according to the MHRA Blue Guide was to heighten patient awareness for self help, which included awareness of treatment choices.

Bayer submitted that SortEDin10 was a disease awareness campaign designed to encourage men experiencing ED to present themselves to their doctor for assessment and potential treatment. The campaign provided essential information to patients, and their partners, about the causes of, and potential treatments available for, ED. The campaign made it clear to patients, and their partners, that the onset of ED might be an indicator of underlying serious disease, such as diabetes or heart disease, and that consultation with their doctor was all the more important to either exclude these conditions or to start treatment as soon as possible.

Bayer submitted that another important objective for the SortEDin10 campaign was to try to alleviate the embarrassment that men might experience when presenting to their doctors with ED. This embarrassment in itself might by enough to stop then seeking help and it was this important point that the campaign tried to address. The involvement of the celebrity in the campaign had been of considerable help in this regard, he was a prominent public figure who was very willing to report that he had experienced ED and that really there was nothing for a man to be embarrassed about when talking to his doctor. The celebrity passionately believed that all men with this condition should see their doctors to seek advice and help and it was this fact that had defined his involvement in the SortEDin10 campaign.

Bayer noted that 'Viagra' was now part of the English language and synonymous with the treatment of ED. However, any treatment for ED did not work for all men. The final objective of the SortEDin10 campaign was, therefore, to make it clear to patients that other treatments existed and to encourage men who might already have seen their doctor and have treatment for their ED to return if this treatment had not been satisfactory.

Bayer submitted that the Department of Health and medical professionals alike recognised the wider benefits of disease awareness programmes of this kind. Some of the extensive work that had been done by Bayer to heighten disease awareness in this market over the last year as part of the SortEDin10 campaign was provided.

PANEL RULING

The Panel noted that when interviewed for the BBC and asked about his treatment for erectile dysfunction, the celebrity stated 'The impotence drug Viagra did not help me and I found an alternative called Cialis did not have very quick results, but a drug called Levitra suited my lifestyle. I took it and within 15 minutes I could be in 'action'. If you take one of these drugs you do not get an erection immediately'.

As with all complaints about articles in the press the Panel examined the briefing materials which prompted the article on the BBC website and not the articles *per se*. The briefing for the celebrity noted that he was a Levitra patient; it was stated that he could respond truthfully, in a factual and descriptive way, to any questions regarding his treatment choice as he felt appropriate. In a section headed 'Treatment', in a statement which appeared to have been written by him, the celebrity stated '… the winning formula is to be fast and effective, so what I wanted was a treatment that worked fast & I could rely on – a treatment in fact, a bit like me!'. In a briefing from the communications agency it was stated that the celebrity would not be encouraged to endorse or recommend Levitra although it was later stated that he would explain about his personal experience of ED.

The Panel considered that as the celebrity, a known Levitra patient, had been briefed to talk about his treatment for, and personal experience of, erectile dysfunction, Bayer was responsible for the remarks that he made to the journalists from the BBC. The celebrity had been briefed by Bayer and the company had facilitated his interview with the BBC. It was therefore not possible for Bayer to dissociate itself from what he had said in the interview; if it were otherwise then the effect would be for companies to use patients as a means of avoiding the restrictions in the Code.

The Panel acknowledged that the celebrity was expressing his own opinions about his treatment with Viagra and Levitra but considered that those opinions would have been known to Bayer; the company knew that he took Levitra and had encouraged him to talk about his treatment. The Panel considered that Bayer was responsible under the Code for the statements made by the celebrity. The Panel considered that the statement about Levitra encouraged members of the public to ask their doctor to prescribe it. A breach of Clause 20.2 was ruled. The Panel considered that the BBC interview in effect advertised Levitra to the public and thus ruled a breach of Clause 20.1 of the Code.

With regard to the statement by the celebrity that '…Viagra did not help me…' the Panel noted that the Code allowed critical reference to another company's product provided that such a reference was fair, balanced etc and could be substantiated. The Panel considered that while the statement was no doubt personally true for the celebrity it lacked balance in that there was no reference to the many men that Viagra would have helped. The Panel thus considered that the celebrity's statement disparaged Viagra. A breach of Clause 8.1 of the Code was ruled.

Complaint received **14 March 2006**

Case completed **3 May 2006**

CASE AUTH/1813/3/06

LILLY v BAYER

SortEDin10 campaign

Lilly complained about the promotion of Levitra (vardenafil) by Bayer and alleged that a sponsored 'Erectile Dysfunction' supplement in Practice Nurse and Doctor, an interview for the 'SortEDin10' disease awareness campaign, which appeared in The Daily Mail, the 'SortEDin10' web chat February 2005 and the distribution of Montorsi *et al* (2004) all promoted Levitra as being effective in 10 minutes. Such claims were inconsistent with the Levitra summary of product characteristics (SPC), misleading and exaggerated in a breach of the Code. Unfounded assurances risked alienating men with erectile dysfunction (ED) by creating further barriers to those experiencing success with treatment. Many UK men with ED (23.3%) waited up to five years to tell their doctor about it. ED was a disease with significant psychological impact and Lilly alleged that irresponsible promotion of unsustainable claims lowered the standards of industry as a whole.

Lilly further alleged that Bayer's disease awareness campaign promoted Levitra and its supposed benefits to the public. There was no clear declaration of sponsorship.

The Panel noted that the Levitra SPC stated that the recommended 10mg dose should be taken approximately 25 to 60 minutes before sexual activity. Montorsi *et al* concluded that the onset of action of vardenafil with subsequent intercourse completion was recognised as early as 10 minutes after dosing. The Panel considered that the distribution of Montorsi *et al* by Bayer in effect promoted the efficacy of Levitra 10 minutes after dosing and that the proactive use of the study was inconsistent with the SPC. Breaches of the Code were ruled.

With regard to the supplement 'Erectile Dysfunction' it appeared that the whole supplement was sponsored by Bayer Healthcare. The Panel had only been provided with the article 'Treating the Problem' which included the statement that 'Vardenafil has also been shown to have a fast onset of action; working as quickly as 10 minutes in some men'. No information was given as to the content of the SPC in this regard. The Panel considered that the material in effect promoted Levitra in a manner inconsistent with the SPC and thus was misleading. Breaches of the Code were ruled.

The article in The Daily Mail was a result of a Bayer global press conference. The associated press release focussed on encouraging those affected by ED to discuss the condition and to take positive steps to seek treatment by visiting their doctor. The press release, which did not refer to any product by name, included quotes by a celebrity including: 'These days there are effective treatments for erectile dysfunction that work as quickly as ten minutes to help you reclaim your sex life'. The article in The Daily Mail quoted the celebrity as mentioning Viagra and Cialis and 'And then [there] are the latest generation of drugs like Levitra which work within ten minutes – so you can keep the all important feeling of spontaneity'.

The Panel considered that the press materials provided by Bayer were misleading regarding the statement that one medicine could work in ten minutes and the materials would encourage patients to ask their doctor to prescribe Levitra. High standards had not been maintained. Breaches of the Code were ruled. On balance, the Panel did not consider that the press materials constituted an advertisement to the public for a prescription only medicine and thus ruled no breach of the Code. The press materials provided by Bayer were clear that the SortEDin10 campaign was sponsored by Bayer and although this was not made clear in The Daily Mail article the Panel did not consider that Bayer was responsible for this. No breach of the Code was ruled.

Lilly noted that the page of the 2006 Levitra calendar for May depicted a solitary sign post stating 'SPEED LIMIT 10' and the claim 'Levitra (10mg) has been shown to start working within 10 minutes'. Lilly alleged that this was an exaggerated and misleading claim, inconsistent with the Levitra SPC in breach of the Code.

The Panel considered that the calendar, by claiming that Levitra started to work within ten minutes, was inconsistent with the Levitra SPC, misleading and not capable of substantiation as ruled above. Breaches of the Code were ruled.

Lilly alleged that the SortEDin10 webchat, where questions from the public were answered by two ambassadors of the disease awareness campaign, a sporting celebrity and a sex expert and relationship guru, advised individuals on personal medical matters and encouraged them to ask for particular prescription only medicines in breach of the Code. In addition, misleading and exaggerated claims of the efficacy of Levitra were made and Bayer's sponsorship was not declared. Lilly alleged that such repeated examples of irresponsible promotion brought the entire industry into disrepute. A breach of Clause 2 was alleged.

The Panel noted that the briefing for the sporting celebrity stated that he was a Levitra patient; it was further stated that he could respond truthfully in a factual and descriptive way to any questions regarding his treatment as he felt appropriate. The brief included background information on ED and specific treatments including Levitra. One of the broadcast messages for treatment referred to a 'winning formula' being 'fast and effective'.

In response to a question about the lack of spontaneity with Viagra, the celebrity was quoted on the webchat as stating 'If you use what I use you will find it fast. Ten minutes works for me because it takes that long to make a cup of tea! Try it!'

The Panel considered that as the celebrity, a known Levitra patient, had been briefed to talk about his treatment for, and personal experience of, erectile dysfunction, Bayer was responsible for the remarks that he made on the webchat. The celebrity had been briefed by Bayer and the company had facilitated his appearance on the webchat. It was therefore not possible for Bayer to dissociate itself from what he had said in the interview; if it were otherwise then the effect would be for companies to use patients as a means of avoiding the restrictions in the Code. The Panel considered the webchat would encourage patients to ask their doctor to prescribe Levitra. A breach of the Code was ruled.

The Panel did not consider that the circumstances were such as to justify a ruling of a breach of Clause 2 of the Code.

Eli Lilly and Company Limited complained about the promotion of Levitra (vardenafil) by Bayer Health Care Pharmaceutical Division of Bayer plc. The items at issue were a sponsored 'Erectile Dysfunction' supplement in Practice Nurse and Doctor, 'SortEDin10' disease awareness campaign – interview in The Daily Mail, a calendar (5LEVI 142), 'SortEDin10' web chat February 2005 and the distribution of Montorsi *et al* (2004).

1 Distribution of Montorsi *et al* (2004), sponsored 'Erectile Dysfunction' supplement in Practice Nurse and Doctor and 'SortEDin10' disease awareness campaign – interview in The Daily Mail

COMPLAINT

Lilly alleged that the materials contained claims that Levitra was effective in 10 minutes and this was a breach of the Code.

Lilly alleged that claims of efficacy at 10 minutes were inconsistent with the Levitra summary of product characteristics (SPC), misleading and exaggerated in breach of Clauses 3.2, 7.2 and 7.4 respectively. Such unfounded assurances risked alienating men with erectile dysfunction (ED) by creating further barriers to men experiencing success with treatment. Many UK men with ED (23.3%) waited up to five years to tell their doctor about it. ED was a disease with significant psychological impact and Lilly alleged that irresponsible promotion of unsustainable claims lowered the standards of industry as a whole. A breach of Clause 9.1 was also alleged.

In addition, Lilly alleged that Bayer's disease awareness campaign 'SortEDin10' contravened the Code. In the examples above, ambassadors of Bayer's disease awareness campaign clearly promoted Levitra and its supposed benefits to the public in breach of Clauses 3.2, 7.2, 7.4, 20.1 and 20.2. Furthermore, there was no clear declaration of sponsorship in breach of Clauses 9.10 and 10.1.

RESPONSE

Bayer submitted separate responses to each allegation as follows.

Distribution of Montorsi *et al*

Bayer submitted that it was not only reasonable but obligatory to make the results of all *bona fide* clinical trials available to health professionals to enable them to make an up-to-date full evaluation of the product. When referring to time to onset of activity the SPC was no more specific than 'approximately 25 to 60 minutes before sexual activity' because at the time of regulatory submission no clinical study had specifically examined this parameter and so it was only possible to give dosing instructions compatible with the registration trial results which were based upon pharmacokinetics and predicted pharmacodynamics.

Bayer submitted that the fact that data were derived from clinical trials performed after marketing authorization, and therefore additional to that within the SPC, did not constitute sufficient grounds for Lilly's consideration that the results presented in Montorsi *et al* were not consistent with the SPC. The dosing instructions suggested in the SPC remained entirely appropriate for most men but Montorsi *et al* showed that some might experience a therapeutic effect as early as 10 minutes.

Bayer agreed that health professionals should not be given the impression that all patients responded to Levitra as early as 10 minutes and consequently no such claim was made. Montorsi *et al* made it quite clear that not all patients responded as early as 10 minutes. This was precisely the manner in which Bayer used this paper.

Bayer submitted that Montorsi *et al* described the patient population, methodology and results to the

extent that health professionals could make their own judgement as to the limitations or otherwise of the study. In this peer reviewed publication the authors made no attempt to misrepresent the data. Bayer did not agree that use of the paper was misleading or that its conclusions were misleading.

Bayer did not believe it had made an irresponsible or unsustainable claim, and therefore denied a breach of Clause 9.1.

Sponsored article in Erectile Dysfunction supplement in Practice Nurse and Doctor

Bayer did not consider that Lilly was entirely clear as to which clauses of the Code were alleged to be in breach in relation to this article for health professionals. Therefore, Bayer addressed the three clauses cited by Lilly. Bayer emphasised that this article was directed solely towards health professionals.

Bayer submitted that the question of promotion being consistent with the SPC, covered by Clause 3.2, had been addressed above.

Bayer noted that Lilly had asserted part of this article was in breach of Clauses 7.2 and 7.4. During intercompany correspondence Lilly had referred to the statement 'Vardenafil has also been shown to have a fast onset of action; working as quickly as 10 minutes for some men' and the company assumed that it was this statement that was now at issue. The statement did not claim, however, that vardenafil worked after 10 minutes in all men. Therefore there could be no question that it was misleading or exaggerated.

SortEDin10 Disease Awareness Campaign – interview in The Daily Mail

Bayer noted that the interview that appeared in the Daily Mail on 6 December 2005 was written as a result of a global press conference that took place at the European Society of Sexual Medicine in Copenhagen. The press conference was attended by journalists from all over the world.

A media celebrity was fronting an international disease awareness campaign for ED. Her role was to provide a platform for women to identify with and convince their partners that it was important that they should go to their doctor for advice and potential treatment.

Bayer submitted that all materials provided to the UK journalists were approved according to the Code and the briefing document provided to the media celebrity by Bayer's global team had not referred to Levitra.

Bayer submitted that in all cases Bayer's declaration as sponsor of a disease awareness programme was made clear. This interview was under the editorial control of the newspaper. Again Bayer did not agree that it was in breach of any of the clauses cited.

PANEL RULING

The Panel noted that the Levitra SPC stated that the recommended 10mg dose should be taken approximately 25 to 60 minutes before sexual activity. Montorsi *et al* concluded that the onset of action of vardenafil with subsequent intercourse completion was recognised as early as 10 minutes after dosing.

The Panel considered that the distribution of Montorsi *et al* by Bayer in effect promoted the efficacy of Levitra 10 minutes after dosing. The SPC referred to a time period of 25 to 60 minutes for the 10mg dose. The Panel considered that the proactive use of Montorsi *et al* was inconsistent with the SPC. Breaches of Clauses 3.2, 7.2 and 7.4 of the Code were ruled.

With regard to the supplement 'Erectile Dysfunction' it appeared that the whole supplement was sponsored by Bayer Healthcare. The Panel had only been provided with the article 'Treating the Problem' which included the statement that 'Vardenafil has also been shown to have a fast onset of action; working as quickly as 10 minutes in some men'. No information was given as to the content of the SPC in this regard. The Panel considered that the material in effect promoted Levitra in a manner inconsistent with the SPC and thus was misleading. Breaches of Clauses 3.2, 7.2 and 7.4 were ruled.

The article in The Daily Mail was a result of a Bayer global press conference. Interviews with the media celebrity had been arranged and a press release was issued. The press release focussed on encouraging those affected by ED to discuss the condition and to take positive steps to seek treatment by visiting their doctor. The press release included a list of approved quotes by the celebrity including: 'These days there are effective treatments for erectile dysfunction that work as quickly as ten minutes to help you reclaim your sex life'.

The press release and other materials did not mention any product by name. The article in The Daily Mail quoted the celebrity as mentioning Viagra and Cialis and 'And then [there] are the latest generation of drugs like Levitra which work within ten minutes – so you can keep the all important feeling of spontaneity'.

The Panel did not agree with Bayer's submission that the interview was under the editorial control of the newspaper. The article in The Daily Mail was under the editorial control of the newspaper. Bayer had arranged the global press conference and had arranged interviews with the media. It was not known whether The Daily Mail had been one of those given an interview with the celebrity who was acting as a spokesperson for Bayer.

The Panel considered that the press materials provided by Bayer were misleading regarding the statement that one medicine could work in 10 minutes and the materials would encourage patients to ask their doctor to prescribe Levitra. Thus the Panel ruled a breach of Clause 20.2 of the Code.

The Panel noted its rulings of breaches of Clauses 3.2, 7.2 and 7.4 with regard to promotion of the efficacy of Levitra 10 minutes after dosing; Lilly had alleged breaches of these clauses. The Panel considered that its ruling of a breach of Clause 20.2 with regard to the information to the public covered the point. Clauses 3.2, 7.2 and 7.4 of the 2003 Code related to the promotion of medicines rather than the provision of information to the public. Some changes in this regard had been made to the 2006 Code.

On balance, the Panel did not consider that the press materials regarding the celebrity constituted an advertisement to the public for a prescription only medicine and thus ruled no breach of Clause 20.1. The press materials provided by Bayer were clear that the SortEDin10 campaign was sponsored by Bayer. This was not clear in the Daily Mail article. The Panel considered that Bayer was not responsible for this. Thus no breach of Clauses 9.10 and 10.1 was ruled.

The Panel considered that the misleading nature of the materials that were inconsistent with the Levitra SPC meant that high standards had not been maintained. A breach of Clause 9.1 was ruled.

2 2006 Levitra calendar

COMPLAINT

Lilly noted that each page of this calendar represented a different month which contained a photographic image and a key message associated with Levitra. May depicted an arctic scene with a solitary sign post stating 'SPEED LIMIT 10'. The claim on this page was 'Levitra (10mg) has been shown to start working within 10 minutes'. This was further evidence of the use of an exaggerated and misleading claim, inconsistent with the Levitra SPC in breach of Clauses 3.2, 7.2 and 7.4.

RESPONSE

Bayer submitted that the statement 'Levitra (10mg) has been shown to start working within 10 minutes' was based on Montorsi *et al*. Hence Bayer referred to its response outlined above.

PANEL RULING

The Panel considered that the calendar, by claiming that Levitra started to work within 10 minutes, was inconsistent with the Levitra SPC, misleading and not capable of substantiation as ruled above. Thus the Panel ruled breaches of Clauses 3.2, 7.2 and 7.4.

3 SortEDin10 webchat February 2005

COMPLAINT

Lilly noted that the SortEDin10 webchat, where questions from the public were answered by two ambassadors of the disease awareness campaign, a sporting celebrity and a sex expert and relationship guru, advised individuals on personal medical matters and encouraged them to ask for particular prescription only medicines in breach of Clauses 20.1 and 20.4. In addition, misleading and exaggerated claims of the efficacy of Levitra were made in breach of Clauses 3.2, 7.2 and 7.4. Sponsorship by Bayer was not declared in breach of Clauses 9.10 and 10.1.

Lilly alleged that such repeated examples of irresponsible promotion brought the entire industry into disrepute and a breach of Clause 2 was alleged in relation to the campaign.

RESPONSE

Bayer provided the briefing materials used to prepare the sporting celebrity and a sex expert and relationship guru, together with press material. Bayer submitted that all materials provided to facilitate the webchat were approved according to the Code and the briefing document provided to the celebrity and the guru by Bayer and its agency referred specifically to the disease awareness campaign, in which Bayer's role as sponsor of this campaign was clearly declared.

Bayer submitted that the interview was under the editorial control of the broadcasters. Again Bayer did not agree that it was in breach of any of the clauses cited.

Bayer submitted that in January 2005, at the launch of SortEDin10, it provided all briefing documents to the MHRA, together with relevant press articles. The MHRA requested no further information and made no comments suggesting that further scrutiny was needed to exclude a breach of the Code.

Bayer submitted that it was important to look at this complaint in the context of the ED market which had exceptionally high brand awareness; 'Viagra' now appeared in at least two English dictionaries, and was common parlance in the English language. Bayer did not intend complaining to the Authority every time the words Viagra or Cialis appeared in the lay press. Some recent examples were provided. Bayer submitted that the remit of a disease awareness campaign, according to the MHRA Blue Guide, was to heighten patient awareness for self help, which included awareness of treatment choices.

Bayer submitted that the SortEDin10 campaign was designed to encourage men with ED to go to their doctor for assessment and potential treatment. The campaign provided essential information to patients, and their partners, about the causes of, and potential treatments available for, ED. It was made clear that the onset of ED might indicate an underlying serious disease, such as diabetes or heart disease, and that consultation with their doctor was all the more important to either exclude these conditions or to start treatment as soon as possible.

Bayer submitted that another important objective for the SortEDin10 campaign was to try to alleviate the embarrassment that men might experience when presenting to their doctors with ED. This embarrassment in itself might be enough to stop them seeking help and it was this important point that the campaign tried to address. The involvement of the celebrity had been of considerable help in this regard; he was a prominent public figure who was willing to report that he had experienced ED and that really there was nothing for a man to be embarrassed about when talking to his doctor. The celebrity's passionate belief that all men with this condition should see their doctors to seek advice and help had defined his involvement in the SortEDin10 campaign.

Bayer submitted that although 'Viagra' was now part of the English language and synonymous with the treatment of ED, as with any treatment for ED it did not work for all men. The final objective of the SortEDin10 campaign was, therefore, to tell patients that other treatments existed and to encourage men who might already have been treated for ED to return to their doctor if this treatment had not been satisfactory.

Bayer submitted that SortEDin10 remained a disease awareness programme to encourage men who might be embarrassed to talk about ED to come forward and discuss their condition with a health professional. It was widely acknowledged that men should consult their doctor because ED could be the first sign of a more serious underlying condition. Many patients did not return after failure on their first treatment, and it was important they were made aware there were other options.

Bayer submitted that the Department of Health and medical professionals alike recognised the wider benefits of disease awareness programmes of this kind. Bayer provided some of the extensive work that it had done to heighten disease awareness in this market over the last year as part of the SortEDin10 campaign. Further examples could also be seen on www.sortedin10.co.uk.

Bayer submitted that given what it had set out above, it did not believe it had breached Clause 2 of the Code.

PANEL RULING

The Panel examined the briefing materials for the SortEDin10 campaign. The briefing for the sporting celebrity noted that he was a Levitra patient; it was stated that he could respond truthfully in a factual and descriptive way to any questions regarding his own treatment choice as he felt appropriate. The brief included background information on ED and treatments. A range of treatments were mentioned, injections, vacuum pumps, pellets, counselling, hormone therapy and tablets. More detailed information was given about tablets including the names of the phosphodiesterase type 5 inhibitors Viagra, Cialis and Levitra.

The brief then included background information on Levitra. The broadcast messages were grouped under the headings General, Impact on ED, Involvement in SortEDin10 Campaign, Treatment and Potential Questions. The broadcast message for Treatment was: 'There are a number of highly effective treatments available. I think most men would prefer to take a tablet to other forms of treatment, and preferably one that allows them to respond in a normal, spontaneous way to their partner. In my world, the winning formula is to be fast and effective, so what I wanted was a treatment that worked fast & I could rely on – a treatment in fact, a bit like me!'

The brief for the sex expert and relationship guru included that five key aims including raising awareness that there is now a range of oral treatments for ED. The guru was not to be encouraged to '…endorse or recommend Levitra as the sponsoring brand of this activity or any other specific treatment'. The webchat page dated 14 February 2005 reported on an interview with the celebrity and the guru.

The webchat reported the celebrity as suggesting mentioning to the doctor 'the treatment I found so good for me…' It also stated that 'I like to hope that my being connected with SortEDin10 and one of the important treatments to help with erectile dysfunction…'.

In response to a question about the lack of spontaneity with Viagra the guru stated that there were three medicines available for ED and alternatives should be discussed with the doctor. Levitra and Cialis were mentioned. The celebrity stated that Viagra did nothing for him, Cialis worked well but not as fast as he wanted because the lack of spontaneity was difficult to handle. 'If you use what I use you will find it fast. Ten minutes works for me because it takes that long to make a cup of tea! Try it!

The Panel considered that as the celebrity, a known Levitra patient, had been briefed to talk about his treatment for, and personal experience of, erectile dysfunction, Bayer was responsible for the remarks that he made on the webchat. The celebrity had been briefed by Bayer and the company had facilitated his appearance on the webchat. It was therefore not possible for Bayer to dissociate itself from what he had said in the interview; if it were otherwise then the effect would be for companies to use patients as a means of avoiding the restrictions in the Code. The Panel considered the webchat would encourage patients to ask their doctor to prescribe Levitra. A breach of Clause 20.2 was ruled.

The Panel did not consider that the circumstances were such as to justify a ruling of a breach of Clause 2 of the Code which was used as a sign of particular censure and reserved for such use.

Complaint received **15 March 2006**

Case completed **9 June 2006**

CASE AUTH/1815/3/06

MERCK SHARP & DOHME v GLAXOSMITHKLINE

Provision of textbook to general practitioners

Merck Sharp & Dohme complained about a letter sent to general practitioners by a representative of Edinburgh Pharmaceuticals which was part of GlaxoSmithKline; the letter was on GlaxoSmithKline headed paper.

Merck Sharp & Dohme noted that the letter offered a free copy of the Oxford Handbook of General Practice and included a reply paid slip/envelope. The letter stated 'If you would like a copy delivered to you, please complete and return the slip below in the freepost envelope (no stamp required)'. It also stated that there was no obligation to grant the representative an interview at the time of delivery. The Oxford Handbook of General Practice had a recommended retail price far in excess of £6 plus VAT.

The letter was written by a medical representative and the activities and actions of all medical representatives were considered to be promotional under the terms of the Code. Merck Sharp & Dohme believed that the method by which this item was distributed at the very least allowed the possibility that its delivery could be linked with a promotional opportunity.

The Panel noted that representatives were inextricably linked to the provision and distribution of the textbooks. The representatives chose which doctors would be offered the books, signed the letters offering the books and then offered to deliver the books. The principal role of a representative was to call on doctors in relation to the promotion of medicines. In that regard the Panel considered that the way in which the textbooks had been provided did not meet the requirements for the provision of medical or educational goods or services and thus a breach of the Code was ruled.

Merck Sharp & Dohme Limited complained about a letter (ref LOM/STA/03/5748) sent to general practitioners by a representative of Edinburgh Pharmaceuticals. Edinburgh Pharmaceuticals was part of GlaxoSmithKline UK Limited and the letter was on GlaxoSmithKline headed paper.

COMPLAINT

Merck Sharp & Dohme noted that the letter offered a free copy of the Oxford Handbook of General Practice and included a reply paid slip/envelope. The letter stated 'If you would like a copy delivered to you, please complete and return the slip below in the freepost envelope (no stamp required)'. It also stated that there was no obligation to grant the representative an interview at the time of delivery.

The Oxford Handbook of General Practice had a recommended retail price far in excess of £6 plus VAT. Whilst Merck Sharpe & Dohme acknowledged that the supplementary information to Clause 18.2 of the 2006 Code stated 'Certain independently produced medical/educational publications such as text books have been held to be acceptable under Clause 18.2 …', it did not believe that initiatives such as the GlaxoSmithKline Book Club could claim exemption under this clause. Rather, Merck Sharp & Dohme believed that this book was a promotional aid and as such was in breach of Clause 18.2. The letter was written by a medical representative and the activities and actions of all medical representatives were considered to be promotional under the Code.

Merck Sharp & Dohme had understood that the exemption to Clause 18.2 allowed companies to provide limited numbers of useful items to medical professionals in a setting completely divorced from promotion. It was not intended to allow companies to circumvent the £6 plus VAT rule for gifts/promotional aids by sending out large quantities of more expensive 'educational items' and delivering them via the representative. Such activities completely undermined the £6 plus VAT limit. Merck Sharp & Dohme believed that the method by which this item was distributed at the very least allowed the possibility that its delivery could be linked with a promotional opportunity.

RESPONSE

GlaxoSmithKline stated that the textbook was provided as a service to medicine and that every aspect of its nature and supply complied with the letter and the spirit of the Code.

The book had been distributed in the same way since March 2003 and GlaxoSmithKline intended to continue in this way for the foreseeable future.

GlaxoSmithKline submitted that the Oxford Handbook of General Practice was clearly of great interest to general practitioners; it did not refer to GlaxoSmithKline or its medicines. GlaxoSmithKline believed it was a high value educational text with no promotional content. It was delivered to the practice exactly in the state it left the printers, with no additional labels, stickers or accompanying letters.

While the value of the textbook was clearly more that £6 (the unit price to GlaxoSmithKline was £13.77, the retail cost was approximately £25) GlaxoSmithKline believed that it should be considered as an item of service to medicine. As such GlaxoSmithKline believed that it fell outside the definition of Clause 18.2 (as a promotional aid of less than £6 in value) but fell within the definition of Clause 18.4 as a medical service which could enhance patient care and benefit the NHS since:

- the book and associated materials did not refer to any medicine brand name;
- the value was greater than £6;
- the book was a non-promotional, independently produced reference text from a reputable publisher by reputable independent authors;
- GlaxoSmithKline had no part or influence in the

production or content of the book;

- the book was a genuinely useful text for a GP to refer to, to improve patient care.

The supplementary information to Clause 18.2 stated:

'Certain independently produced medical/educational publications such as textbooks have been held to be acceptable gifts under Clause 18.2 …. It might be possible to give certain medical/educational publications in accordance with Clause 18.4 – Provision of Medical and Educational Goods and Services'.

GlaxoSmithKline believed therefore that the textbook in question was an appropriate item to provide to GPs as a service to medicine and it believed the way the book was provided complied with Clause 18.4 and its supplementary information. The item had been appropriately certified under Clause 14 as such.

The process whereby the letter in question was sent to a practice and the subsequent delivery of the textbook was as follows:

- the local GlaxoSmithKline representative chose which GPs would receive the letter offering the textbook;
- the representative generated a mailing from a third party mailing house which sent the letter to the GP's surgery address. The letter contained only a GlaxoSmithKline logo and no brand logos or product mentions; asked the GP to respond if interested; clearly stated that there was no obligation to see a representative; asked the GP the best time for the representative to call should a call be desired and had been appropriately signed off as defined in the Code by a commercial and medical signatory;
- if the GP wanted a textbook, the representative was notified and ordered it;
- the representative then delivered the book to the practice:
    - representatives were trained to not insist on seeing a doctor to deliver an item and to leave the item with receptionists if required;
    - this training was underpinned by a briefing document, a copy of which was provided;
    - this guidance was available to every representative via an icon on their laptops and had been covered in Code of Practice training updates with field based staff.

In summary GlaxoSmithKline believed the provision of the Oxford Handbook of General Practice was a valid service to medicine as defined in the Code. Neither the book nor any associated mailing had any brand mention or logo associated with it. The book and letters were appropriately certified under the Code.

The book was delivered by a representative who had been trained and who had guidance to avoid the book being used or perceived as being used as an incentive to see a GP.

GlaxoSmithKline believed the letter and textbook complied with the spirit and letter of the Code.

PANEL RULING

The Panel noted that the letter at issue was dated 9 February 2006 and so the textbook was offered before changes made in the 2006 Code came fully into operation. The relevant requirements were similar in both the 2003 and the 2006 Codes.

The Panel noted that companies were allowed to provide gifts in the form of promotional aids provided that such gifts were inexpensive (no more than £6 plus VAT cost to the company) and relevant to the practice of the recipient's profession or employment. The 2006 Code stated that the perceived value to the recipient must be similar. Clearly the textbooks at issue were relevant to a doctor's profession but as each one had cost GlaxoSmithKline more than £6 plus VAT then they could not be regarded as promotional aids.

The 2003 Code, however, allowed companies to provide medical and educational goods and services which enhanced patient care or benefited the NHS. The 2006 Code stipulated that goods and services which benefited the NHS must maintain patient care. These items could cost more than £6 plus VAT. The textbook could be an appropriate medical good. To benefit from this exemption, however, the books must not be provided in such a way as to be an inducement to prescribe, supply, administer, recommend or buy any medicine. The Panel considered that the manner of the provision of medical and educational goods and services should be clearly differentiated from the provision of promotional aids. If this were not so then companies could distribute any items costing more than £6 plus VAT via their sales force and just claim that they were medical and educational goods and services. The relevant supplementary information to Clause 18.1 in the 2003 Code (Clause 18.4 in the 2006 Code) stated that companies should consider using staff other than representatives and that if representatives provided, delivered or demonstrated medical and educational goods and services this must not be linked to the promotion of medicines.

The Panel noted that representatives were inextricably linked to the provision and distribution of the textbooks. The representatives chose which doctors would be offered the books, signed the letters offering the books and then offered to deliver the books. The principal role of a representative was to call on doctors in relation to the promotion of medicines. In that regard the Panel considered that the way in which the textbooks had been provided did not meet the requirements for the provision of medical or educational goods or services and thus a breach of Clause 18.1 of the 2003 Code was ruled.

Complaint received **16 March 2006**

Case completed **25 April 2006**

GENERAL PRACTITIONER v PFIZER

Exubera price information

In Case AUTH/1816/3/06 a general practitioner complained that a website, an advertisement and a 'Dear Doctor' letter relating to Exubera (inhaled human insulin), produced by Pfizer, did not state the product's cost.

The journal advertisement and the 'Dear Doctor' letter both stated in the prescribing information 'price yet to be agreed'. The website stated 'The exact NHS price for inhaled insulin is currently unknown – however the anticipated price range for inhaled insulin is approximately £965-£1,240 per patient per year, depending on dosing requirements'. To not provide the cost of the product was not only misleading, but importantly did not allow the complainant to judge the comparative budgetary impact of Exubera with respect to the insulin products he currently prescribed.

In Case AUTH/1818/3/06 the GP further complained about a letter he had received from Pfizer about Exubera training sessions. The complainant queried whether it was premature to train diabetes care specialists on a product which they might not even be able to afford; in the absence of cost information was the training programme not falsely raising the expectation that this treatment would be affordable and that cost was not a consideration in deciding the relevance of this product regardless of any consideration of its efficacy or otherwise? Not providing cost information was tantamount to misleading doctors.

In relation to both cases the Panel noted that as soon as a marketing authorization had been granted for a medicine a company could promote that medicine. The Panel noted that the prescribing information in the printed material at issue referred to the cost of Exubera and stated that the price had yet to be agreed; the website stated that the cost of treatment per patient per year was anticipated to be approximately £965-£1,240. The Panel considered that in the circumstances such statements regarding the cost of the product were acceptable. No breach of the Code was ruled.

In Case AUTH/1818/3/06 the Panel did not consider that the statements about cost were misleading. No breach of the Code was ruled.

In Case AUTH/1816/3/06 a GP complained by email that a website, an advertisement and a 'Dear Doctor' letter relating to Exubera (inhaled human insulin), and produced by Pfizer Limited, did not state the product's cost.

The journal advertisement (ref EXU428) and the 'Dear Doctor' letter (ref EXU485) both stated in the prescribing information 'price yet to be agreed'. The website stated 'The exact NHS price for inhaled insulin is currently unknown – however the anticipated price range for inhaled insulin is approximately £965-£1,240 per patient per year, depending on dosing requirements'.

In Case AUTH/1818/3/06 the GP also complained about a letter (ref EXU490) sent to him by a manager at Pfizer Limited, about training sessions on Exubera (inhaled human insulin).

COMPLAINT

Case AUTH/1816/3/06

The complainant stated that Pfizer had been extensively advertising the impending availability of Exubera but had not provided the cost of the product in the prescribing information, where he would have expected it to be.

This was not only misleading, but importantly did not allow the complainant to judge the comparative budgetary impact of the product with respect to the insulin products he currently prescribed. What was the point of promoting the product if prescibers could not decide whether it was affordable or not?

The complainant said that he had had no joy with respect to his recent enquiries to Pfizer.

When writing to Pfizer the Authority asked it to respond in relation to Clause 4.1 of the Code.

Case AUTH/1818/3/06

The complainant stated that the letter informed him that training sessions were now taking place on Exubera. If that was indeed the case was it not somewhat premature to train diabetes care specialists on a product which they might not even be able to afford; in the absence of cost information was the training programme not falsely raising the expectation that this treatment would be affordable and that cost was not a consideration in deciding the relevance of this product regardless of any consideration of its efficacy or otherwise? Why would anyone take the time and effort to learn about this product if cost prevented its use? Surely Pfizer was putting the cart before the horse by promoting the availability of the Exubera support package in the absence of cost information being made available; trainees could ill afford to waste time on training on a potentially unaffordable product. Any relevance of this product had to be decided by a consideration of cost-efficacy or some assessment. Not providing cost information was tantamount to misleading doctors.

When writing to Pfizer the Authority asked it to respond in relation to Clauses 4.1 and 7.2 of the Code.

RESPONSE

Case AUTH/1816/3/06

Pfizer explained that a requirement of its European marketing authorization, granted on 24 January 2006, was that it must conduct an educational programme prior to the launch of Exubera. This was to ensure that health professionals involved in the care of diabetics could familiarise themselves with this entirely new way of delivering insulin, including learning about new dosing and monitoring requirements and about those for whom Exubera was

contraindicated or not recommended. This was admittedly an unusual situation and Pfizer was not aware of other products which had had a compulsory educational commitment imposed by the European regulatory authority prior to the product launch.

The consequences of the timing of the educational programme meant that Pfizer had still to agree prices with the Department of Health (DoH) for the various components of the Exubera inhaled insulin system when the advertisements for the education and training programme were published.

Prior to publication, Pfizer sought informal advice from the Authority, which advised that not including a price in the prescribing information was acceptable since the price was truly not known, the medicine was not yet available, Pfizer was being transparent about the educational programme (not promotional) and that there was no attempt to mislead the readers of the advertisement for the programme. In addition the Medicines and Healthcare products Regulatory Agency (MHRA) had pre-vetted all Exubera materials and had approved all materials relating to the educational programme including the website.

Finally it should be noted that all educational material without a price in the prescribing information would be withdrawn immediately prior to the launch and the promotion of Exubera.

Pfizer noted that Exubera was not yet available to prescribe and this was very clearly communicated in the advertisements. These advertisements were for a training programme, not a product. But since Exubera was mentioned by name Pfizer considered it appropriate to include its draft prescribing information even though prices were not yet agreed with the DoH. This contained a summary of important information that a health professional would need to know prior to prescribing Exubera. It was important to note that, unlike a promotional advertisement for a product, no efficacy and safety claims were made in these advertisements. The advertisements clearly invited health professionals to arrange training by contacting the INH Programme Healthcare Team directly (secondary care mailings) or to visit the relevant website (primary care mailings).

Pfizer agreed that the ability to assess the budgetary impact of a new medicine was important. Pfizer had approached budget holders with annual cost guidelines for Exubera of between £965 and £1240. The website above also had a downloadable formulary pack which contained this price banding and all GPs had been directed to this website. It was not clear why the complainant considered that he did not have access to this information. Without knowing more it was impossible to comment as to who in his primary care trust might have been approached by a Pfizer representative and would also have had knowledge of this price banding. It was important to stress that only budget holders were approached prior to the marketing authorization being granted at the end of January 2006.

Pfizer submitted that it had been completely transparent in its communications with health professionals stating very clearly that there was currently no product available and that the price was yet to be established. Pfizer was obliged to educate health professionals and considered it unacceptable to wait until a price had been agreed before commencing this educational programme. Inhaled insulin was an important development in insulin delivery and to delay its introduction would have caused disappointment to many people who had been awaiting its arrival. As stated above, any materials without a price would be withdrawn immediately prior to the launch, which was planned for May. Pfizer therefore failed to see how its advertisements or other activities could have been any more transparent and did not agree that it had either deliberately or accidentally misled health professionals.

Pfizer noted that it was unable to deal with the complainant's comments the he had failed to get information from the company as it did not know who he was. Pfizer had a field-based team of primary care account managers who would certainly have been able to provide this information. In addition, pricing information was available on the website (in the formulary pack, available from 13 February) and the mailings which went to health professionals on the week commencing 20 February, meaning that recipients had immediate access to the information. The price banding was also available from Pfizer's medical information officers who, in calls after 24 February, were instructed to advise GPs of the cost banding given above. Pfizer regretted that the complainant considered he was unable to obtain this information and would be happy to investigate this further, with further details with the complainant's permission.

In summary Pfizer had been careful not to promote Exubera itself, despite having a marketing authorization and had put in place a comprehensive educational programme about which it had alerted health professionals through mailings, advertisements and a website. Pfizer did not accept that, in these unusual circumstances, there had been a breach of Clause 4.2 of the Code and it hoped that it had reassured the Authority that consultations with agreement had taken place with both the MHRA and the Authority before the advertisements for the educational programme were published and the letter was sent.

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Pfizer made an almost identical response to that above but noted in addition that the letter at issue was sent in March to those health professionals with a specialist interest in diabetes (senior hospital doctors in diabetes, diabetes specialist nurses and GPs with a specialist interest), to remind them about the training programme for Exubera.

PANEL RULING

In relation to both cases the Panel noted that as soon as a marketing authorization had been granted for a medicine a company could promote that medicine. Some companies, however, occasionally found themselves in the position of having a marketing authorization but no agreed price. A pragmatic approach had to be taken. The Panel noted that the

prescribing information in the printed material at issue referred to the cost of Exubera and stated that the price had yet to be agreed; the website stated that the cost of treatment per patient per year was anticipated to be approximately £965-£1,240. The Panel considered that in the circumstances such statements regarding the cost of the product were acceptable. No breach of Clause 4.1 was ruled.

In Case AUTH/1818/3/06 the Panel did not consider that the statements about cost were misleading. No breach of Code 7.2 was ruled.

Complaints received:

Case AUTH/1816/3/06	**24 March 2006**
Case AUTH/1818/3/06	**30 March 2006**
Cases completed	**15 May 2006**

CASE AUTH/1824/4/06 *NO BREACH OF THE CODE*

MEDIA/DIRECTOR v SERVIER

Promotion of Protelos

An article entitled 'Strontium ranelate for osteoporosis' which appeared in the Drug and Therapeutics Bulletin (D&TB) of April 2006 criticised the promotion of Protelos (strontium ranelate) by Servier. In accordance with established practice the matter was taken up by the Director as a complaint under the Code. Protelos was indicated for the treatment of postmenopausal osteoporosis (PMO) to reduce the risk of vertebral and hip fractures.

The authors of the article stated that in their view there was no convincing published clinical evidence to support the claims 'the first dual action bone agent' and 'the only drug to simultaneously increase bone formation and decrease bone resorption'. Although the evidence base for the claims was bone marker data from clinical trials, the authors noted that bone biopsies provided a more definitive assessment of bone formation and resorption and had not shown that Protelos stimulated bone formation or resulted in positive remodelling imbalance.

The Panel noted that Section 5.10 of the Protelos summary of product characteristics (SPC) referred to *in vitro* pharmacodynamic data and concluded that there was a rebalance of bone turnover in favour of bone formation. Non clinical models showed increases in certain parameters which were said to result in an improvement in bone strength. Biopsies obtained after up to 60 months of treatment showed no deleterious effects on bone quality or mineralisation. Phase III studies showed bone mineral density increased from baseline by approximately 4% per year at the lumbar spine and 2% per year at the femoral neck, reaching 13-15% and 5-6% respectively after 3 years, depending on the study. Biochemical markers of bone formation increased and those of bone resorption decreased from the third month of treatment up to 3 years.

With regard to the clinical data the Panel noted that Meunier *et al* studied the effects of Protelos on the risk of vertebral fracture in PMO. Serum biochemical markers of bone formation were statistically significantly increased in the Protelos group compared with placebo; markers showing bone resorption were statistically significantly decreased compared with placebo. The authors stated that the mechanism of action of strontium ranelate was yet to be understood but was probably different from other agents. Most antiresorptive agents prevented bone loss by reducing the rate of bone remodelling as reflected by a decrease in markers of bone resorption and bone formation.

Arlot *et al* assessed the mechanism of action of strontium ranelate at the cell or bone tissue level and evaluated bone safety. Bone biopsies confirmed the positive effects on bone formation. The authors stated that the findings '…indicate the stimulating effects of strontium ranelate on the osteoblastic population and [mineral apposition rate] and a moderate decrease on bone resorption. They are in agreement with the increase of biochemical markers of formation and the decrease of those of resorption shown in clinical studies and confirm the dual mode of action of strontium ranelate, rebalancing the bone metabolism in favor of formation'.

The Panel did not consider that given all the data the basis of the claim that Protelos was a dual action bone agent was sufficiently clinically robust. In relation to the mechanism of action of strontium ranelate, Meunier *et al*, on the basis of biochemical data, used the phrases '…being probably different to other medicines' and 'apparent dissociation between reduced bone resorption and increased bone formation'. The bone biopsy data, Arlot *et al* showed that Protelos had a statistically significant positive effect on bone formation but produced only a trend towards a decrease in bone resorption. Arlot *et al* also stated that at the tissue level there was no significant change in activation frequency. The Panel accepted that there was some data to show that Protelos both increased bone formation and decreased bone resorption but considered that the situation was more complicated than implied by the strong, unequivocal claim 'dual action bone agent'. Readers would assume in the absence of information to the contrary that there was clinical evidence for the claim. In the Panel's view the clinical data, particularly with regard to bone resorption, was not sufficient. The Panel considered that the claim was misleading and not capable of substantiation. Breaches of the Code were ruled. The Panel similarly ruled the claim 'the only drug to simultaneously increase bone formation and

decrease bone resoprtion' to be in breach of the Code.

Upon appeal by Servier the Appeal Board noted that the article in the D&TB had not criticised the context in which the claims had been used, just the claims *per se*.

The Appeal Board considered that there was data to show that, as statements of fact, Protelos was 'the first dual action bone agent' and 'the only drug to simultaneously increase bone formation and decrease bone resorption'. The Appeal Board noted that in this therapy area biochemical markers were well accepted as surrogate markers of clinical action. The biochemical data showed that Protelos increased bone formation and decreased bone resorption. Although the bone biopsy data was less robust it nonetheless mirrored the biochemical data. The Appeal Board noted that it was difficult to obtain bone biopsies, particularly paired biopsies. Such data contributed to the evidence base for the medicine but was only a part of it.

The Appeal Board considered that there was data to support the claims that Protelos was 'the first dual action bone agent' and that it was 'the only drug to simultaneously increase bone formation and decrease bone resorption'. No breach of the Code was ruled.

The Appeal Board noted that its rulings above were based on the claims at issue as statements of fact; it had not ruled on their use in promotional material. The context in which such claims were used, however, was important. The Appeal Board was concerned that the claims, although true in themselves, had been used in such a way in the Protelos promotional material supplied by Servier as to imply clinical superiority over other medicines. There was no data to support this implication. The Appeal Board requested that Servier be advised of its concerns in this regard and should review the context in which the claims were made.

An article entitled 'Strontium ranelate for osteoporosis' which appeared in the Drug and Therapeutics Bulletin of April 2006 criticised the promotion of Protelos (strontium ranelate) by Servier Laboratories Ltd. In accordance with established practice the matter was taken up by the Director as a complaint under the Code.

Protelos was indicated for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures.

COMPLAINT

The authors of the article stated that in their view there was no convincing published clinical evidence to support the claims 'the first dual action bone agent' and 'the only drug to simultaneously increase bone formation and decrease bone resorption'. Although the evidence base for the claims was bone marker data from clinical trials, the authors noted that bone biopsies provided a more definitive assessment of bone formation and resorption and had not shown that Protelos stimulated bone formation or resulted in positive remodelling imbalance.

When writing to Servier, the Authority asked it to respond in relation to Clauses 7.2 and 7.4 of the Code.

RESPONSE

Servier disagreed with the views of the authors and did not agree that the claims 'the first dual action bone agent' and 'the only drug to simultaneously increase bone formation and decrease bone resorption' were not accurate, balanced, fair, objective and unambiguous. Servier considered that the claims did not mislead either directly or by implication and that they could be substantiated.

Overall, Servier was very disappointed with the article for a number of reasons. Servier did not consider that the article was a balanced and fair reflection of all the data for Protelos and there appeared to be a number of crucial factual inaccuracies within it. Additionally, specific opinions of the authors did not seem to be consistent with those of other independent experts as detailed in a number of peer reviewed publications and documents approved by regulatory agencies.

The mode of action of Protelos had been clearly demonstrated and acknowledged to increase bone formation and decrease bone resorption. The summary of product characteristics (SPC) for Protelos, section 5.1, Pharmacodynamic properties, stated:

'*In vitro*, strontium ranelate:
increases bone formation in bone tissue culture as well as osteoblast precursor replication and collagen synthesis in bone cell culture;
reduces bone resorption by decreasing osteoclast differentiation and resorbing activity.
This results in a rebalance of bone turnover in favour of bone formation.

The activity of strontium ranelate was studied in various non-clinical models. In particular, in intact rats, strontium ranelate increases trabecular bone mass, trabeculae number and thickness; this results in an improvement of bone strength.

In phase III studies, as compared to placebo, biochemical markers of bone formation (bone-specific alkaline phosphatase and C-terminal propeptide of type I procollagen) increased and those of bone resorption (serum C-telopeptide and urinary N-telopeptide cross links) decreased from the third month of treatment up to 3 years.'

Additionally, in the patient information leaflet (PIL), approved by the EMEA, in the section titled 'How Protelos works', it was stated 'Protelos works by reducing bone breakdown and stimulating rebuilding of bone and therefore reduces the risk of fracture. The newly formed bone is of normal quality'.

Servier considered that the above text taken directly from the SPC and PIL for Protelos clearly reflected that, from the sum of *in vitro*, *in vivo* and clinical data, Protelos did increase bone formation and decrease bone resorption as claimed.

In the promotion of Protelos Servier simply acknowledged that Protelos had been shown to 'de-couple' the otherwise tightly linked resorption-formation sequence of adult bone remodelling causing

an increase in bone formation and decrease in bone resorption. As no other product had been shown to 'de-couple' bone formation and resorption (on the contrary all other products that increased bone formation also increased bone resorption and all other products that decreased bone resorption also decreased bone formation), Protelos was the only medicine that actually increased bone formation and decreased bone resorption simultaneously.

Servier could therefore justify the claim 'the only drug to simultaneously increase bone formation and decrease bone resorption'.

There were a number of peer-reviewed publications that also supported the dual action of Protelos in humans. Meunier *et al* (2004) stated:

'Most antiresorptive agents prevent bone destruction by reducing the rate of bone remodeling, as reflected by a decrease in both markers of bone resorption (more than 50 percent with bisphosphonates and about 30 percent with raloxifene) and markers of bone formation (about 50 percent with bisphosphonates and 20 percent with raloxifene). Treatment with parathyroid hormone increases both bone formation and bone resorption. When parathyroid hormone and alendronate are combined, there is, unexpectedly, no potentiation of their effects on biochemical bone markers. The mechanism of action of strontium ranelate is probably different from those of these drugs. Each time the patients were evaluated during our study, bone formation had increased in the group assigned to strontium ranelate, on the basis of serum concentrations of bone-specific alkaline phosphatase, and bone resorption had decreased, on the basis of serum concentrations of C-telopeptide cross-links, as compared with the values in the placebo group. The changes in biochemical markers of bone resorption and formation were most pronounced during the first six months; the dissociation between the bone markers was evident throughout the study. The mechanisms for the apparent disassociation between reduced bone resorption and increased bone formation are not yet understood, but they probably differ from the mechanisms of current treatments.'

Reginster *et al* (2003) stated: 'Strontium ranelate (SR) is a new antiosteoporotic agent demonstrated to increase in bone formation and decrease bone resorption in preclinical and clinical studies.'

Drugs in Context (2005) stated: 'Strontium ranelate is an antiosteoporotic agent with a unique mechanism of action, and is indicated for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures.'

'By promoting bone formation and reducing bone resorption, strontium ranelate uncouples the bone remodeling process in a favourable manner.'

Disease Reviews in Primary Care (2005) stated: 'In contrast to agents such as SERMs and bisphosphonates, which act by inhibiting bone resorption and anabolic agents such as parathyroid hormone which increase bone formation, pharmacological studies have demonstrated that strontium ranelate has a novel dual mechanism of action resulting in a decrease in bone resorption and an increase in bone formation, thereby resulting in increased bone mass.'

The authors of the article in The Drug and Therapeutics Bulletin stated 'However, bone biopsies provide a more definitive assessment of bone formation and resorption and have not shown that strontium ranelate stimulates bone formation or results in positive remodelling imbalance.'

This statement was factually incorrect; bone biopsy data for strontium ranelate showed a statistically significant increase in bone formation and a decrease in bone resorption (the latter did not reach statistical significance, Arlot *et al* 2005).

The published bone biopsy data for strontium ranelate considered in isolation without taking into account *in vitro*, animal data and human clinical trial (bone biomarker data) would not provide an accurate, balanced, fair, objective and unambiguous assessment of bone formation and resorption or be an up-to-date evaluation of all the evidence. Arlot *et al* performed a limited number of biopsies only five of which were paired biopsies. The second biopsies in the pairs were taken at varying time points, 1 to 5 years, and the results pooled. Clearly this data should not be used in isolation to support or oppose the dual action of strontium ranelate.

Interestingly Arlot *et al* concluded that 'These results demonstrate that the primary mineralization rate is not impaired, but on the contrary stimulated by SR [strontium ranelate]. All these findings indicate the stimulating effects of strontium ranelate on the osteoblastic population and MAR [mineral apposition rate] and a moderate decrease in bone resorption. They are in agreement with the increase of biochemical markers of formation and the decrease of those of resorption shown in clinical studies and confirm the dual mode of action of strontium ranelate, rebalancing the bone metabolism in favour of formation.'

In summary, it had been clearly demonstrated and acknowledged that Protelos was 'The first dual action bone agent' and 'the only drug to simultaneously increase bone formation and decrease bone resorption'. Servier considered that these claims in its materials complied with the requirements of Clauses 7.2 and 7.4 of the Code.

PANEL RULING

The Panel noted that Protelos was indicated for the treatment of postmenopausal osteoporosis (PMO) to reduce the risk of vertebral and hip fractures. Information was given in Section 5.1 of the SPC regarding pharmacodynamics. This referred to *in vitro* data which concluded that there was a rebalance of bone turnover in favour of bone formation. Non clinical models showed increases in certain parameters which were said to result in an improvement in bone strength. Biopsies obtained after up to 60 months of treatment at 2g per day showed no deleterious effects on bone quality or mineralisation. Phase III studies showed bone mineral density increased from baseline by approximately 4% per year at the lumbar spine and

2% per year at the femoral neck, reaching 13-15% and 5-6% respectively after 3 years, depending on the study. Biochemical markers of bone formation increased and those of bone resorption decreased from the third month of treatment up to 3 years.

With regard to the clinical data the Panel noted that Meunier *et al* studied the effects of Protelos on the risk of vertebral fracture in PMO. Serum biochemical markers of bone turnover were measured. Markers showing bone formation were statistically significantly increased in the Protelos group compared with placebo. Markers showing bone resorption were statistically significantly decreased in the Protelos group compared with placebo. The authors stated that the mechanism of action of strontium ranelate '… is probably different from ...' antiresorptive agents, bisphosphonates, raloxifene and parathyroid hormone. Most antiresorptive agents prevented bone destruction by reducing the rate of bone remodelling as reflected by a decrease in both markers of bone resorption (more than 50% with bisphosphonates and about 30% with raloxifene) and bone formation (about 50% with bisphosphonates and 20% with raloxifene).

Meunier *et al* also stated that the mechanisms for the apparent dissociation between reduced bone resorption and increased bone formation were not yet understood but they probably differed from those of current treatments.

Reginster *et al* stated that strontium ranelate demonstrated an increase in bone formation and a decrease bone resorption in preclinical and clinical studies but did not produce any primary data in support of that statement.

Arlot *et al* assessed the mechanism of action of strontium ranelate at the cell or bone tissue level and evaluated bone safety. Bone biopsies were obtained in a subset of patients from SOTI, TROPOS and STRATOS studies (49 treated and 87 untreated). The positive effects on bone formation were confirmed by a significant higher osteoblastic surfaces in treated compared with untreated (+38% p=0.047) and by a significantly greater Mineral Apposition Rate in cancellous and cortical bone. (+8% p=0.008 and +11% p=0.033 respectively). At the tissue level there was no significant change in activation frequency. The effects on resorption consisted of a trend towards lower endosteal eroded surfaces, endosteal and cancellous osteoclast surfaces and osteoclast number (–14, –6% –9%, –9% NS respectively). The authors stated that with the higher osteoblastic surfaces in treated patients it was expected to also observe higher osteoclast surfaces, which was not the case, confirming the dual mode of action of strontium ranelate.

The authors stated that the findings '…indicate the stimulating effects of strontium ranelate on the osteoblastic population and MAR and a moderate decrease on bone resorption. They are in agreement with the increase of biochemical markers of formation and the decrease of those of resorption shown in clinical studies and confirm the dual mode of action of strontium ranelate, rebalancing the bone metabolism in favor of formation'.

The Panel noted that the Drugs and Therapeutic Bulletin stated that bone biopsies provided a more definitive assessment of bone formation and resoprtion and these had not shown that strontium ranelate stimulated bone formation or resulted in positive remodelling imbalance. It was not clear to which data the article was referring to in this regard. The article had not cited Arlot *et al* which had been presented in late September 2005 and was available as an abstract. It was thus unclear whether the authors of the Drugs and Therapeutics Bulletin article had considered Arlot *et al*.

Servier stated that Arlot *et al* performed a limited number of biopsies only five of which were paired biopsies with the second biopsies taken at varying time points, 1 to 5 years, and the results pooled. Servier stated that this data should not be used in isolation to support or oppose the dual action of Protelos.

The Panel noted the claims highlighted by the Drugs and Therapeutic Bulletin were 'dual action bone agent' and 'the only drug to simultaneously increase bone formation and decrease bone resorption'.

On examining the promotional material provided by Servier, the Panel noted that the claim 'a dual action bone agent' was made in for example a GP fact file (05PR335) and the claim 'the first dual action bone agent' was made on post it notes (05PR288) and a detail aid (05PR294).

The Panel did not consider that given all the data the basis of the claim that Protelos was a dual action bone agent was sufficiently clinically robust. In relation to the mechanism of action of strontium ranelate, Meunier *et al*, on the basis of biochemical data, used the phrases '…being probably different to other medicines' and 'apparent dissociation between reduced bone resorption and increased bone formation'. The bone biopsy data was not as described in the Drug and Therapeutics Bulletin; Arlot *et al* showed that Protelos had a statistically significant positive effect on bone formation but produced only a trend towards a decrease in bone resorption. Arlot *et al* also stated that at the tissue level there was no significant change in activation frequency. The Panel accepted that there was some data to show that Protelos both increased bone formation and decreased bone resorption but considered that the situation was more complicated than implied by the strong, unequivocal claim 'dual action bone agent'. Readers would assume in the absence of information to the contrary that there was clinical evidence for the claim. In the Panel's view the clinical data, particularly with regard to bone resorption, was not sufficient. The Panel considered that the claim was misleading and not capable of substantiation. Breaches of Clauses 7.2 and 7.4 of the Code were ruled.

The claim 'the only drug to simultaneously increase bone formation and decrease bone resoprtion' appeared in the GP fact file (O5PR11) and a leavepiece 05PR386 referenced to Arlot *et al* and Marie *et al* (2001). The Panel considered its ruling with regard to the claim 'dual action bone agent' was relevant. The clinical data, particularly with regard to bone

resorption, was not as equivocal as the impression given by the claim now at issue. Thus the Panel ruled breaches of Clauses 7.2 and 7.4 of the Code.

APPEAL BY SERVIER

Servier submitted that healthy human bone was maintained by a constant turnover of bone tissue. Bone was constantly being broken down (or resorbed) and new bone was constantly being laid down (or formed); formation and resorption were tightly linked and in balance in healthy bone. After the menopause there was an increase in bone resorption and a decrease in bone formation. This led to a decrease in bone mass and caused bone thinning resulting in reduced bone strength and increased fracture risk.

Servier submitted that all anti-osteoporotic agents on the market in the UK worked by having a beneficial effect either on bone formation or on bone resorption. As formation and resorption were tightly linked, all agents also had a negative feedback effect opposite to their single beneficial mode of action. Therefore antiresorptive therapies also reduced bone formation. Likewise bone-forming therapies also increased bone resorption. The beneficial effect of all anti-osteoporotic agents either on resorption or formation was greater than the complementary negative effect and hence restored the overall ratio of formation:resorption in a positive manner (Meunier *et al*).

Servier submitted that in medical practice all anti-osteoporotic treatments were classified and referred to relative to their mode of action. For example bisphosphonates were known as antiresorptives (or inhibitors of bone resorption) and teriparatide was known as a bone-forming agent (or a stimulator of bone formation). This terminology was widely accepted in medical practice and in only one product (teriparatide) was there definitive histomorphometric (bone biopsy) data. For all other anti-osteoporotic agents this terminology was based solely on biochemical markers of bone turnover from clinical trials.

Servier submitted that the importance of biochemical markers of bone turnover as clinical data to evaluate the mode of action of anti-osteoporotic agents could not be overstated. It was widely accepted not only in medical practice but also by the regulatory authorities that biochemical markers of bone turnover provided clinically robust evidence to support the mode of action of medicines used in the treatment of PMO. Servier noted that biochemical markers of bone turnover were surrogate markers but they were surrogate markers of fracture/bone mineral density (BMD) not of bone biopsy data. Even though biochemical markers of bone turnover were surrogate markers for fracture/BMD they were also used directly to establish the mode of action of anti-osteoporotic agents.

Servier submitted that the EMEA note for guidance on PMO (adopted by the CPMP January 2001), which was intended to provide guidelines for the evaluation of new medicines in the prevention and treatment of PMO stated in Section 4.3 'Criteria of efficacy and their assessment 4.3.4 Biochemical Markers' that 'Biochemical markers of bone turnover are used to evaluate the mechanism of action of drugs and the integrated effect on bone'. Thus from a regulatory perspective biochemical markers of bone turnover were used to categorise anti-osteoporotic agents as either inhibitors of bone resorption or stimulators of bone formation. The only mention of histomorphometry (bone biopsies) in the EMEA guideline was in Section 4.4 entitled 'Criteria of safety and their assessment'. Here it was clearly recommended that bone biopsies should be taken 'with the aim to disclose any potentially negative effects of the drug on bone remodelling as well as in an attempt to characterise its effects on bone remodelling balance or mineralization'. In summary, from a regulatory perspective, biochemical markers of bone turnover were used to evaluate the mechanism of action of anti-osteoporotic agents. Bone biopsies should primarily be taken to assess safety on bone but also in an attempt to characterize effects on bone remodelling.

Protelos was studied in two large phase III clinical trials SOTI (The Spinal Osteoporosis Therapeutic Intervention Trial) (Meunier *et al*) and TROPOS (Treatment of Peripheral Osteoporosis) (Reginster *et al* 2005). Strontium ranelate was studied in over 1700 patients in these two trials, patient numbers far in excess of any other phase III osteoporosis program to date. In both clinical trials strontium ranelate simultaneously had statistically significant effects on markers of bone formation and bone resorption.

Marker	*SOTI*	*TROPOS*
Bone alkaline phosphatase (formation)	($p < 0.005$)	($p < 0.012$)
C-terminal propeptide of type 1 procollagen (formation)	($p < 0.001$)	($p < 0.001$)
Serum N-terminal cross-linked telopeptide (resorption)	($p < 0.001$)	Not measured
Urinary N-terminal cross-linked telopeptide (resorption)	Not measured	($p < 0.001$)

Data in both studies using the ITT population, from 0-36 months, compared to placebo,
n = 1649 in SOTI, n = 5091 in TROPOS.

Servier submitted that strontium ranelate clearly had a beneficial effect on both bone formation and bone resorption in humans. This was different to all other anti-osteoporotic agents as detailed above (an increase in formation would normally be accompanied by an increase in resorption and vice versa). Strontium ranelate therefore uncoupled the otherwise tightly linked formation: resorption process, having a positive effect on both aspects of the bone remodelling process. As a result, strontium ranelate could not be classified simply as an antiresorptive agent or a bone-forming agent as this would clearly be misleading.

Servier noted that in the promotion of Protelos it was not making any comparisons to any other therapies or

any claims around the magnitude of increase in bone formation or decrease in bone resorption. Servier simply stated that Protelos had been shown to 'uncouple' the otherwise tightly linked resorption-formation sequence of adult bone remodeling causing an increase in bone formation and decrease in bone resorption. All data to date supported this dual mode of action.

Servier submitted that the limited bone biopsy data (Arlot *et al*) for strontium ranelate (only 5 paired biopsies) demonstrated a statistically significant increase in bone formation and a decrease in bone resorption. Whilst the decrease in bone resorption did not reach statistical significance there was a decrease. As described previously, due to the tightly linked process of bone formation and bone resorption it would be expected to see an increase in bone resorption as well as bone formation from biopsy data. This was not the case with strontium ranelate. Whilst the biopsy data, in relation to bone resorption did not reach statistical significance it had demonstrated a reduction in bone resorption and therefore was consistent with the *in vitro*, animal and human biochemical markers of bone turnover data supporting the dual mode of action of strontium ranelate.

Servier submitted that all the data considered above (biochemical markers of bone turnover and histomorphometric data) were available and submitted to the EMEA and evaluated during the licensing procedure. There were no new data that might alter any conclusions reached by the EMEA after evaluation of the data for strontium ranelate and therefore this was an up-to-date evaluation of all the evidence.

Servier submitted that as strontium ranelate had a positive effect on bone formation and a positive effect on bone resorption it had two actions. Because no other anti-osteoporotic agent had a positive effect on both aspects of bone remodeling, strontium ranelate was the only osteoporosis treatment to have these two actions and therefore was the 'only dual action bone agent' which 'simultaneously increases bone formation and decreased bone resorption' as claimed.

Servier stated again that there were a large number of independent peer-reviewed publications that had also assessed the data for strontium ranelate and described the 'dual mode of action'. Furthermore both the BNF and MIMS described strontium ranelate as a 'dual action bone agent'.

Servier submitted that in addition to the large number of independent, peer-reviewed publications and widely accepted independent medical publications which described the 'dual mode of action' of strontium ranelate, there were two independent reviews commissioned by the National Institute for Health and Clinical Excellence (NICE) during the Health Technology Appraisal of strontium ranelate in 2005. The first review stated:

'Strontium ranelate is a dual action bone agent, which reduces bone resorption and increases bone formation. Biochemical markers of bone turnover suggest that the antiresorptive effect of strontium is less than observed with bisphosphonate treatment, whereas the anabolic action is weaker than seen with teriparatide. Nevertheless, this uncoupling of bone resorption and formation is not seen with other osteoporosis treatments and might be expected to improve bone mineral density (BMD) and architecture, thereby decreasing the risk of fracture'.

The second review, stated:

'It is different in its mode of action by being a dual action bone agent (DABA) with properties of increasing bone formation and reducing bone resorption. These actions are in contrast to commonly used antiresorptive agents such as the bisphosphonates and selective estrogen receptor modulators …'.

Servier submitted that in summary, biochemical markers of bone turnover were used scientifically, in medical practice and by regulatory authorities as an appropriate and accepted evaluation of the mechanism of action of anti-osteoporotic agents. In extensive phase III clinical trials strontium ranelate had demonstrated statistically significant increases in biochemical markers of bone formation and statistically significant decreases in biochemical markers of bone resorption. Servier considered that this data, consistent with all other data for strontium ranelate demonstrated an increase in bone formation and a decrease in bone resorption, was sufficiently clinically robust to support the claims that Protelos was 'The first dual action bone agent' and 'the only drug to simultaneously increase bone formation and decrease bone resorption'. Servier submitted that data presented above supported the reasons why these claims were accurate, balanced, fair, objective and unambiguous and based on an up-to-date evaluation of all the evidence and reflected that evidence clearly. The evidence presented demonstrated that the claims in question did not mislead either directly or by implication, by distortion, exaggeration or undue emphasis and that they were capable of substantiation.

Therefore, Servier submitted that the claims in question complied with the requirements of Clauses 7.2 and 7.4 of the Code.

COMMENTS FROM DRUG AND THERAPEUTICS BULLETIN

The Drug and Therapeutics Bulletin (D&TB) stated that it had concerns about the self regulation process and consequently did not in general take complaints to the Authority and rarely commented on appeals. It however wanted to take the opportunity of restating the D&TB position on the promotion of Protelos.

The D&TB noted that the article stated 'In our view, there is no convincing published evidence to support promotional claims that the drug simultaneously stimulates bone formation and reduces bone resorption. Such claims should, therefore, be treated with scepticism and should not sway decisions on whether or not to use the drug'. In reaching this view, the D&TB stated that it had considered the available data on biochemical markers of bone formation and bone resorption and this evidence was cited and discussed in its article. The D&TB accepted that such

evidence was useful in helping to classify the mechanism of action of medicines in osteoporosis. However, as the article indicated, the D&TB considered that data on biochemical markers alone were insufficient and that bone biopsies provided a more definitive assessment of bone formation and resorption, particularly where a wholly new mechanism of action was being suggested. The D&TB found no fully published data to confirm that strontium ranelate simultaneously increased bone formation and reduced bone resorption. The D&TB stated that it had assessed the bone biopsy data (Arlot *et al*) but had not cited it in the article because the study was published only as an abstract and its general policy was to base conclusions primarily on data that had been published in full in peer-reviewed journals. In addition, the study was small. Even if these key limitations were overlooked, the data did not provide convincing confirmatory evidence of a 'dual action' for strontium ranelate, given that it did not find a statistically significant reduction in bone resorption.

The D&TB noted that Servier had widely publicised on a European news release the idea that Arlot *et al* 'provided scientific proof that the novel anti-osteoporotic agent [strontium ranelate] had a dual mechanism of action that was completely different from existing treatments'. The notion that bone-biopsy data would 'provide scientific proof' of the mechanism of action seemed entirely in keeping with the D&TB's view that 'bone biopsies provide a more definitive assessment of bone formation and resorption'. The D&TB submitted that this fact, and the described limitations of Arlot *et al*, made it difficult to see on what basis Servier could question its opinion about the place of and need for bone-biopsy evidence without contradicting its own publicly expressed view on this topic. This view was echoed in Servier's appeal, which stated 'in only one product was there definitive histomorphometric (bone biopsy) data'. Servier's use of the word 'definitive' in describing bone biopsy data was very similar to its suggestion that such evidence would represent 'scientific proof' of strontium ranelate's mechanism of action. It therefore followed that the lack of such 'proof' must be legitimate grounds for questioning the promotional claims of a dual action for strontium ranelate.

The D&TB stated that while it continued to question the evidential basis for the claims about Protelos, it was important to note that these doubts were not, in fact, the main problem associated with the promotion. The key issue was how these claims had been used and could easily be misinterpreted, regardless of whether or not the medicine had been proven to have a dual mechanism of action. The use of the claims 'the first dual action bone agent' and the 'the only drug to simultaneously increase bone formation and decrease bone resorption' in the promotional material more than merely indicated a new mechanism of action in osteoporosis. In particular, 'first' and 'only' obviously marked a contrast with other medicines; and in this context, the repeated, unqualified emphasis of dual action suggested that Protelos offered definite therapeutic advantages over, 'single-action', therapies. This was unhelpful and served only to obscure a key question: how the clinical efficacy (and not simply the mechanism of action) of Protelos compared with that of other, longer-established treatments for osteoporosis. Given the absence of any published randomised comparisons between Protelos and other treatments, the claimed dual action of Protelos had no proven relevance in terms of the absolute and comparative magnitude of Protelos's clinical benefit, as the company appeared to accept in its appeal. This was the basis of the D&TB's view that the claims about the mechanism of action of Protelos should not be allowed to sway clinical decisions on whether to use the medicine.

In summary, D&TB alleged that there was a lack of convincing bone-biopsy data to confirm that Protelos both stimulated bone formation and reduced bone resorption. Since Servier had publicly labelled this type of evidence as 'scientific proof' of Protelos' claimed mechanism of action, the company was now poorly placed to downgrade the need for such confirmatory information. Also, promotional claims that Protelos was the first and only dual-action medicine for osteoporosis should not masquerade as, or hide the absence of, published evidence that the treatment's clinical efficacy matched, let alone exceeded, that of other longer-established therapy.

APPEAL BOARD RULING

The Appeal Board noted that the article in the D&TB, which had formed the basis of the complaint, had stated that there was no convincing published clinical evidence to support the claims 'the first dual action bone agent' and 'the only drug to simultaneously increase bone function and decrease bone resorption'. The article had not criticised the context in which the claims had been used, just the claims *per se*. The Appeal Board noted that although in its response to the appeal, the D&TB had expressed concerns about the way in which the claims had been used, these concerns could not be considered as part of the appeal as they had not been raised in the original article.

The Appeal Board considered that there was data to show that, as statements of fact, Protelos was 'the first dual action bone agent' and 'the only drug to simultaneously increase bone formation and decrease bone resorption'. The Appeal Board noted that in this therapy area biochemical markers were well accepted as surrogate markers of clinical action. The biochemical data showed Protelos increased bone formation and decreased bone resorption. Although the bone biopsy data was less robust it nonetheless mirrored the biochemical data. The Appeal Board noted that it was difficult to obtain bone biopsies, particularly paired biopsies. Such data contributed to the evidence base for the medicine but was only a part of it.

The Appeal Board considered that there was data to support the claim that Protelos was 'the first dual action bone agent' and thus ruled no breach of Clauses 7.2 and 7.4 of the Code. The appeal on this point was successful.

The Appeal Board similarly considered that there was data to support the claim that Protelos was 'the only drug to simultaneously increase bone formation and

decrease bone resorption' and thus ruled no breach of Clauses 7.2 and 7.4 of the Code. The appeal on this point was successful.

The Appeal Board noted that its rulings above were based on the claims at issue as statements of fact; it had not ruled on their use in promotional material. The context in which such claims were used, however, was important. The Appeal Board was concerned that the claims, although true in themselves, had been used in such a way in the Protelos promotional material supplied by Servier as to imply clinical superiority over other medicines. There was no data to support this implication. The Appeal Board requested that Servier be advised of its concerns in this regard and should review the context in which the claims were made.

Proceedings commenced **6 April 2006**

Case completed **21 June 2006**

CASE AUTH/1825/4/06

PROSTRAKAN v SHIRE

Calcichew-D_3 Forte journal advertisement

ProStrakan complained about a journal advertisement for Calcichew-D_3 Forte (calcium carbonate, colecalciferol) issued by Shire. The claim at issue, 'Chew Calcichew-D_3 Forte for Ten Seconds for a pleasant surprise. In a comparative study, Calcichew-D_3 Forte was preferred over Adcal-D_3 by 80% of patients', was referenced to Rees and Howe (2001).

ProStrakan alleged that the claim was unfair and misleading. Calcichew-D_3 Forte was a chewable tablet containing 1250mg calcium carbonate (equivalent to 500mg of elemental calcium) plus 400 IU vitamin D_3. Adcal-D_3 was a chewable tablet containing 1500mg calcium carbonate (equivalent to 600mg of elemental calcium) plus 400 IU cholecalciferol (vitamin D_3). Rees and Howe was a randomised, investigator-blind, crossover, multicentre study of seven days' treatment in 102 patients ≥ 60 years already receiving daily calcium and vitamin D supplements. At the time of recruitment 64% had been established on Calcichew-D_3 Forte; the proportion of patients already on Adcal-D_3 was unknown, although its market share at the time was 4-8%. This was important as the trial was open from the patients' perspective and the tablets were quite different in terms of calcium carbonate content and this could have a significant impact on the results as calcium carbonate contributed the vast majority of the bulk of the tablet. Assessment of preference was determined through the use of a questionnaire using a visual analogue scale. The results were statistically in favour of the Calcichew-D_3 Forte, with a preference of 79.8%. ProStrakan stated that there were no explanations of the rationale for the questions within the study, nor the clinical relevance to the patient as this was a non-standardised questionnaire.

ProStrakan alleged that there might have been statistical differences generated, apparently using a methodology not pre-specified in the protocol, despite this the median values were very similar in most cases, with significant overlap in the range. On closer examination of the results, the questions appeared biased against a tablet containing more calcium carbonate eg chalky and gritty. This would naturally bias the study against Adcal-D_3.

Currently there were two other combination supplements on the market, Cacit D3 (calcium 1250mg, vitamin D_3 440 IU) and Calceos (calcium 1250mg, vitamin D_3 440 IU), which were the same dose as Calcichew-D_3 Forte. For a taste preference study to be fair a comparison between brands with the same constitution would seem fair.

In addition ProStrakan alleged that the claim would mislead readers into believing that preferred was not quantified, which could potentially lead the reader to believe that there was a compliance difference between the products, data for which had not been provided.

ProStrakan alleged that this unfair comparison of Adcal-D_3 and Calcichew-D_3 Forte was of significant importance clinically, as a substantial body of evidence demonstrated a clinical benefit for a 1200mg dose of calcium carbonate (Adcal-D_3) compared with a 1000mg dose (Calcichew-D_3 Forte). This was misleading as the two products were not comparable and the claim was out of context. The relevant clinical papers and a review of this data were provided for context.

Section 5.1 of the Adcal-D_3 summary of product characteristics (SPC) further reinforced the differences which stated that there was strong evidence that supplemental calcium and vitamin D_3 could reduce the incidence of hip and other non-vertebral fractures. In a randomised placebo controlled study, 3270 patients treated with 1200mg elemental calcium and 800 IU vitamin D_3 daily, ie, the same dose delivered by two tablets of Adcal-D_3, the number of hip fractures was 43% lower (p=0.043) and the total number of non-vertebral fractures was 32% lower than among those who received placebo. A positive effect on bone mineral density was also observed. The Calcichew-D_3 Forte SPC contained the same data (Chapuy *et al*) stating the important dose was 1200mg/day of elemental calcium.

ProStrakan alleged that Rees and Howe and the subsequent claims were unfair and misleading, as the two products were not comparable in outcomes or dosing and the claim was out of context.

The Panel noted that the aim of Rees and Howe was to compare the acceptability of Calcichew-D_3 Forte with Adacal-D_3. Both products had similar

indications and although they had different constituents the Panel considered that it was not unreasonable to compare the two. Patients (n=102) took Calcichew-D_3 for seven days followed by Adcal-D_3 for seven days or vice versa. At the end of each study period patients used visual analogue scales to indicate palatability in terms of grittiness, chalkiness, taste (bitter or sweet), ease of chewing, ease of swallowing and stickiness of each product; there was no difference between the two with regard to taste. The five other parameters were statistically significantly in favour of Calcichew-D_3 Forte. After the second study period patients were asked which treatment they preferred.

The Panel considered that most readers of the advertisement would assume that 80% of patients preferred Calcichew-D_3 Forte to Adacal-D_3 because they thought it tasted better. Women in the advertisement were pictured with a smile, the claim was positioned next to their mouth and the product logo incorporated a picture of lemons. In Rees and Howe, however, patients were asked to assess palatability in terms of grittiness, chalkiness, ease of chewing, swallowing and stickiness on teeth as well as taste. The Panel considered that the patients' views on these other parameters had influenced their preference given that there was no difference between the two as to perception of taste.

The Panel queried whether the seven day treatment periods were long enough to assess medicines that were intended for long term use. All patients recruited into the study were already taking calcium supplements; 64% of them were established on Calcichew-D_3 Forte.

The Panel was concerned that insufficient detail was given about what it was that patients preferred about treatment with Calcichew-D_3 Forte compared to treatment with Adcal-D_3. The claim implied that not only did patients prefer Calcichew-D_3 Forte to Adcal-D_3 but they also found it pleasant to take. There was no data in that regard.

The Panel disagreed with Shire's view that the data on efficacy evaluations and health economics were irrelevant to the current complaint which only dealt with the issue of patient preference. The Panel considered that in addition to palatability a patient's knowledge of some of the efficacy evaluations and differences in clinical outcomes between two products might affect their preference for one or the other. Without such knowledge patients would be unable to express a genuine, well informed preference.

Overall the Panel considered that the claim at issue, 'Chew Calcichew-D_3 Forte for Ten Seconds for a pleasant surprise. In a comparative study, Calcichew-D_3 Forte was preferred over Adcal-D_3 by 80% of patients', was a misleading comparison. Thus the Panel ruled breaches of the Code.

ProStrakan Group Plc complained about an advertisement (ref 003/0419a) for Calcichew-D_3 Forte (calcium carbonate, colecalciferol) issued by Shire Pharmaceuticals Ltd which appeared in Pulse, 2 March 2006. The claim at issue, 'Chew Calcichew-D_3 Forte for Ten Seconds for a pleasant surprise. In a comparative study, Calcichew-D_3 Forte was preferred over Adcal-D_3 by 80% of patients', was referenced to Rees and Howe (2001).

Calcichew-D_3 Forte was indicated for the treatment and prevention of vitamin D/calcium deficiency (characterised by raised serum alkaline phosphatase levels associated with increased bone loss, raised levels of serum PTH and lowered 25-hydroxyvitamin D) particularly in the housebound and institutionalised elderly subjects. It was also indicated for the supplementation of vitamin D and calcium as an adjunct to specific therapy for osteoporosis, in pregnancy, in established vitamin D dependent osteomalacia, and in other situations requiring therapeutic supplementation of malnutrition.

ProStrakan marketed Adcal-D_3 which was indicated as an adjunct to specific therapy for osteoporosis and in situations requiring therapeutic supplementation of malnutrition eg in pregnancy and established vitamin D dependent osteomalacia. It was also indicated for the prevention and treatment of calcium deficiency/vitamin D deficiency especially in the housebound and institutionalised elderly subjects. Deficiency of the active moieties was indicated by raised levels of PTH, lowered 25-hydroxy vitamin D and raised alkaline phosphatase levels which were associated with increased bone loss.

COMPLAINT

ProStrakan alleged that the claim was unfair and misleading. Calcichew-D_3 Forte was a chewable tablet containing 1250mg calcium carbonate (equivalent to 500mg of elemental calcium) plus 400 IU vitamin D_3. Adcal-D_3 was a chewable tablet containing 1500mg calcium carbonate PhEur (equivalent to 600mg of elemental calcium) plus 400 IU cholecalciferol (vitamin D_3). Rees and Howe was a randomised, investigator-blind, crossover, multicentre study of seven days' treatment in 102 patients ≥ 60 years already receiving daily calcium and vitamin D supplements as part of their routine management. At the time of recruitment 64% had been established on Calcichew-D_3 Forte; the proportion of patients already on Adcal-D_3 was unknown although its market share at the time was 4-8%. This was important as the trial was open from the patients' perspective and the tablets were quite different in terms of calcium carbonate content (12.5% more in Adcal-D_3). This could have a significant impact on the results (in addition to the significant clinical outcomes delivered by the different doses), as calcium carbonate contributed the vast majority of the bulk of the tablet. The comparison groups were well balanced at baseline. Assessment of preference was determined through the use of a questionnaire assessed using a visual analogue scale designed specifically for this trial. The results were statistically in favour of the Calcichew-D_3 Forte, with a preference of 79.8%.

ProStrakan stated that there were no explanations of the rationale for the questions within the study, nor the clinical relevance to the patient as this was a non-standardised questionnaire. ProStrakan alleged that there might have been statistical differences

generated, apparently using a methodology not pre-specified in the protocol, despite this the median values were very similar in most cases, with significant overlap in the range. On closer examination of the results, the questions appeared biased against a tablet containing more calcium carbonate eg chalky and gritty. This would naturally bias the study against Adcal-D_3.

ProStrakan noted that currently there were two other combination supplements on the market, Cacit D3 (calcium 1250mg, vitamin D_3 440 IU) and Calceos (calcium 1250mg, vitamin D_3 440 IU), which were the same dose as Calcichew-D_3 Forte. For a taste preference study to be fair a comparison between brands with the same constitution would seem fair.

In addition ProStrakan alleged that this claim would mislead readers into believing that preferred was not quantified, which could potentially lead the reader to believe that there was a compliance difference between the products, data for which had not been provided.

ProStrakan alleged that this unfair comparison of Adcal-D_3 and Calcichew-D_3 Forte was of significant importance clinically, as a substantial body of evidence demonstrated a clinical benefit for a 1200mg (Adcal-D_3) compared with a 1000mg dose (Calcichew-D_3 Forte). This was misleading as the two products were not comparable and the claim was out of context. The relevant clinical papers and a review of this data were provided for context.

Chapuy *et al* (1992) was a double-blind placebo controlled randomised trial of 3270 participants in which interim analysis had demonstrated that hip fracture rate was 43% lower (p=0.043), total non-vertebral fractures 32% lower (p=0.015) in the calcium (1200mg)/vitamin D3 (800 IU) group compared to placebo. These results were further reinforced by Chapuy *et al* (2004), in which the results from the end of the 36 months confirmed that non-vertebral fractures were significantly less than placebo ($p<0.01$) as well as hip fractures ($p<0.01$).

ProStrakan further stated that these results were reinforced in Chapuy *et al* (2002) on an at risk population. These data agreed with those from previous studies and indicated that 1200mg of elemental calcium and vitamin D_3 800 IU in combination reversed senile secondary hyperparathyroidism and reduced both hip bone loss and the risk of hip fracture in elderly institutionalised women.

ProStrakan stated that a pharmacoeconomic review of the (elemental) 1200mg calcium and vitamin D 800 IU data, covering seven European countries by Lilliu *et al* (2003) had demonstrated that the supplementation strategy was cost saving with this dose, estimated to be 79,000 – 711,000 Euro per 1000 women.

ProStrakan alleged that the significant body of evidence generated for 1000mg of calcium combined with vitamin D_3 800 IU (Porthouse *et al* 2005, Grant *et al* 2005 and Deroisy *et al* 1998), failed to show the clinically significant reductions in clinically relevant endpoints.

ProStrakan noted that further studies had examined the impact of 1000mg elemental calcium combination vs separate 1200mg calcium and vitamin D. Deroisy *et al* was a one year, open-label, randomised prospective study of two parallel groups in 119 patients. ProStrakan alleged that that this study was methodologically poor with several design flaws, leading to a significant difference in compliance to treatment. This had led to confusing and inconsistent results, with no evidence of equal clinical efficacy.

This large and significant body of evidence suggested that 1000mg of elemental calcium with at least 800 IU vitamin D had a positive effect on bone mineral density (BMD) (Chapuy *et al*, Porthouse *et al*, Grant *et al* and Deroisy *et al*), although there was no significant evidence for clinically and health service relevant outcomes.

ProStrakan noted that Section 5.1 of the Adcal-D_3 SPC further reinforced the differences which stated that there was strong evidence that supplemental calcium and vitamin D_3 could reduce the incidence of hip and other non-vertebral fractures. In a randomised placebo controlled study, 3270 patients treated with 1200mg elemental calcium and 800 IU vitamin D_3 daily, ie, the same dose delivered by two tablets of Adcal-D_3, the number of hip fractures was 43% lower (p=0.043) and the total number of non-vertebral fractures was 32% lower than among those who received placebo. A positive effect on bone mineral density was also observed.

ProStrakan noted that the Calcichew-D_3 Forte SPC contained the same data (Chapuy *et al*) stating the important dose was 1200mg/day of elemental calcium.

ProStrakan alleged that Rees and Howe and the subsequent claims were unfair and misleading, as the two products were not comparable in outcomes or dosing and the claim was out of context and in breach of Clauses 7.2 and 7.3.

RESPONSE

Shire stated that following earlier discussions with ProStrakan, it had agreed on 31 March 2006 to withdraw the advertisement from circulation as soon as was feasible. In particular, Shire agreed to withdraw use of the terms 'Ten Second Trial' and 'Surprisingly Good' which appeared on the second page of the advertisement from future promotional pieces.

Shire submitted that the only point of contention remained the use of material from the comparative palatability and preference study (Rees and Howe), which was justifiable. The emphasis of the complaint concerned the sentence: 'In a comparative study, Calcichew-D_3 Forte was preferred over Adcal-D_3 by 80% of patients'. This study was conducted by an independent clinical research organisation. Shire had not influenced the conduct of the study; Shire's medical director appeared as a co-author only because Shire sponsored the study. This was normal practice and in no way implied any influence on the results by Shire. The study had ethics approval, was conducted in 11 separate GP surgeries and involved 102 patients.

Shire submitted that it was not surprising that 64% of patients had been established on Calcichew-D_3 Forte

as it was the overwhelming market leader at that time. No attempt was made to bias the population in terms of this medicine history. The patients had the clear opportunity to express their preferences and opinions on various palatability parameters, regardless of which product they had previously received. The 64% of patients who had previously received Calcichew-D_3 Forte could have expressed preferences and opinions in favour of Adcal-D_3. The study was of a randomised crossover design to avoid bias and a treatment period on each medicine of seven days was chosen as a reasonable duration in which the patient could form some conclusions about the respective medicines. Inevitably each of the medicines was presented as in the commercial formulation otherwise any conclusions would loose validity.

Shire acknowledged that Adcal-D_3 contained more calcium carbonate than Calcichew-D_3 Forte (20% more, not 12.5% as stated by ProStrakan). The study compared the licensed dosing regimens of the two products. The comparison could not have legitimately been performed in any other way, since one could not break up the tablets. The objective of the study was to compare palatability and preference – not efficacy or safety. Therefore such differences in doses of active constituents were legitimate in the context of this comparison.

Shire submitted that ProStrakan had suggested that the differences in calcium carbonate content of the respective tablets could have a significant impact on the results. The difference was too small for such an inference. In any event, the suggestion provided a reason for an observed difference in preference and differences in palatability of the licensed dosing regimens used in clinical practice. The results in favour of Calcichew-D_3 Forte over Adcal-D_3 reflected the considerable difference between excipients in the two formulations, rather than the small difference in concentrations of one of the active ingredients.

Shire noted that ProStrakan had questioned the rationale for the questions employed in the study. Shire submitted that questions were chosen to investigate palatability differences and preferences between the two products. These comparisons were chosen for the benefit of the patient because of reports from doctors of such differences. The six questions asked on palatability were assessed via the well-established and validated visual analogue scales. The questions were clearly defined in the protocol. The questions were designed to investigate differences between the tablets using obvious features of palatability (grittiness, chalkiness, ease of chewing, ease of swallowing, stickiness, and taste). The p-values for differences in the median visual analogue values for the two products were calculated and quoted.

Shire submitted that it was not clear why ProStrakan raised an issue with palatability questions and answers, since they were not referred to in the advertisement.

Shire submitted that the question on preference was simple and unambiguous; at the end of the 14-day treatment period, the investigator asked the patient:

'Which week's trial treatment did you prefer taking?

Last week's ? This week's ? No preference'

Shire submitted that ProStrakan suggested that the study should have compared Calcichew-D_3 Forte with Cacit D3 or Calceos. There was no reason for Shire to have made such a comparison. There were no reports of poor palatability regarding these products. Incidentally, minimum doses of these two products contained 500mg of calcium – not 1250mg as stated by ProStrakan; and Calceos contained 400 IU (not 440 IU as stated by ProStrakan) of vitamin D. Cacit D3 was presented as a dispersible formulation – which would make palatability comparisons against a Calcichew-D_3 Forte tablet difficult. Further, Cacit D3 contained calcium citrate, not calcium carbonate, as the active calcium source.

Shire noted that ProStrakan had stated that readers might believe that the word 'preferred' was not quantified in the statement 'Calcichew-D_3 Forte was preferred over Adcal-D_3 by 80% of patients'. This statement directly reflected the answer to the simple question specified in the protocol and asked to the patients at the end of the study. Shire submitted that it had been very careful in using this study in its promotional material not to state any compliance advantage for Calcichew-D_3 Forte, as suggested by ProStrakan.

Shire noted that ProStrakan had described at length results from a variety of studies, concentrating on efficacy evaluations and even utilising one health economic argument. Shire submitted that these cited publications were not relevant to the current complaint, which only dealt with the issue of patient preference.

Shire submitted that none of the publications cited by ProStrakan reported results on Adcal-D_3. Published data on Adcal-D_3 (other than those in Rees and Howe) did not exist and ProStrakan had not quoted any Adcal-D_3 studies in its complaint. Some of the publications cited by ProStrakan did not use calcium carbonate (used in Calcichew-D_3 Forte and Adcal-D_3) as the calcium source. For example, calcium phosphate (in sachet formulation) was the active calcium constituent in the 'landmark' Chapuy *et al* study quoted by ProStrakan.

Shire submitted that the comparisons were accurate, balanced, fair, objective and unambiguous. They reflected all the evidence, in that it was not aware of other such comparisons apart from those in the quoted study. The comparisons were not misleading: it was clear that palatability and preference were being compared – not compliance, efficacy or safety. Shire submitted that the cited study had compared medicines intended for the same purpose and compared material, relevant, substantiable and representative features that were important in the practice of clinical medicine. Shire submitted that the claim in question was not in breach of Clauses 7.2 and 7.3 of the Code.

Shire submitted that in conclusion it had merely stated a preference result from a scientifically well-run independent study between licensed doses of two products having the same therapeutic indications.

PANEL RULING

The Panel noted that the aim of Rees and Howe was to compare the acceptability of Calcichew-D_3 Forte with Adacal-D_3. Both products had similar indications and although they had different constituents the Panel considered that it was not unreasonable to compare the two. Patients (n=102) took Calcichew-D_3 for seven days followed by Adcal-D_3 for seven days or vice versa. At the end of each study period patients used visual analogue scales to indicate palatability in terms of grittiness, chalkiness, taste (bitter or sweet), ease of chewing, ease of swallowing and stickiness of each product; there was no difference between the two with regard to taste. The five other parameters were statistically significantly in favour of Calcichew-D_3 Forte. After the second study period patients were asked which treatment they preferred.

The Panel considered that most readers of the advertisement would assume that 80% of patients preferred Calcichew-D_3 Forte to Adacal-D_3 because they thought it tasted better. Women in the advertisement were pictured with a smile, the claim was positioned next to their mouth and the product logo incorporated a picture of lemons. In Rees and Howe, however, patients were asked to assess palatability in terms of grittiness, chalkiness, ease of chewing, swallowing and stickiness on teeth as well as taste. The Panel considered that the patients' views on these other parameters had influenced their preference given that there was no difference between the two as to perception of taste.

The Panel queried whether the seven day treatment periods were long enough to assess medicines that were intended for long term use. All patients recruited into the study were already taking calcium supplements; 64% of them were established on Calcichew-D_3 Forte.

The Panel was concerned that insufficient detail was given about what it was that patients preferred about treatment with Calcichew-D_3 Forte compared to treatment with Adcal-D_3. The claim implied that not only did patients prefer Calcichew-D_3 Forte to Adcal-D_3 but they also found it pleasant to take. There was no data in that regard.

The Panel disagreed with Shire's view that the data on efficacy evaluations and health economics were irrelevant to the current complaint which only dealt with the issue of patient preference. The Panel considered that in addition to palatability a patient's knowledge of some of the efficacy evaluations and differences in clinical outcomes between two products might affect their preference for one or the other. Without such knowledge patients would be unable to express a genuine, well informed preference.

Overall the Panel considered that the claim at issue, 'Chew Calcichew-D_3 Forte for Ten Seconds for a pleasant surprise. In a comparative study, Calcichew-D_3 Forte was preferred over Adcal-D_3 by 80% of patients', was a misleading comparison. Thus the Panel ruled breaches of Clauses 7.2 and 7.3 of the Code.

Complaint received **7 April 2006**

Case completed **5 June 2006**

MEMBER OF THE PUBLIC v PROSTRAKAN

Newspaper article about Rectogesic

A member of the public complained about an article in The Herald in which ProStrakan discussed its reaction to the recent rejection of Rectogesic (glyceryl trinitrate (GTN) rectal ointment) by the Scottish Medicines Consortium (SMC).

ProStrakan was quoted as saying that Rectogesic was 'an ointment for the treatment of anal fissures'. The complainant noted that Rectogesic was licensed only to relieve pain associated with chronic anal fissures. It was not licensed to heal chronic anal fissures nor was it licensed for use in acute anal fissures.

Furthermore, a ProStrakan spokesman was quoted as saying that '[Rectogesic] costs much less than surgery'. The complainant alleged that this comparison was not accurate, balanced, fair, objective and unambiguous, or based on an up-to-date evaluation of all the evidence. Rectogesic was not licensed as an alternative to surgery and nor did the summary of product characteristics (SPC) indicate that its use would prevent the need for surgery. Further, the SMC report did not indicate that ProStrakan had submitted any data that Rectogesic was a cost-effective alternative to surgery for the relief of chronic anal fissure pain.

Furthermore, a ProStrakan spokesman stated that Rectogesic was 'currently the only alternative to surgical treatment'. Putting aside the fact that Rectogesic was not licensed for this purpose this statement was still untrue. The SMC report identified three products which were licensed for the relief of anal fissure pain (Anusol, Anacal and Xyloproct) and stated that there were alternative treatments which were of similar effectiveness to Rectogesic and 'somewhat cheaper'. The comparison was misleading.

Surgery was carried out in order to promote healing of fissures, prevent recurrence and relieve pain and Rectogesic was only licensed for the relief of pain associated with chronic anal fissures. Thus the complainant alleged that comparisons of Rectogesic with surgery were not substantiable.

The complainant alleged that the article presented information on a prescription only medicine to the public in a way which was not fair or balanced. Furthermore, the most common side effect of Rectogesic, headache, was not mentioned in the article. Thus a misleading impression was given that Rectogesic was an entirely safe alternative to surgery.

The Panel noted that the article in the Glasgow Herald included quotations from ProStrakan's spokesperson other statements were not in quotation marks.

The statement that Rectogesic was an ointment for the treatment of anal fissures was not in quotation marks in the article but was attributed to ProStrakan. The article was misleading in this regard but the Panel did not consider this was the responsibility of ProStrakan. In the absence of any detail of what ProStrakan said to the journalist no breach of the Code was ruled.

The Panel did not consider that the claim 'costs much less than surgery' implied that Rectogesic was licensed as an alternative to surgery as alleged but nonetheless noted that if treatment with GTN was unsuccessful surgery might be an option. The Panel did not consider that the statement '… costs much less than surgery' was a comparison that failed to reflect the requirements of the Code and no breach was ruled.

The statement that Rectogesic was the only alternative to surgical treatment was not in quotation marks in the article but was attributed to a ProStrakan spokesman. The article was misleading in this regard but the Panel did not consider this was the responsibility of ProStrakan. In the absence of any detail of what ProStrakan said to the journalist no breach of the Code was ruled.

The Panel did not consider that the fact that the article made no mention of the most common side effect meant that a misleading impression was given that Rectogesic was an entirely safe alternative to surgery. No breach of the Code was ruled.

A member of the public complained about an article in The Herald (a newspaper in Scotland) regarding Rectogesic (glyceryl trinitrate (GTN) rectal ointment), a product of ProStrakan Group plc. Rectogesic was indicated for the relief of pain associated with chronic anal fissure. Treatment was for a maximum of eight weeks.

COMPLAINT

The complaint concerned an article in which ProStrakan discussed its reaction to the recent rejection of Rectogesic by the Scottish Medicines Consortium (SMC). The company was quoted as saying that Rectogesic was 'an ointment for the treatment of anal fissures'. Treatment of anal fissures had two components which were the promotion of healing and the relief of pain. Rectogesic was licensed only for the relief of pain associated with chronic anal fissures. It was not licensed for the healing of chronic anal fissures and it was not licensed for anything at all relating to acute anal fissures. A breach of Clause 3.2 of the Code was alleged.

Furthermore, a ProStrakan spokesman was quoted as saying that '[Rectogesic] costs much less than surgery'. However, Rectogesic was not licensed as an alternative to surgery and nor was there any information in its summary of product characteristics (SPC) indicating that use of Rectogesic would prevent the need for surgery. Neither was there any indication in the report of the SMC that any data was presented to it by ProStrakan indicating that Rectogesic was a cost-effective alternative to surgery for the relief of chronic anal fissure pain. Hence a further breach of Clause 3.2 was alleged.

All claims and comparisons should be accurate, balanced, fair, objective and unambiguous. They should be based on an up-to-date evaluation of all the

evidence and that evidence should be presented clearly. The comparisons of Rectogesic with surgery discussed above did not meet these criteria in breach of Clause 7.2.

Furthermore, a ProStrakan spokesman stated that Rectogesic was 'currently the only alternative to surgical treatment'. If one put to one side for a moment the fact that Rectogesic was not licensed for this purpose and there appeared to be no data or information either in the SMC report or on the SPC to support its use in this way, this statement was still blatantly untrue. The SMC itself, in its report, identified three products which were licensed for the relief of anal fissure pain (Anusol, Anacal and Xyloproct) and stated that there were alternative treatments which were of similar effectiveness to Rectogesic and 'somewhat cheaper'. Hence a further clear breach of Clause 7.2.

A comparison could only be allowed if it was not misleading. The complainant alleged, for reasons stated above, that the comparison with surgery was misleading and hence in breach of Clause 7.3. Furthermore, comparisons should only be made between medicines or services for the same needs or intended for the same purpose. Surgery was carried out in order to promote healing of the fissures, prevent recurrence and relieve pain. Rectogesic was only licensed for the relief of pain associated with chronic anal fissures and hence there was a further breach of Clause 7.3.

Any information, claim or comparison must be capable of substantiation. The comparisons with surgical treatment discussed above were not supported by any information in the article, the SMC report or the SPC and hence one must assume that no substantiation was possible. A breach of Clause 7.4 was alleged.

Information on a prescription only medicine which was made available to the public (either directly or indirectly) must be presented in a fair and balanced way. The complainant did not believe that this article, and ProStrakan's involvement in it, met this criterion and hence Clause 20.2 was breached. Furthermore, particular emphasis was placed in the Code on the fact that information should not be misleading with respect to the safety of the product. The most common side effect of treatment with Rectogesic was apparently headache (SMC report and SPC) but no mention of this was made in the article. Thus a misleading impression was given that Rectogesic was an entirely safe alternative to surgery. A further breach of Clause 20.2.

RESPONSE

ProStrakan provided the press statement from the SMC website which led The Herald newspaper to write the article in question. The publication of the SMC decision was part of its standard operating procedure following a process of review. ProStrakan strongly supported the SMC and actively engaged in a constructive dialogue with it. ProStrakan was surprised at the SMC's decision and had recently been granted an opportunity to resubmit its case for this product in light of new and restructured evidence.

As with all journalists the article's author obtained his information from many sources and, in this case, ProStrakan's discussions with him followed a telephone approach from him precipitated by the public posting of the press statement on the SMC website. In his article the journalist quite clearly differentiated which statements were made by ProStrakan's spokesperson through the use of quotation marks, the rest of his article was his own interpretation and paraphrasing derived from his research. ProStrakan was disappointed that the complainant felt aggrieved by the article; however, ProStrakan believed it had acted within the Code.

ProStrakan provided a copy of the publicly available Prodigy (NHS independent information source) patient information leaflet as well as the SPC, which detailed current treatment practices, and the licensed indication.

ProStrakan addressed each issue in turn:

Clause 3.2 – an ointment for the treatment of anal fissures. The press release quite clearly stated that Rectogesic should be used 'for the relief of pain associated with chronic anal fissures'; the journalist had not quoted ProStrakan directly on this matter and it did not have any editorial control over his work. It was probable that as a lay person he had not understood the differentiation. Therefore, ProStrakan did not believe it was in breach of the Code.

Clauses 3.2 and 7.2 – cost effective, in that it cost much less than surgery. ProStrakan did not believe this was promoting Rectogesic as it was commenting on the press release and the SMC documentation, clarifying the economic statement. This also applied to Clauses 7.3 and 7.4. In ProStrakan's submission to the SMC it pointed out that there were no licensed alternatives to Rectogesic that had proven efficacy in the treatment of chronic anal fissures, which was why no cost effectiveness analysis against medical treatments was conducted. ProStrakan's position had been clarified with the SMC and a broader cost effectiveness case would be included in ProStrakan's resubmission to allow the SMC to re-assess its position.

ProStrakan provided the health economic section that was submitted to the SMC regarding Rectogesic and surgery; this clarified the position of Rectogesic used within the SMC process.

Also provided was a detailed evidence search for the products mentioned in the SMC report ie Anusol, Xyloproct and Anacal, which was submitted as part of the review process detailing that there was no evidence that these products worked in chronic anal fissures and that their broad licence was a historical anomaly rather than a reflection of the evidence. This was reinforced in the current recommendations for the treatment as shown in the Prodigy document.

A study versus surgery was included in ProStrakan's original submission, the pdf on the website did not show these data as it was not part of the SMC process to include all submitted data.

Clause 7.2 – currently the only alternative to surgical treatment. As stated above this was not a direct quote from ProStrakan as the journalist had been consistent

in his use of quotation marks for those statements directly attributed to ProStrakan. ProStrakan had no editorial control over what the journalist had produced; it therefore did not believe this was a breach of the Code.

As a point of clarification on the complaint, Anusol, Anacal and Xyloproct were identified as comparator medications, not alternative treatments of similar effectiveness. As stated above ProStrakan had provided the SMC with a detailed search for evidence, which showed there was no data to show that they were effective in the treatment of chronic anal fissures. Indeed literature was available that showed that lignocaine (the main constituent of these products) could be detrimental. The historical licence for anal fissures was granted prior to the appreciation that chronic anal fissures were not simple tears, rather they had a more complicated pathophysiology as described in the Prodigy document.

Clause 20.2 – ProStrakan believed it had reacted in a considered and appropriate manner to a request for its comments on the SMC press release; it had been clearly quoted in the article and commented on information freely available to the public. ProStrakan believed it had not promoted Rectogesic in this article which had been promoted by a third party. ProStrakan's comments in the article had been directed at addressing the SMC press release, ProStrakan therefore could not understand the extrapolation of the complainant to the side effects for Rectogesic and did not believe it was in any way misleading.

PANEL RULING

The Panel noted that complaints about articles in the press were considered with regard to the information supplied by the pharmaceutical company to the press and not on the content of the article itself. The conversation with the journalist from a national newspaper had to meet the requirements of Clause 20 of the Code. Rectogesic should not be promoted to the public as it was a prescription only medicine. Clauses 3.2, 7.2 and 7.4 of the 2003 Code related to the promotion of medicines rather than the provision of information to the public. Some changes in this regard had been made to the 2006 Code. This complaint was being considered under the 2003 Code using the Constitution and Procedure set out in the 2006 Code of Practice booklet.

The article in the Glasgow Herald included quotations from ProStrakan's spokesperson for which ProStrakan took responsibility.

The statement that Rectogesic was an ointment for the treatment of anal fissures was not in quotation marks in the article but was attributed to ProStrakan. The article was misleading in this regard but the Panel did not consider this was the responsibility of ProStrakan. In the absence of any detail of what ProStrakan said to the journalist no breach of Clauses 3.2 and 20.2 of the Code was ruled.

With regard to the quotation that Rectogesic '… costs much less than surgery', the Panel noted that the information from Prodigy, which was described by ProStrakan as an NHS independent information source, stated that about 7 in 10 of patients with a chronic anal fissure were successfully treated with a course of GTN ointment and about 5 in 10 would heal with regular warm baths and use of an anaesthetic cream for pain relief. Surgery was described as an option if GTN treatment did not work and was an option for recurring fissures. Treatment with Rectogesic was limited to a maximum of eight weeks. The Panel did not consider that the claim 'costs much less than surgery' implied that Rectogesic was licensed as an alternative to surgery as alleged but nonetheless noted that if treatment with GTN was unsuccessful surgery might be an option. The Panel did not consider that the statement '… costs much less than surgery' was a comparison that failed to reflect the requirements of Clauses 3.2, 7.2 and 20.2 of the Code. Thus no breach was ruled.

The statement that Rectogesic was the only alternative to surgical treatment was not in quotation marks in the article but was attributed to a ProStrakan spokesman. The article was misleading in this regard but the Panel did not consider this was the responsibility of ProStrakan. In the absence of any detail of what ProStrakan said to the journalist no breach of Clauses 7.2, 7.3, 7.4 and 20.2 of the Code was ruled.

The Panel did not consider that the fact that the article made no mention of the most common side effect meant that a misleading impression was given that Rectogesic was an entirely safe alternative to surgery. No breach of Clause 20.2 of the Code was ruled.

Complaint received **17 April 2006**

Case completed **19 May 2006**

CASE AUTH/1827/4/06

ANONYMOUS v MERCK SHARP & DOHME

Meeting at a Chinese restaurant

An anonymous complainant provided some photographs which were said to show a Merck Sharp & Dohme representative entertaining a group of doctors and their wives at a Chinese restaurant. It was alleged that a large percentage of the GPs' partners had no affiliation to the medical profession. Furthermore, the meeting was held in the public domain and had no medical educational content.

The Panel noted from the list of attendees provided by Merck Sharp & Dohme that eight male doctors, one female doctor and one female pharmacist had been invited to the meeting. The Panel queried Merck Sharp & Dohme's submission that two wives who had attended the restaurant, and did not qualify as delegates to the meeting in their own right, had sat at a separate table. Photographs provided by the complainant clearly showed at least four different women around the same table as everyone else.

The restaurant receipt, for £253.70, did not give details of the number of meals served. However, assuming that it was for the ten delegates and the representative, then the Panel did not consider that the amount paid was unreasonable *per se*. It was, however, impossible to assess the merits of the educational content of the meeting in question. There was no written invitation, no agenda and little other information. The meeting did not have a sufficiently clear educational content to justify the provision of hospitality. The meeting had been held on a Friday night in a part of a restaurant where the public were also present. The venue was unsuitable. The representative had not maintained a high standard of ethical conduct.

The Panel considered that the arrangements for the meeting were totally unacceptable. The informal arrangements compounded the impression of a mainly social event on a Friday night paid for by the pharmaceutical industry. The Panel ruled breaches of the Code as acknowledged by Merck Sharp & Dohme. The Panel further considered that the arrangements were such as to bring discredit upon the industry. A breach of Clause 2 was also ruled.

An anonymous complaint was received about a meeting arranged by a representative from Merck Sharp & Dohme Limited.

COMPLAINT

The complainant provided some photographs which were said to show a representative from Merck Sharp & Dohme Limited entertaining a group of doctors and their wives in December 2005 at a Chinese restaurant. It was alleged that a large percentage of the partners of the general practitioners had no affiliation to the medical profession. Furthermore, the meeting was held in the public domain and had no medical educational content.

The complainant was sure that the Authority would deal with the matter appropriately as, in the current climate, the last thing the pharmaceutical industry needed was further controversy.

When writing to Merck Sharp & Dohme the Authority asked it to respond in relation to Clauses 2, 9.1 and 19 of the Code.

RESPONSE

Merck Sharp & Dohme confirmed that the meeting was organized by one of its representatives; it was attended by nine local GPs and a pharmacist, and the total cost of the meal, including drinks was £253.70. Two wives who were not health professionals attended the restaurant. The representative informed the two spouses that under the Code and Merck Sharp & Dohme company policy they could not attend the medical meeting and the company could not pay for their meal or drinks. The spouses sat at a separate table and the costs were not paid by Merck Sharp & Dohme but by their respective spouses. Merck Sharp & Dohme had spoken to one of the GPs and he confirmed this account.

The representative invited a small group of local GPs to participate in a medical discussion concerning recent guidelines dealing with non-steroidal anti-inflammatories and Cox 2 inhibitors. The discussion was facilitated by a primary care trust lead physician with a particular interest in musculoskeletal medicine. The invitation was made verbally and there was no formal written invitation and no written agenda. The meeting was held in a public part of the restaurant, although efforts had been made to position the table away from the main part of the restaurant.

Whilst Merck Sharp & Dohme refuted the suggestion that there was no medical educational content at the meeting, it conceded that the arrangements for this particular meeting fell below acceptable standards and it accepted that it was in breach of Clause 9.1 in that high standards should be maintained at all times.

Merck Sharp & Dohme accepted that the venue was not appropriate and the medical content of the meeting should have been conducted in a private room. Merck Sharp & Dohme believed that the level of hospitality and the payment arrangements for the non qualifying spouses were consistent with the Code. However the arrangements within the venue did amount to a breach of Clause 19.1.

Merck Sharp & Dohme was actively taking steps to remind its representatives of Code requirements to ensure future compliance with regard to arranging and carrying out meetings with health professionals.

PANEL RULING

The Panel noted that as the event had been held in December the 2003 Code applied. The case was considered in accordance with the Constitution and Procedure set out in the 2006 Code of Practice booklet.

The Panel noted that, from the list of attendees provided by Merck Sharp & Dohme, eight male doctors, one female doctor and one female pharmacist had been invited to the meeting. The Panel queried Merck Sharp & Dohme's submission that two wives who had attended the restaurant, and did not qualify as delegates to the meeting in their own right, had sat at a separate table. Photographs provided by the complainant clearly showed at least four different women around the same table as everyone else.

The restaurant receipt, for £253.70, did not give details of the number of meals served. However, assuming that it was for the ten delegates and the representative, then the Panel did not consider that the amount paid was unreasonable *per se*. It was, however, impossible to assess the merits of the educational content of the meeting in question. There was no written invitation, no agenda and little other information. The meeting did not have a sufficiently clear educational content to justify the provision of hospitality. The meeting had been held on a Friday night in a part of a restaurant where the public were also present. The venue was unsuitable. The representative had not maintained a high standard of ethical conduct.

The Panel considered that the arrangements for the meeting were totally unacceptable. The informal arrangements compounded the impression of a mainly social event on a Friday night paid for by the pharmaceutical industry. The Panel ruled breaches of Clauses 9.1 and 19.1 as acknowledged by Merck Sharp & Dohme. The Panel further considered that the arrangements were such as to bring discredit upon the industry. A breach of Clause 2 was ruled.

Complaint received **18 April 2006**

Case completed **15 May 2006**

CASE AUTH/1829/4/06 *NO BREACH OF THE CODE*

DOCTOR v ALLERGAN

Vistabel advertisement in Aesthetic Medicine

A doctor complained that an advertisement for Vistabel (botulinum toxin type A), a prescription only medicine (POM), had been placed by Allergan in Aesthetic Medicine which in his view was not a *bona fide* medical journal circulated exclusively to the medical profession; it was distributed freely to beauty salons and was readily accessible to unqualified individuals.

The Panel noted that whether Aesthetic Medicine was a *bona fide* medical journal with exclusive circulation to the medical profession was not the criterion which had to be applied. Most medical journals, including the BMJ for example, were available to anyone who cared to buy them. They could nonetheless contain advertisements for POMs because they were intended mainly for health professionals. Companies were also permitted to promote their products to appropriate administrative staff. The Code stated that promotional material should only be sent or distributed to those categories of persons whose need for or interest in the particular information could reasonably be assumed.

It appeared from Allergan's submission that Aesthetic Medicine was aimed at a mixed audience. Many of the intended readers were health professionals, but others such as owners of beauty salons or spas, where a doctor or nurse were present, appeared not to be. The Panel had no way of knowing who the 3% of recipients classified as 'other' were. The Panel also noted that the readership figures only added up to 95% and not 100%.

The Panel considered that the journal was intended for both health professionals and appropriate administrative staff; it was thus acceptable to include an advertisement for a POM. Such advertising had to be tailored to be appropriate for the combined audience.

The Panel considered that given the distribution of the journal, the advertisement did not promote a POM to the public. No breach of the Code was ruled.

A doctor complained about an advertisement for Vistabel (botulinum toxin type A) placed by Allergan Limited in the journal Aesthetic Medicine.

COMPLAINT

The complainant stated that Aesthetic Medicine was not a *bona fide* medical journal with an exclusive circulation to the medical profession; it was distributed freely to beauty salons and was readily accessible to unqualified individuals and therefore in breach of the advertising regulations as well as contravening the Code.

The Authority informed the complainant that the advertising regulations were a matter for the Medicines and Healthcare products Regulatory Agency but that the matter would be taken up under the Code.

When writing to Allergan, the Authority asked it to respond in relation to Clause 20.1 of the Code.

RESPONSE

Allergan stated that Vistabel was a prescription only medicine (POM). Allergan reviewed the aims and the circulation of the journal Aesthetic Medicine prior to placing the advertisement. It believed this journal to be a suitable publication in which to place a Vistabel advertisement.

Allergan provided a copy of the media pack for Aesthetic Medicine which detailed its circulation. The journal was aimed at the medical aesthetic community, including doctors, plastic surgeons, medical aesthetic nurses, dermatologists and cosmetic dentists. The readership was listed as aesthetic medical practices, plastic surgeons, aesthetic nurses, cosmetic doctors, cosmetic dentists, dermatologists, laser clinics, selected departments of NHS and private hospitals, selected spas and skincare centres.

The circulation was restricted to medical aesthetic professionals and their practices; it was not freely circulated to unqualified individuals as alleged by the complainant. In particular, it was not circulated to members of the public. Therefore, Allergan did not believe the advertisement was in breach of Clause 20.2 of the Code.

In response to a request for further information about the proportion of the circulation of Aesthetic Medicine to health professionals, compared to other recipients, Allergan advised that 10,000 copies were circulated each month. It was a trade magazine focussing on health professionals. From figures provided by the journal the readership could be broken down as follows: 31% managing directors of medical aesthetic clinics of whom 90% were estimated to be health professionals, 7% skin specialists, 7% dermatologists, 7% clinic managers, 5% cosmetic surgeons, 9% cosmetic dentists, 4% GPs, 9% nurses, 4% plastic surgeons, 5% beauty salon owner where doctor or nurse is present, 4% spa owner where doctor or nurse is present and 3% other.

PANEL RULING

The Panel noted that the complainant had stated that Aesthetic Medicine was not a *bona fide* medical journal with exclusive circulation to the medical profession. That was not, however, the criterion which had to be applied. Most medical journals, including the BMJ for example, were available to anyone who cared to buy them. They could nonetheless contain advertisements for POMs because they were intended mainly for health professionals. Companies were also permitted to promote their products to appropriate administrative staff as set out in Clause 1.1. Clause 12.1 of the Code stated that promotional material should only be sent or distributed to those categories of persons whose need for or interest in the particular information could reasonably be assumed.

It appeared that Aesthetic Medicine was aimed at a mixed audience. Many of the intended readers were health professionals, but others such as owners of beauty salons or spas, where a doctor or nurse were present, appeared not to be. The Panel had no way of knowing who the recipients classified as 'other' were. The Panel also noted that the readership figures only added up to 95% and not 100%.

The Panel considered that the journal was intended for both health professionals and appropriate administrative staff; it was thus acceptable to include an advertisement for a POM. Such advertising had to be tailored to be appropriate for the combined audience.

The Panel considered that given the distribution of the journal, the advertisement did not promote a POM to the public. No breach of Clause 20.1 of the Code was ruled.

Complaint received	**20 April 2006**
Case completed	**13 June 2006**

PRIMARY CARE TRUST PHARMACIST v GW PHARMACEUTICALS

Alleged promotion of Sativex

A prescribing support pharmacist with a primary care trust (PCT) was concerned that GW Pharmaceuticals was trying to promote its unlicensed product, Sativex (a cannabis derivative), to the public. The complainant provided a copy of a letter written by the local multiple sclerosis (MS) specialist co-ordinator to a practice manager. The letter asked the recipient to let GPs and others know that at a meeting of the local branch of the MS Society there would be a presentation about Sativex given by GW. The complainant understood that MS sufferers would be anxious to have information about a new product which might offer potential benefit but patient expectation of a prescription might be inappropriately raised.

The Panel noted that GW had accepted an invitation for one of its employees to speak about Sativex at the meeting; anyone connected with MS, whether patient or practitioner, was welcome to attend. Sativex was unlicensed in the UK. A letter from the MS specialist co-ordinator confirmed that the planned meeting had been cancelled.

The Panel was concerned about the proposed arrangements. It was difficult to see that the planned presentation would do anything other than heighten awareness about and stimulate demand for Sativex, an unlicensed medicine. The Panel noted, however, that GW had done no more than accept the invitation to speak; the meeting had been cancelled. No information had been given to the patient group. There was no evidence that high standards had not been maintained. No prescription only or unlicensed medicine had been promoted to the public and nor had patients been encouraged to ask their doctor to prescribe Sativex. No breaches of the Code were ruled.

A prescribing support pharmacist with a primary care trust (PCT) complained about the promotion of Sativex by GW Pharmaceuticals plc. The complainant provided a copy of a letter written by the multiple sclerosis (MS) specialist co-ordinator to a practice manager. The letter asked the recipient to let GPs and others know that the local branch of the MS Society would be holding a meeting at which there would be a presentation about Sativex (a cannabis derivative) given by the head of research and development at GW.

COMPLAINT

The complainant was concerned that the planned meeting might breach the Code:

- Prescription only medicines must not be advertised to the public. Non-promotional information could be provided to the public directly or via the media.
- A medicine must not be promoted prior to being authorized for UK use. An exception was factual information made available as advance notification to those responsible for policy decisions, so that the NHS could plan financially.

The complainant understood that MS sufferers would be anxious to have information about a new product which might offer potential benefit but patient expectation of a prescription might be inappropriately raised.

When writing to GW the Authority asked it to respond in relation to the requirements of Clauses 2, 3.1, 9.1, 20.1 and 20.2 of the Code.

RESPONSE

GW noted that the complaint was about a meeting at which it had been specifically invited to speak. The invitation had come from the MS co-ordinator of a PCT, who had been approached for information from a number of local GPs, the local branch of the MS Society and a local consultant neurologist. This meeting had not yet taken place. GW was surprised that the Authority regarded this complaint as valid, since it referred to a meeting that had not yet occurred, and could only therefore be a complaint against the potential content of such a meeting, or against the fact that a meeting had been arranged at the request of an independent patient organisation and a specialist representative of a PCT.

GW supplied copies of a letter from the organiser of the proposed meeting confirming this invitation and a letter from the secretary of the local branch of the MS Society confirming that the original suggestion for such a meeting came from them. These confirmed that the company had responded to a request for information by a branch of the MS Society and the MS specialist co-ordinator of a PCT.

GW did not solicit such a meeting and indeed went out of its way to tell organisers about the limitations placed on pharmaceutical companies by the Code. In the company's view, however, a research-based pharmaceutical company had an ethical responsibility to supply accurate and up-to-date information to patients and to health care workers who specifically and spontaneously requested it.

GW noted that Sativex was of significant interest to people with MS. The company was always careful to ensure absolute adherence to the Code and as such considered it appropriate to accept unsolicited invitations to meetings and ensured that any information provided at such meetings in response to questions was factual and balanced. GW provided no information or advice to any members of the public on personal medical matters.

GW noted that Sativex was an approved prescription medicine in Canada where it had been available on prescription since July 2005. Sativex was not currently under regulatory review in the UK and there was therefore no prospective date for potential approval.

With regard to Clause 2, GW stated that when a health professional, or a reputable patient organisation requested that it provide information to them regarding the basic research and development status of a new approach to the treatment of a disabling condition, then the company considered that it had a duty so to do. The company sought to ensure at all times that the request to speak was a *bona fide* request and that the organisation understood that it was neither permitted to, nor did it wish to, solicit prescriptions.

With regard to the meeting in question, GW considered that in responding to a *bona fide* request from the MS co-ordinator of a PCT, coupled with a request from the secretary of the local branch of the MS Society, it had behaved responsibly and ethically. Indeed, the company considered that to fail to provide accurate information in response to such a request would be irresponsible. GW therefore contended that acceptance of the invitation to provide information at this meeting did not in any way bring the industry into disrepute.

With regard to Clause 3.1, GW stated that acceptance of an invitation to provide information at a meeting could not on its own be regarded as promotion, since no exchange of information had taken place. The company did not consider that the legitimate exchange of medical and scientific information during the development of a medicine – especially a medicine with the level of public interest that Sativex had engendered – was prohibited under the Code. With the meeting in question there was no involvement of GW in the planning, financing, issuing of invitations, agenda (in fact, the company had not seen the agenda for the meeting), or sponsorship of the meeting in any way.

GW was unclear in what way it might be considered not to be exhibiting high standards in breach of Clause 9.1. The planned exchange of information had not taken place, so the only way in which it could be guilty of failing to exhibit high standards could be in accepting an invitation to speak at a meeting proposed and organised by the MS co-ordinator of a PCT, and at the request of the secretary of a local branch of the MS Society.

As stated above, GW had not been involved in any aspect of the planning or execution of the proposed meeting, and it had not given any undertaking to provide funding or to accept payment. The company logo had not to its knowledge been used in the documentation associated with the meeting.

GW repeated that, in its view, an ethical and responsible company had a duty to provide factual and accurate information in response to *bona fide* requests for such.

With respect to Clause 20.1, GW stated that no promotional activity had taken place, and no meeting had taken place, so no information had been exchanged. Again, the only way in which the company could be promoting would be by accepting an invitation to present scientific and clinical information regarding a medicine under active development. As stated above, GW had not been involved in any way in the sponsorship or support of this meeting, and there was no financial involvement of the company in any way.

With regard to Clause 20.2, GW stated that MS patients were very interested in the development of new and promising approaches to the treatment and management of their condition. The company had a constructive relationship with the MS Society in this regard and considered it appropriate to provide, in response to an unsolicited request, an update on its scientific progress in the Society's research area of interest. Similarly, there was a high level of interest in the progress of potential new MS treatments among the medical community. For this community also, GW considered it appropriate to provide factual information in response to *bona fide* requests. GW undertook no sponsorship of patient groups, it had no stands at meetings, it provided no samples etc.

Furthermore, in responding to requests from patient organisations and healthcare organisations or individuals, GW was careful to state that it was not permitted to solicit either such meetings, or prescriptions for Sativex, although its understanding was that it was permitted to solicit relevant physicians regarding their inclusion in clinical trials.

All GW had done in respect of the meeting at issue was to accept an invitation to provide information; it was difficult to see how this could constitute a breach of the Code.

In summary, the extent of GW's involvement had been to accept what it regarded as a *bona fide* invitation to provide medical and scientific information to a group of interested parties with a strong and legitimate interest in the company's research. The company's understanding of the Code was that this was a legitimate exercise. The company would be surprised if its agreement to accept an invitation to this meeting was not permissible under the Code.

PANEL RULING

The Panel noted that GW had been invited to speak at a meeting of a local branch of the MS Society; anyone connected with MS, whether patient or practitioner, was welcome to attend. GW had accepted the invitation and one of its employees planned to give a talk on Sativex. Sativex was unlicensed in the UK. The Panel had some sympathy with a local branch of a patient organization wanting to find out more about new medicines that might become available but nonetheless noted that in meeting such requests companies still had to conform with the requirements of the Code. Patients' wishes could not override the Code. A letter from the MS specialist co-ordinator confirmed that the planned meeting had been cancelled.

The Panel noted that Clause 3.1 stated that a medicine must not be promoted prior to the grant of the marketing authorization which permitted its sale or supply. Clause 20.1 prohibited the advertising of prescription only medicines to the general public. Clause 20.2 of the Code permitted information about prescription only medicines to be supplied directly or indirectly to the general 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 health professional to prescribe a specific prescription only medicine.

The Panel was concerned that an employee of GW had planned to give a talk on Sativex to members of the public at a local branch meeting of the MS Society. It was difficult to see that such a presentation would do anything other than heighten awareness about and stimulate demand for Sativex, an unlicensed medicine. Whilst it was not necessarily unacceptable for companies to present at patient group meetings they should exercise extreme caution when embarking on such activity and take great care to ensure that all of the arrangements complied with the Code, especially the provisions of Clause 20. Talking about specific medicines to such groups would leave companies vulnerable with regard to the Code.

The Panel noted that in this case GW had done no more than accept the invitation to speak; the meeting had been cancelled. No information had been given to the patient group. There was no evidence that high standards had not been maintained. No prescription only or unlicensed medicine had been promoted to the public and nor had patients been encouraged to ask their doctor to prescribe Sativex. No breach of Clauses 2, 3.1, 9.1, 20.1 and 20.2 was ruled.

Complaint received **26 April 2006**

Case completed **11 July 2006**

CASE AUTH/1834/5/06

PFIZER CONSUMER HEALTHCARE v NOVARTIS CONSUMER HEALTH

Nicotinell journal advertisement

Pfizer Consumer Healthcare complained about a journal advertisement for Nicotinell (nicotine transdermal patches) issued by Novartis Consumer Health. Nicotinell released nicotine over 24 hours. Pfizer Consumer Healthcare supplied Nicorette transdermal patches which released nicotine over 16 hours.

Pfizer Consumer Healthcare alleged that the claims 'When cravings peak in the afternoon… and the evening… …Nicotinell: a 24-hour patch with a profile to match', 'Recommend a patch to match their craving profile…' and 'A recent study showed that 93% of your patients' lapses occurred during the afternoon and evening. Nicotinell's patch delivers peak plasma concentrations during the afternoon with consistent nicotine delivery whatever the time of day' were misleading with regard to the efficacy profile of Nicotinell.

The advertisement emphasised the importance of controlling afternoon and evening cravings when the majority of relapses occurred.

The claims, in conjunction with the graph which showed plasma nicotine concentration vs hours from initial dose, implied that Nicotinell had a profile that was specifically suited to cover the afternoon and evening periods, and that this was clinically beneficial. However, this was not the case. Nicotinell delivered nicotine at a steady rate over 24 hours, and there was no data to suggest that it provided greatest craving relief in the afternoon and evening. It was therefore misleading to imply that Nicotinell was particularly suitable for controlling afternoon and evening cravings.

The Panel considered that the advertisement implied that the pharmacokinetic profile of Nicotinell was such that plasma nicotine levels peaked in the afternoon and evening and so coincided with craving peaks in smokers trying to quit. Fant *et al* showed that at steady state T_{max} for Nicotinell was 8 hours which, if the patch had been applied in the morning, would mean that plasma levels peaked somewhere between 2pm and 4pm according to the time of application. Between 10 and 24 hours post dose plasma nicotine levels fell although at around 13 hours post dose, and again at about 20 hours there were slight rises in otherwise declining levels. The Panel considered that the advertisement implied two completely separated peaks in nicotine plasma levels which was not so. Fant *et al* concluded by stating that further study was required to determine the clinical advantages of the profile of nicotine delivery. No data had been submitted to show that the pharmacokinetic profile of Nicotinell had a positive impact on afternoon or evening cravings. The Panel considered that the advertisement was misleading as alleged. A breach of the Code was ruled.

Pfizer Consumer Healthcare also alleged that the claim 'Combined with an intensive behavioural support programme Nicotinell's patch can increase quit rates by up to four times compared to unaided levels' represented an unbalanced view of smoking cessation using nicotine replacement therapy (NRT); a Cochrane Review concluded that all commercially available forms of NRT increased quit rates by 1.5 to 2 fold.

Furthermore, the 20% quit success figure quoted by West and Shiffman was an estimated figure for the optimal treatment available (the best combination of NRT/bupropion plus behavioural support), whereas

patch-specific data from Cochrane gave a quit success rate of 13.6% (OR 1.86) for nicotine patches plus low intensity support and 15.6% (OR 1.79) for nicotine patches plus high intensity support.

The 'four times' claim was based upon the Cochrane Review of all forms of NRT/bupropion plus behavioural support for smoking cessation, and not specifically nicotine patches, Nicotinell or otherwise. Furthermore, the 'four times' quit rate was only achieved with intensive behavioural support which was received by relatively few NRT patients.

The Panel considered that the claim implied that a study had compared Nicotinell plus intensive behavioural support with no aid which was not so. The Panel considered that the claim was misleading in that regard. A breach of the Code was ruled.

Pfizer Consumer Healthcare alleged that the graph, from Fant *et al*, had been inaccurately reproduced, with the values for plasma nicotine levels being exaggerated.

The Panel noted that the graph in the advertisement showed the pharmacokinetic profile of Nicotinell from 0 to 72 hours. In the first 24 hours C_{max} was shown as approximately 17.5ng/ml; Fant *et al* had reported a C_{max} of 17.6ng/ml. The graph in the advertisement showed higher C_{max} values on days 2 and 3 of just less than 20ng/ml; Fant *et al* had reported a C_{max} of 19.5ng/ml during that time. The Panel thus did not consider that the graph was inaccurate as alleged. No breach of the Code was ruled.

Pfizer Consumer Healthcare complained about a journal advertisement (ref Nico001-01/06) for Nicotinell (nicotine transdermal patches) issued by Novartis Consumer Health UK Ltd. Nicotinell released nicotine over 24 hours. Pfizer Consumer Healthcare supplied Nicorette transdermal patches which released nicotine over 16 hours.

Pfizer Consumer Healthcare stated that in its opinion both the content and overall impression of the advertisement were misleading and in breach of the Code.

1 Efficacy profile

COMPLAINT

Pfizer Consumer Healthcare believed that the following claims misled as to the nature of the efficacy profile of the Nicotinell patch:

i) 'When cravings peak in the afternoon… and the evening… …Nicotinell: a 24-hour patch with a profile to match.'

ii) 'Recommend a patch to match their craving profile – it needn't be hell with Nicotinell.'

iii) 'A recent study showed that 93% of your patients' lapses occurred during the afternoon and evening [Ussher and West 2003]. Nicotinell's patch delivers peak plasma concentrations during the afternoon with consistent nicotine delivery whatever the time of day.'

The advertisement emphasised the importance of controlling afternoon and evening cravings. This was clearly an important time for quitters; Ussher and West demonstrated that this was the time when the majority of relapses occurred.

The claims listed above, in conjunction with the graph [adapted from Fant *et al* 2000] which showed plasma nicotine concentration vs hours from initial dose, strongly implied that Nicotinell had a profile that was specifically suited to cover the afternoon and evening periods, and that this pharmacokinetic profile implied a clinical benefit. However, this was not the case. Unlike 16 hour patches which released nicotine in the daytime only, Nicotinell delivered nicotine at a steady rate over 24 hours, and there was no data to suggest that it provided greatest craving relief in the afternoon and evening. It was therefore misleading to imply that Nicotinell was particularly suitable for controlling afternoon and evening cravings.

Pfizer Consumer Healthcare considered that this particular issue was similar to a previous case, Case AUTH/1563/3/04, where Pharmacia (subsequently Pfizer Consumer Healthcare) had a complaint upheld against it with regard to a similar claim which linked plasma nicotine levels to craving control.

RESPONSE

Novartis Consumer Health stated that in its view the Fant *et al* pharmacokinetic study could not be correlated to clinical efficacy. As the authors had noted, further clinical studies were needed to demonstrate whether the different pharmacokinetic profiles related into clinical differences.

The creative expectations of the advertisement were to use the 24-hour pharmacokinetic profile of Nicotinell and create an image of 24 hour cover. The graphical representation began on the left hand side of the page and travelled over the cake and cocktail, through the graph finally encompassing the Nicotinell TTS 30 box. The Nicotinell box clearly showed the 24-hour patch program and the graph represented the consistent nicotine levels over 24 hours and extrapolated over a 3 day period. The graph was a smaller part of the overall advertisement and while close examination of it showed the peak nicotine levels in the afternoon and evening, this was not easily discernable at first glance. The reader had to look very carefully to realise the peak at these times. The important message was that Nicotinell was a 24-hour patch and could provide cover for the whole 24 hours. Consequently the patch could offer cover to those who failed in the afternoon and evening. The findings of Ussher and West were not unexpected. Afternoon and evening was a time when it would be expected that a smoker's determination to stop was reduced.

Furthermore, to avoid any comparative advertising and complaint from competitors, the pharmacokinetic profiles of the Niquitin and Nicorette patches were removed.

With respect to the individual claims, claim (i), the rhyme of patch and match in the claim 'Nicotinell: a 24-hour patch with a profile to match' could be justified as it was a 24-hour patch which could cover the cravings over the whole 24-hour period, no matter when they occurred.

On reflection, combining the patch to match in the claim 'When cravings peak in the afternoon … and the evening … … Nicotinell: a 24-hour patch with a profile to match' could be less challengeable if 'with a profile to match' was deleted, to read 'When cravings peak in the afternoon … and the evening … … Nicotinell: a 24-hour patch'.

Bearing in mind the above, claim (ii) could also be made less challengeable by using 'cover' rather then 'match' so the statement read 'Recommend a patch to cover their craving profile – it needn't be hell with Nicotinell'.

Finally in claim (iii) there was an inconsistency between 'delivers peak plasma concentrations' and 'consistent nicotine delivery'. This statement would be clearer by deleting 'delivers peak plasma concentrations' to read: 'A recent study showed that 93% of your patients' lapses occurred during the afternoon and evening. Nicotinell's patch delivers consistent nicotine delivery, whatever the time of the day'.

In the previous case, Case AUTH/1563/3/04, the claim used by the complainant was that '…. Nicorette 16-hour patch also provided maximum craving control when patients are most vulnerable'. The Nicotinell advertisement was different in that it highlighted when the relapse was highest and that Nicotinell offered support by having high nicotine blood levels in the afternoon and evening but also provided consistent nicotine delivery, whatever the time of the day.

As far as Novartis was concerned, this advertisement was not intended to mislead. It was no longer in print and there was no intention to use it again in its original form.

PANEL RULING

The Panel considered that the advertisement implied that the pharmacokinetic profile of Nicotinell patches was such that plasma nicotine levels peaked in the afternoon and evening and so coincided with peaks in cravings for smokers trying to quit. Fant *et al* showed that at steady state T_{max} for Nicotinell was 8 hours which, if the patch had been applied in the morning, would mean that plasma levels peaked somewhere between 2pm and 4pm according to the time of application. Between 10 and 24 hours post dose plasma nicotine levels fell although not consistently; at around 13 hours post dose, and again at about 20 hours there were slight rises in otherwise declining levels. The Panel considered that the advertisement implied two completely separate peaks in nicotine plasma levels which was not so. Fant *et al* concluded by stating that further study was required to determine the clinical advantages of the profile of nicotine delivery. No data had been submitted to show that the pharmacokinetic profile of Nicotinell had a positive impact on cravings in the afternoon or evening. The Panel considered that the advertisement was misleading as alleged. A breach of Clause 7.2 was ruled.

2 Smoking cessation data

COMPLAINT

Pfizer Consumer Healthcare alleged that the claim 'Combined with an intensive behavioural support programme Nicotinell's patch can increase quit rates by up to four times compared to unaided levels' represented an unbalanced view of smoking cessation using nicotine replacement therapy (NRT); the Cochrane Review of NRT for smoking cessation recognised the heterogeneity of NRT and concluded that all commercially available forms of NRT increased quit rates by 1.5 to 2 fold, regardless of setting. The above 'four times' claim thus misled the reader.

Furthermore, the 20% quit success figure quoted by West and Shiffman (reference used to support claim iii) was an estimated figure for the optimal treatment available (the best combination of NRT/bupropion plus behavioural support), whereas patch-specific data from Cochrane gave a quit success rate of 13.6% (OR 1.86) for nicotine patches plus low intensity support and 15.6% (OR 1.79) for nicotine patches plus high intensity support.

Furthermore, the 'four times' claim gave the misleading impression that it was based upon Nicotinell clinical trial(s) – ie '… Nicotinell's patch can increase quit rates …', when in fact the claim was based upon the Cochrane Review of all forms of NRT/bupropion plus behavioural support for smoking cessation, and not specifically nicotine patches, Nicotinell or otherwise.

The claim was further misleading as the 'four times' quit rate was only achieved with intensive behavioural support (eg group therapy to include coping skills, training and social support, approximately five sessions of behavioural support of about one hour over approximately one month, and follow up) which was received by relatively few patients who used NRT.

Pfizer Consumer Healthcare considered that this particular issue had distinct similarities to a previous case (Case AUTH/1402/12/02) where Pharmacia (subsequently Pfizer Consumer Healthcare) had a complaint upheld against it with regard to making the similar claim 'Up to 4 times the success of placebo at 1 year'.

RESPONSE

Novartis Consumer Health stated that this claim was based on the effect of intensive behavioural support which could increase quit rates by up to four times.

Novartis Consumer Health noted that the Cochrane Collaboration was a meta analysis of clinical studies to determine the effectiveness of NRT in achieving long-term smoking cessation. Only studies with 6 or 12 months follow up were included in the analysis. Under the limitations of the trial selection, some assessment was made regarding the intensity of behavioural support but this was not relevant in this case.

The reference supporting the four times claim was West and Shiffman. The results were initially published as West *et al* (2000). This reference was

different to the Cochrane Collaboration in that it concentrated on the effect of different levels of behavioural support in smoking cessation. Here West *et al* quoted brief opportunistic advice given by a physician to smokers attending a GP surgery or an outpatient clinic as having an effective result of 2% (with 95% confidence limits between 1% to 3%). Intensive behavioural support plus NRT or bupropion in moderate to heavy smokers seeking help from a smokers clinic gave an effective result of 13 – 19%. Taking the upper confidence limits of 3% effect with opportunistic advice and lower confidence limits of 13% with intensive behavioural support showed an increase quit rate of up to 4 times for nicotine replacement therapy.

What was confusing was that Pfizer Consumer Healthcare acknowledged the validity of the four times claim. It acknowledged that the four times claim was supportable with intensive behavioural support but then went on to object to the level of support needed. West *et al*, suggested that that intensive smoking cessation treatment was effective and like all smoking cessation interventions was extremely cost effective in producing population health gain. With respect to the definition of intensive behavioural support, Pfizer Consumer Healthcare had referred to the National Electronic Library for Health. However this reference was not taken from West *et al* but from Raw *et al* (1998). Raw *et al* recommended that intensive smoking cessation support should, where possible, be conducted in groups, include coping skills training and social support, and should offer around five sessions and follow up, together with nicotine replacement therapy. This was achievable in a smoking cessation clinic.

With regard to the noted similarity between this claim and the claim at issue in Case AUTH/1402/12/02, Novartis Consumer Healthcare stated that the claim now at issue was quite different; the previous claim was based on 'up to four times the success of placebo at 1 year' and referenced to Tonnesen *et al* (1991).

In conclusion the claim was generic and applied to any NRT and could be used by Pfizer Consumer Healthcare.

PANEL RULING

The Panel disagreed with the submission that the claim 'Combined with an intensive behavioural support programme Nicotinell's patch can increase quit rates by up to four times compared with unaided level' was a generic claim. The inclusion of the product name made it specific to Nicotinell. The claim implied that a study had compared Nicotinell plus intensive behavioural support with no aid which was not so. The Panel considered that the claim was misleading in that regard. A breach of Clause 7.2 was ruled.

3 Graph from Fant *et al*

COMPLAINT

Pfizer Consumer Healthcare stated that the graph had been inaccurately reproduced, with the values for plasma nicotine levels being exaggerated – eg maximum plasma nicotine levels achieved with Nicotinell 30 in the advertisement were approximately 20ng/ml, whereas the original publication had maximum values of approximately 18ng/ml.

RESPONSE

Novartis Consumer Health stated that with reference to the graphical representation it was unclear as to what Pfizer Consumer Healthcare was referring. Table 1 of Fant *et al* referred to 0 to 24 hour pharmacokinetic profiles of Nicotinell. In this instant C_{max} (ng/ml) was 17.6 and T_{max} of 10 hours.

Table 2 Pharmacokinetic profiles from 48 to 72 hours (modelled on steady state) gave C_{max} 19.5ng/ml and T_{max} of 8 hours.

These were the figures reflected on the graph. It was not clear as to how Pfizer Consumer Healthcare could claim the values were exaggerated.

PANEL RULING

The Panel noted that the graph in the advertisement showed the pharmacokinetic profile of Nicotinell from 0 to 72 hours. In the first 24 hours C_{max} was shown as approximately 17.5ng/ml; Fant *et al* had reported a C_{max} of 17.6ng/ml. The graph in the advertisement showed higher C_{max} values on days 2 and 3 of just less than 20ng/ml; Fant *et al* had reported a C_{max} of 19.5ng/ml during that time. The Panel thus did not consider that the graph was inaccurate as alleged. No breach of Clause 7.8 was ruled.

Complaint received	**4 May 2006**
Case completed	**23 June 2006**

CASE AUTH/1835/5/06

GENERAL PRACTITIONER v RECORDATI

Conduct of representative

A general practitioner complained about a letter received from a Recordati medical representative. The letter, which was not on company headed notepaper, asked the addressee if it was possible to have a brief appointment. The representative continued by stating that she was selling a dihydropyridine calcium channel blocker which was an inexpensive, long-acting treatment for hypertension. The letter also included information about the draft NICE/British Hypertension Society (BHS) Guidelines and stated that the changes made to these guidelines were prompted, at least in part, by the outcome of the Anglo Scandinavian Cardiac Outcomes Trial which showed benefits for the use of a dihydropyridine calcium antagonist. The representative stated that she would not try to sell her drug as a 'miracle cure' but asked that the reader might consider it second line in patients who had failed on first line therapy; she further stated that she was modestly hopeful that the reader would be surprised at how inexpensive and effective her medicine was. The draft guidelines from NICE/BHS were sent with the letter together with a proforma for the recipient to indicate whether they wanted to see the representative. A stamped addressed envelope was also enclosed for the doctor's reply.

The Panel noted that the principal role of a representative was to promote medicines. By discussing the efficacy of the dihydropyridine calcium channel blocker, and stating that it was inexpensive, the representative had made claims for the product. The letter was clearly written with the intention of seeking to promote the prescription, supply, sale or administration of Zanidip (lercandipine).

The Panel considered that the representative's actions were totally unacceptable; there appeared to be a serious lack of understanding of the requirements of the Code. The representative had, in effect, created her own promotional material for Zanidip but had not had it certified prior to use in accordance with the Code. The letter did not include prescribing information. A breach of the Code was ruled.

The Panel considered that the representative had failed to maintain a high standard of ethical conduct; neither had she complied with all the relevant clauses of the Code. A breach of the Code was ruled.

The Panel noted that although the letter was not on company headed notepaper, from the first two sentences it was clear that it had been written by a representative who was seeking an appointment to promote a dihydropyridine calcium channel blocker. In that regard the Panel did not consider that the letter was disguised promotion. No breach of the Code was ruled.

A general practitioner complained about a letter he had received from a medical representative with Recordati Pharmaceuticals Ltd. In the letter, which was not on company headed notepaper, the representative asked the addressee if it was possible to have a brief appointment. The representative continued by stating that she was selling a dihydropyridine calcium channel blocker which was an inexpensive, long-acting treatment for hypertension. The letter also included information about the draft NICE/British Hypertension Society (BHS) Guidelines and stated that the changes made to these guidelines were prompted, at least in part, by the outcome of the Anglo Scandinavian Cardiac Outcomes Trial (ASCOT) which showed benefits for the use of a dihydropyridine calcium antagonist. The representative stated that she would not try to sell her drug as a 'miracle cure' but asked that the reader might consider it second line in patients who had failed on first line therapy; she further stated that she was modestly hopeful that the reader would be surprised at how inexpensive and effective her medicine was. The draft guidelines from NICE/BHS were sent with the letter together with a proforma for the recipient to indicate whether they wanted to see the representative. A stamped addressed envelope was also enclosed for the doctor's reply.

Recordati marketed Zanidip (lercandipine) a dihydropyridine calcium channel blocker.

COMPLAINT

The complainant considered that the letter was in breach of the Code; he was concerned that it was not on company headed notepaper.

When writing to Recordati, the Authority asked it to respond in relation to Clauses 4.1, 10.1 and 15.2 of the Code.

RESPONSE

Recordati explained that its representative had written to a number of GPs in her area as part of her efforts to secure appointments in order to discuss its medicine. The letter was not written directly to advocate the use of a particular medicine but rather to engage the recipient's attention sufficiently to grant the representative an appointment. This purpose was clearly stated in the opening line. The letter continued by explaining why the representative considered a meeting would be useful without promoting the use of any identifiable medicine. The letter did not mention Zanidip either by brand name or generic name and made clear that its intention was to ask for an appointment. Recordati therefore considered that the letter was not promotion as defined in Clause 1.2 and therefore was not in breach of Clause 4.1 of the Code. Further the letter did not purport to be a personal communication and its purpose was not disguised – although the letter was not on company headed paper, its opening lines, together with the inclusion of an email address and business card made clear that this was a business letter from Recordati. For both these reasons Recordati therefore did not consider that the letter was disguised promotion and denied a breach of Clause 10.1.

Recordati considered that neither the reason for writing the letter (responding to difficulties in obtaining appointments) nor its purpose (to seek appointments) was unethical. Although the third paragraph (beginning 'I have been very frustrated …') could have been somewhat less blunt the company did not consider it was unethical.

Recordati submitted that a decision as to whether the representative had complied with all relevant requirements of the Code hinged on whether the letter was deemed to promote a medicine or was simply an attempt to secure an appointment. Recordati believed that the latter was the case and thus did not consider that the representative's conduct was in breach of the Code.

Recordati stated that all of its representatives had been trained in the spirit and letter of the Code. In addition the company had a number of procedures in place to minimize the risk of unintended breaches of the Code. These procedures were periodically reinforced with individual members of staff and across the company as a whole.

PANEL RULING

The Panel noted that it was not a foregone conclusion under the Code that only materials which mentioned a product by brand name or generic name were promotional. Materials which did not refer to a product by name could also be considered promotional. Each case would have to be considered on its own merits. The principal role of a representative was to promote medicines. By discussing the efficacy of the dihydropyridine calcium channel blocker, and stating that it was inexpensive, the representative had made claims for the product. The letter was clearly written with the intention of seeking to promote the prescription, supply, sale or administration of Zanidip.

The Panel considered that the representative's actions were totally unacceptable; there appeared to be a serious lack of understanding of the requirements of the Code. The representative had, in effect, created her own promotional material for Zanidip but had not had it certified prior to use in accordance with Clause 14 of the Code. The letter did not include prescribing information. A breach of Clause 4.1 was ruled.

The Panel considered that the representative had failed to maintain a high standard of ethical conduct; neither had she complied with all the relevant clauses of the Code. A breach of Clause 15.2 was ruled.

The Panel noted that although the letter was not on company headed notepaper, from the first two sentences it was clear that it had been written by a representative who was seeking an appointment to promote a dihydropyridine calcium channel blocker. In that regard the Panel did not consider that the letter was disguised promotion. No breach of Clause 10.1 was ruled.

Complaint received **5 May 2006**

Case completed **12 June 2006**

JOHNSON & JOHNSON WOUND MANAGEMENT v BAXTER HEALTHCARE

Promotion of Tisseel Fibrin Sealant Kit

Johnson & Johnson Wound Management complained that Baxter had promoted Tisseel Fibrin Sealant Kit in a large number of hospital departments, including burns and plastic surgery as a haemostat and sealant. As there had previously been some confusion about the licensed indication for Tisseel (Case AUTH/1751/8/05), Johnson & Johnson wrote to the Medicines and Healthcare products Regulatory Agency (MHRA) asking it to clarify the meaning of the sentence 'Tisseel is intended to complement good surgical technique in achieving haemostasis, or obtaining a watertight seal of the dura mater' and to comment as to whether Tisseel was authorised for use outside the areas of cardiovascular surgery and neurosurgery.

The MHRA had replied that the haemostasis could only reflect the benefit in relation to neurosurgery. It could not be used to promote the product for a general haemostasis indication. The presence of the comma should not be used as justification.

Johnson & Johnson therefore considered that Baxter's promotional activities in respect of Tisseel were in breach of the Code as described in Case AUTH/1751/8/05. As well as promoting Tisseel in neurosurgery and cardiovascular surgery (for which it was licensed), Baxter also promoted it for use in burns and plastic surgery. As the MHRA had ruled that Tisseel had in fact a narrow indication, Johnson & Johnson alleged that Baxter's promotional activities breached the Code.

The Panel noted its ruling in Case AUTH/1751/8/05 that, according to Section 4.1 of its SPC dated January 2005, the therapeutic indications were that Tisseel was intended, *inter alia*, to 'complement good surgical technique in achieving haemostasis, or obtaining a watertight seal of the dura mater'. The Panel considered that the punctuation was such that this could be interpreted in one of two ways; either Tisseel was indicated for haemostasis generally, or it was only so indicated in relation to obtaining a watertight seal of the dura mater. The following paragraph of the SPC gave details about the use of Tisseel in cardiopulmonary surgery and as an adjunct to dura sealing. The Panel noted the submissions of the parties.

The Panel noted the advice from the MHRA that the haemostasis could only reflect the benefit in relation to neurosurgery. However there had been no change to the SPC since the previous case. The Panel noted that the product was alleged to be promoted in hospital departments other than neurosurgery and cardiovascular surgery.

The promotional material provided by Baxter Healthcare discussed the use of Tisseel. The Panel did not consider that the material provided, nor the promotion in hospital departments other than neurosurgery and cardiovascular surgery, was inconsistent with the SPC as alleged. No breach of the Code was ruled.

Johnson & Johnson Wound Management complained about the promotion of Tisseel Fibrin Sealant Kit by Baxter Healthcare Ltd.

COMPLAINT

Johnson & Johnson stated that Tisseel was promoted in a large number of hospital departments, including burns and plastic surgery as a haemostat and sealant, Clause 3.2 of the Code stated that the promotion of a medicine must be in accordance with the terms of its marketing authorization and must not be inconsistent with the particulars listed in its summary of product characteristics. As there had previously been some confusion about the licensed indication for Tisseel (Case AUTH/1751/8/05), Johnson & Johnson wrote to the Medicines and Healthcare products Regulatory Agency (MHRA) asking for clarification of the sentence, 'Tisseel is intended to complement good surgical technique in achieving haemostasis, or obtaining a watertight seal of the dura mater.' and to comment on its use outside the areas of cardiovascular surgery and neurosurgery.

The MHRA replied that the haemostasis could only reflect the benefit in relation to neurosurgery. It could not be used to promote the product for a general haemostasis indication. The presence of the comma should not be used as justification.

Johnson & Johnson therefore considered that Baxter's current promotion of Tisseel was in breach of the Code as described in Case AUTH/1751/8/05. As well as promoting Tisseel in neurosurgery and cardiovascular surgery (for which it was licensed), Baxter had promoted it for use in burns and plastics surgery.

As the MHRA had ruled that Tisseel had in fact a narrow indication, Johnson & Johnson alleged that Baxter's current promotional activities breached the Code.

RESPONSE

Baxter Healthcare stated that it did not understand why the MHRA would, if it had passed guidance on Baxter Healthcare's licence to a competitor company, not share their response openly with Baxter. The summary of product characteristics (SPC) for a medicine was the agreed text between the marketing authorization holder and the MHRA, so it seemed strange that the MHRA did not raise any concerns directly with Baxter Healthcare.

Johnson & Johnson correctly quoted the current licensed indication but claimed that Baxter Healthcare was in breach of Clause 3.2 of the Code. Baxter Healthcare would refute this and believed firmly its promotion of Tisseel in the situations described were appropriate and in accordance with the marketing authorization.

Baxter Healthcare acknowledged that when Tisseel was originally licensed in the UK the indication was

limited to haemastasis in cardio-pulmonary bypass surgery only and its promotional material reflected this limitation. In December 2003 the Tisseel indication was broadened following a thorough review by the CSM. This resulted in the addition of the first sentence of the current licence;

'Tisseel is intended to complement good surgical technique in achieving haemostasis, or obtaining a watertight seal of the dura mater.'

and also the specific neurosurgical indication;

'Tisseel kit is used as an adjunct to dural sealing when control of cerebrospinal fluid leakage by conventional neurosurgical techniques including sutures and patches is considered insufficient or impractical.'

Baxter Healthcare acknowledged that Johnson & Johnson had asked it in writing, for evidence of the MHRA's intention as to the interpretation of the Tisseel approved indication. The wording of the current Tisseel SPC reflected the approved indications by the MHRA.

Baxter Healthcare could only assume that the apparent reply from the MHRA, might be a section of a more full email response. The response suggested that Baxter Healthcare had seen the addition of the neurosurgical indication, alone, as justification for a general haemostasis indication. This was not the case. When the variation was approved in 2003 the wording of the indication changed significantly following the full review by the committee on safety of medicines, as outlined previously.

Baxter Healthcare therefore refuted Johnson & Johnson's conclusion, that 'the MHRA have ruled that Tisseel in fact has a narrow indication', since it did not consider that the quoted section of the email from the MHRA reflected the official view of the MHRA.

It was most unfortunate that Johnson & Johnson seemed determined to pursue this issue rather than accepting that it and Baxter Healthcare worked alongside one another in what had been credible and appropriate marketing activities. Baxter Healthcare hoped that the Authority felt the previous guidance provided by it was not impacted by this and equally that Baxter Healthcare's explanations were satisfactory.

PANEL RULING

The Panel noted its ruling in the previous case, Case AUTH/1751/8/05, that according to Section 4.1 of its SPC dated January 2005 the therapeutic indications were that Tisseel was intended, *inter alia*, to 'complement good surgical technique in achieving haemostasis, or obtaining a watertight seal of the dura mater'. The Panel considered that the punctuation was such that this could be interpreted in one of two ways; either Tisseel was indicated for haemostasis generally, or it was only so indicated in relation to obtaining a watertight seal of the dura mater. The following paragraph of the SPC gave details about the use of Tisseel in cardiopulmonary surgery and as an adjunct to dura sealing. The Panel noted the submissions of the parties.

The Panel noted the advice from the MHRA that the haemostasis could only reflect the benefit in relation to neurosurgery. However there had been no change to the SPC since the previous case. The Panel noted that the product was alleged to be promoted in hospital departments other than neurosurgery and cardiovascular surgery.

The promotional material provided by Baxter Healthcare discussed the use of Tisseel. The Panel did not consider that the material provided, nor the promotion in hospital departments other than neurosurgery and cardiovascular surgery, was inconsistent with the SPC as alleged. No breach of Clause 3.2 was ruled.

Complaint received **8 May 2006**

Case completed **19 July 2006**

CASE AUTH/1839/5/06

GENERAL PRACTITIONER v MERCK SHARP & DOHME

Communications from Univadis

A general practitioner complained about a Univadis mailing from Merck Sharp & Dohme. Univadis was a free on-line service from Merck Sharp & Dohme which provided medical information, news and general information to health professionals.

The complainant noted that the mailing gave his name, user name and password but as it was not labelled private and confidential it had been opened by his surgery staff. The complainant did not consider this appropriate or ethical.

The complainant further noted that he had twice asked Univadis to deregister him and not send him any further information. At least once deregistration had been confirmed so the complainant was upset to receive the mailing which showed yet again that he had not been fully deregistered in spite of asking to be. The complainant understood that this also broke data protection regulations.

The Panel noted that Univadis was an internet information service from Merck Sharp & Dohme and a mechanism through which it sent promotional material. It further noted from Merck Sharp & Dohme that in January 2006 the complainant was removed from the promotional mailing list. This did not delete his Univadis account altogether which remained active. It appeared that this led to the personally addressed mailing at issue, sent in May.

The Panel considered that it was most unfortunate that following the complainant's request in January to unsubscribe so that no further emails were sent, Merck Sharp & Dohme did not check with him that he was still happy to receive non-promotional emails and mail. Subscribers could unsubscribe from promotional emails as well as every email or overland mail sent. It was reasonable to assume from the complainant's email to Univadis in January that he did not want any mailings from Univadis.

The Panel further noted that the complainant's confidential data had been posted to him in an envelope which had not been suitably marked such as to prevent others opening it. The terms of use agreement referred to 'Registration and privacy' and stated 'We take your privacy very seriously. Signing up to the Univadis service guarantees the safety of your data'.

The Panel noted that the complainant's name had been removed from a promotional mailing list as requested and that his email address had thus not been used for further promotional mailings. The Panel ruled no breach of the Code. However the Panel considered that in its administration of the Univadis service Merck Sharp & Dohme had not maintained high standards. The Panel ruled a breach of the Code.

A general practitioner complained about a Univadis mailing from Merck Sharp & Dohme Limited. Univadis was a free on-line service from Merck Sharp & Dohme which provided medical information, news, general information to health professionals and communication from Univadis. The document stated that it was a service from Merck Sharp & Dohme.

COMPLAINT

The complainant stated that he had recently received a mailing in the post which was not labelled private and confidential and gave his name, user name and password. As it was not labelled confidential it had been opened by his surgery staff. The complainant did not consider this appropriate or ethical.

The complainant further noted that he had twice asked Univadis to deregister him and not send him any further information about it. On at least one of these occasions it had been confirmed by Univadis so the complainant was extremely upset to receive the mailing which showed yet again that he had not been fully deregistered in spite of registering this. The complainant understood that this also broke data protection regulations.

When writing to Merck Sharp & Dohme, the Authority asked it to respond in relation to Clauses 9.1, 9.9 and 12.3 of the Code.

RESPONSE

Merck Sharp & Dohme stated that Univadis was a free, medical internet site which provided UK physicians, and other individually approved health professionals, access to a range of unbiased and relevant medical news, non medical news and interactive services.

The complainant had registered on the portal in 2003 and had visited the site infrequently. At the time of registration he opted in to receive relevant information about medical news and related services on the portal. The site clearly stated that promotional updates could take the form of emails or overland mail sent to the addresses he specified.

On 5 January 2006, the complainant emailed the Univadis helpdesk to complain that he had tried to unsubscribe from the Univadis email subscriptions. This was achieved by clicking on a link at the bottom of every email. However, some emails continued to be sent to him and he wished this to stop immediately. Appropriate action was taken on the same day by the helpdesk to remove him from all internally held email lists.

This did not delete his Univadis account but simply ensured he would receive no further promotional emails.

The 'Terms and Conditions of Use' for Univadis – which must be read and accepted at sign-up – clearly outlined the policy for contact between Univadis and a member. It specifically stated that even if a new registrant did not give agreement to receive promotional emails (or unsubscribed from them at any time), Univadis still reserved the right to contact

them, should the need arise, with information about their account, or major changes to the Univadis service. Merck Sharp & Dohme submitted that this was standard practice for all membership based websites and was clearly essential to be able to service all active accounts, which included the complainant's.

On 2 May 2006, as part of Merck Sharp & Dohme's communication plan when launching the new version of the portal in April, all currently registered users were sent a personally addressed, sealed, 'security' envelope via overland mail. This envelope could only be opened by tearing off the three perforated edges. Enclosed and printed on the inside of the envelope was the recipient's username and password.

On 4 May 2006, the complainant telephoned the Univadis helpdesk and complained about receiving an envelope with his username and password enclosed and that it did not have private and confidential on the outside. As a result of this his secretary had opened the envelope and he now considered that he had to change a number of other login details for other sites that he used. The Univadis helpdesk took immediate and appropriate action to ensure that the complainant's account was completely deleted on that day.

On 5 May 2006, as requested by the complainant, a letter was sent to his surgery confirming that his account was deleted and that he would not receive any further correspondence from Univadis. The letter also stated that the Univadis team had taken his comments very seriously and all future overland mailings containing personal information would have 'confidential – addressee only' written prominently on the front of each envelope.

PANEL RULING

The Panel noted that Univadis was an internet information service from Merck Sharp & Dohme and a mechanism through which it sent promotional material. It further noted from Merck Sharp & Dohme that on 5 January 2006 the complainant was removed from the promotional update mailing list. This did not delete his Univadis account which remained active. It appeared that this led to the personally addressed letter sent to the complainant in May.

The Panel considered that it was most unfortunate that following the complainant's request in January to unsubscribe so that no further emails were sent, Merck Sharp & Dohme did not check with him that he was still happy to receive other emails and mail. The terms of use agreement stated that subscribers could unsubscribe from promotional emails as well as every email or overland mail sent. The email from the complainant to the Univadis helpdesk, dated 5 January, clearly stated that he did not want emails from Univadis. In the Panel's view, given the tone of that email and the use of block capitals, it was reasonable to assume that the complainant was referring to all mailings, not just promotional ones.

The Panel further noted that the complainant's confidential data had been posted to him in an envelope which had not been suitably marked such as to prevent others opening it. The terms of use agreement referred to 'Registration and privacy' and stated 'We take your privacy very seriously. Signing up to the Univadis service guarantees the safety of your data'.

The Panel noted that the complainant's name had been removed from a promotional mailing list as requested and that his email address had thus not been used for further promotional mailings. The Panel ruled no breach of Clauses 12.3 and 9.9 respectively. However the Panel considered that in its administration of the Univadis service Merck Sharp & Dohme had not maintained high standards. The Panel ruled a breach of Clause 9.1 of the Code.

Complaint received **11 May 2006**

Case completed **4 July 2006**

PRIMARY CARE TRUST PHARMACIST v GLAXOSMITHKLINE

Patient poster on restless legs syndrome

A pharmacist at a primary care trust complained about a poster issued by GlaxoSmithKline, which asked 'Do you suffer from Restless Legs Syndrome [RLS]?' and went on to ask four other questions eg 'Do you have an urge to move your legs?' and 'Is it worse in the evenings or at night?'. Readers were told that if they answered yes to all of the questions then they might have RLS. They were advised to ask their doctor for advice. The GlaxoSmithKline logo appeared in the bottom right-hand corner.

The poster, issued to GP practices, was aimed at the general public and the complainant considered that raising the profile of RLS in this way was wholly inappropriate and misleading in its implication that it could be resolved. The complainant also alleged that the poster was misleading in that it would encourage patients who might, or who might not, be suffering from RLS to seek treatment for it from their GP. It would be more appropriate to encourage patients with the symptoms listed to seek advice rather than implying a diagnosis before they had even seen their GP.

The complainant stated that pharmacological intervention would only be required in an estimated 20-25% of patients with symptoms of RLS. In the majority of cases, non-pharmacological treatments were effective, but required a degree of commitment from patients. Patients were far more likely to request pharmacological treatment. The only licensed treatment for this condition was Adartrel, recently launched by GlaxoSmithKline.

The Panel noted that the poster encouraged readers to ask their doctor for advice as opposed to treatment. GlaxoSmithKline had sponsored the poster and also marketed Adartrel, a prescription only medicine for the symptomatic treatment of moderate to severe idiopathic RLS. Adartrel was not the only medicine so licensed. The Panel considered that although the poster raised awareness about RLS, and thus might facilitate the market development of Adartrel, it did not promote the product to the general public. No breach of the Code was ruled.

The Panel accepted that the poster might encourage patients to ask their doctors for advice about RLS but it did not encourage them to ask for a specific prescription only medicine. The Panel ruled no breach of the Code.

A pharmacist at a primary care trust complained about a poster (ref RLS/PSR/06/25194/1), issued by GlaxoSmithKline UK Ltd. The poster asked the reader 'Do you suffer from Restless Legs Syndrome [RLS]?' and went on to ask four other questions eg 'Do you have an urge to move your legs?' and 'Is it worse in the evenings or at night?'. Readers were told that if they answered yes to all of the questions then they may have RLS. They were advised to ask their doctor for advice. The GlaxoSmithKline logo appeared in the bottom right-hand corner. The poster had been distributed to 14,000 practice managers and 4,500 secondary care physicians.

COMPLAINT

The complainant noted that the poster, issued to GP practices for display, was aimed at the general public. Whilst increasing public awareness of diseases and other medical conditions was commendable when conducted appropriately, the complainant considered that raising the profile of RLS in this way was wholly inappropriate and misleading in its implications that there was a way in which it could be resolved.

It was also misleading in that the poster would encourage such patients who might – or more importantly who might not – be suffering from RLS to seek treatment for it from their GP. It would be far more appropriate to encourage patients with the symptoms listed to seek advice on what might be causing them (eg pregnancy, iron deficiency, renal failure, diabetes and some medicines) rather than implying a diagnosis before the patient had even seen their GP.

This approach was of particular concern given the present therapies available for RLS, particularly when pharmacological intervention would only be required in an estimated 20-25% of patients with symptoms of RLS. In the majority of cases non-pharmacological treatments were effective but required a degree of commitment from patients coupled with lifestyle changes. Patients were far more likely to request pharmacological treatment, which in this case would put the GP in a very difficult position – to either prescribe an unlicensed product such as the majority of dopamine receptor agonists, an opioid or an anticonvulsant or to prescribe a licensed product. Presently the only licensed treatment for this condition was Adartrel, a prescription only medicine recently launched by GlaxoSmithKline. The complainant also considered this was particularly an issue given the black triangle status of the product. The legal classification of the product suggested that the poster might therefore be in breach of the Medicines and Healthcare products Regulatory Agency (MHRA Blue Guide, Section 5.2 (Medicines suitable for advertising to the public).

When writing to GlaxoSmithKline, the Authority asked it to respond in relation to Clauses 20.1 and 20.2 of the Code.

RESPONSE

GlaxoSmithKline disagreed with the complainant's position that the way in which it had tried to raise the profile of RLS was 'wholly inappropriate and misleading in its implications that there was a way in which it could be resolved'.

GlaxoSmithKline firmly considered that the poster provided no information which either directly or

indirectly advertised a prescription only medicine to the general public, and therefore strongly denied a breach of Clause 20.1.

GlaxoSmithKline considered that the poster was entirely appropriate in both its format and content and noted that:

- The poster provided information only to raise patients' awareness that this set of symptoms might indicate RLS, a recognised condition, and that they should consult their GP for further advice. GlaxoSmithKline agreed with the complainant that the GP would be expected to investigate for underlying causes, confirm or refute the diagnosis, and advise on either non-pharmacological treatment or pharmacological treatment as dictated by the patient's clinical status.
- The poster provided no information on, or implied as to which way the condition should be managed. In particular, the poster did not refer to any management interventions.
- There was no branding on the poster that coincided with that of any of GlaxoSmithKline's products.

GlaxoSmithKline also strongly denied a breach of Clause 20.2. The poster did not , either directly or indirectly, refer to any product nor any inference as to the need for treatment, be that non-pharmacological or pharmacological. Thus, GlaxoSmithKline firmly believed that the poster did not prompt patients to ask their doctor for a specific medicine, let alone one marketed by GlaxoSmithKline.

GlaxoSmithKline also noted that Adartrel was not the only licensed treatment for RLS. Pramipexole (marketed by Boehringer Ingelheim as Mirapexin), was granted a marketing authorization for the treatment of moderate to severe RLS on 5 April 2006, over one month before Adartrel received its licence for the same use.

In summary, the poster was developed with the sole objective of raising patients' awareness of a condition which was under-recognised and under-diagnosed. This under-recognition caused distress to patients and repeated consultations.

The poster provided no information on the way in which the condition should be managed, and in particular, did not either directly or indirectly refer to any specific product(s) or management pathways. These were matters between the physician and the patient based on the status of the individual. The poster merely stated that if patients answered 'yes' to the four mentioned questions (based on criteria developed by the International Restless Legs Syndrome Study Group) then they might have RLS and that the doctor should be asked for advice.

GlaxoSmithKline strongly refuted any breach of the Code and believed this poster to be within both the letter and spirit of the Code.

GlaxoSmithKline did not consider the complainant's point about the MHRA Blue Guide was relevant. The poster mentioned no products, but solely raised awareness about a disease area where there was more than one licensed therapy, as well as many established non-pharmacological management interventions, GlaxoSmithKline took the safety of all of its medicines extremely seriously, be they marked with a black triangle or not.

PANEL RULING

The Panel noted that the poster posed a number of questions related to RLS and encouraged those readers who had answered 'yes' to them to go and ask their doctor for advice. There was no direct or implied reference to medicines in the poster. In that regard the Panel noted that readers were encouraged to ask their doctor for advice as opposed to treatment. The Panel noted that Clause 20.1 of the Code stated that prescription only medicines (POMs) must not be advertised to the general public. GlaxoSmithKline had sponsored the poster in question and also marketed Adartrel, a POM for the symptomatic treatment of moderate to severe idiopathic RLS. Adartrel was not the only medicine so licensed. The Panel considered that although the poster raised awareness about RLS, and thus might facilitate the market development of Adartrel, it did not promote the product to the general public. No breach of Clause 20.1 was ruled.

The Panel noted the requirements of Clause 20.2 of the Code that information about prescription only medicines which was made available to the general public must 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 doctors to prescribe a specific prescription only medicine. The Panel accepted that the poster might encourage patients to ask their doctors for advice about RLS but it did not encourage them to ask their doctor to prescribe a specific prescription only medicine. The Panel ruled no breach of Clause 20.2 of the Code.

Complaint received **30 May 2006**

Case completed **5 July 2006**

CODE OF PRACTICE REVIEW – AUGUST 2006

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

1790/1/06 and 1791/1/06	**Merck Sharp & Dohme v Roche and GlaxoSmithKline**	**Promotion of Bonviva**	**Breaches Clauses 7.2 and 7.3**	**Appeal by respondents**	**Page 3**
1797/2/06	Editor of a pharmacy journal v Bayer	Celebrity endorsement	No breach	No appeal	Page 13
1798/2/06	**Media/Director v Bayer**	**Levitra online articles**	**Breaches Clauses 20.1 and 20.2**	**No appeal**	**Page 14**
1799/2/06	Media/Director v Abbott	Arrangements for a meeting	No breach	Appeal by respondent	Page 16
1800/2/06	**Primary Care Trust Head of Prescribing v AstraZeneca**	**Invitation to a meeting**	**Breaches Clauses 4.1 and 4.3**	**No appeal**	**Page 19**
1801/2/06	**General Practitioner v GlaxoSmithKline**	**Reference to a patient website**	**Breaches Clauses 3.2 and 20.2**	**Appeal by respondent**	**Page 20**
1803/2/06 and 1804/2/06	**Procter & Gamble and Sanofi-Aventis v Roche and GlaxoSmithKline**	**Bonviva Once Monthly slide kits**	**Three breaches Clause 7.2 Three breaches Clause 7.4**	**No appeal**	**Page 25**
1806/3/06 and 1809/3/06	The Sunday Times/Director and a General Practitioner v GlaxoSmithKline	Sponsored nurses	No breach	No appeal	Page 29
1808/3/06 and 1811/3/06	The Sunday Times/Director and a General Practitioner v Wyeth	Sponsored nurses	No breach	No appeal	Page 34
1812/3/06	**Pfizer v Bayer**	**SortEDin10 campaign**	**Breaches Clauses 8.1, 20.1 and 20.2**	**No appeal**	**Page 37**
1813/3/06	**Lilly v Bayer**	**SortEDin10 campaign**	**Three breaches Clause 3.2 Three breaches Clause 7.2 Three breaches Clause 7.4 Breach Clause 9.1 Two breaches Clause 20.2**	**No appeal**	**Page 39**
1815/3/06	**Merck Sharp & Dohme v GlaxoSmithKline**	**Provision of textbook to general practitioners**	**Breach Clause 18.1**	**No appeal**	**Page 44**
1816/3/06 and 1818/3/06	General Practitioner v Pfizer	Exubera price information	No breach	No appeal	Page 46
1824/4/06	Media/Director v Servier	Promotion of Protelos	No breach	Appeal by respondent	Page 48
1825/4/06	**ProStrakan v Shire**	**Calcichew – D_3 Forte journal advertisement**	**Breaches Clauses 7.2 and 7.3**	**No appeal**	**Page 55**

1826/4/06	Member of the Public v ProStrakan	Newspaper article about Rectogesic	No breach	No appeal	Page 60
1827/4/06	**Anonymous v Merck Sharp & Dohme**	**Meeting at a Chinese restaurant**	**Breaches Clauses 2, 9.1 and 19.1**	**No appeal**	**Page 63**
1829/4/06	Doctor v Allergan	Vistabel advertisement in Aesthetic Medicine	No breach	No appeal	Page 64
1830/4/06	Primary Care Trust Pharmacist v GW Pharmaceuticals	Alleged promotion of Sativex	No breach	No appeal	Page 66
1834/5/06	**Pfizer Consumer Healthcare v Novartis Consumer Health**	**Nicotinell journal advertisement**	**Two breaches Clause 7.2**	**No appeal**	**Page 68**
1835/5/06	**General Practitioner v Recordati**	**Conduct of representative**	**Breaches Clauses 4.1 and 15.2**	**No appeal**	**Page 72**
1836/5/06	Johnson & Johnson Wound Management v Baxter Healthcare	Promotion of Tisseel Fibrin Sealant Kit	No breach	No appeal	Page 74
1839/5/06	**General Practitioner v Merck Sharp & Dohme**	**Communications from Univadis**	**Breach Clause 9.1**	**No appeal**	**Page 76**
1840/5/06	Primary Care Trust Pharmacist v GlaxoSmithKline	Patient poster on restless legs syndrome	No breach	No appeal	Page 78

PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

The Prescription Medicines Code of Practice Authority was established by The Association of the British Pharmaceutical Industry (ABPI) in 1993 to operate the Code of Practice for the Pharmaceutical Industry at arm's length from the ABPI itself.

Compliance with the Code is obligatory for ABPI member companies and, in addition, about sixty non member companies have voluntarily agreed to comply with the Code and to accept the jurisdiction of the Authority.

The Code covers the advertising of medicines to health professionals and administrative staff and also covers information about 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 sponsorship of promotional meetings
- the sponsorship of scientific and other meetings, including payment of travelling and accommodation expenses
- the provision of information to the public either directly or indirectly, including by means of the Internet
- all other sales promotion in whatever form, such as participation in exhibitions, the use of audio-cassettes, films, records, tapes, video recordings, electronic media, interactive data systems, the Internet and the like.

Complaints submitted under the Code are considered by the Code of Practice Panel which consists of the three members of the Code of Practice Authority acting with the assistance of independent expert advisers where appropriate. Both complainants and respondents may appeal to the Code of Practice Appeal Board against rulings made by the Panel. The Code of Practice Appeal Board is chaired by an independent legally qualified Chairman, Mr William Harbage QC, and includes independent members from outside the industry.

In each case where a breach of the Code is ruled, the company concerned must give an undertaking that the practice in question has ceased forthwith and that all possible steps have been taken to avoid a similar breach in the future. An undertaking must be accompanied by details of the action taken to implement the ruling. Additional sanctions are imposed in serious cases.

Complaints about the promotion of medicines, or the provision of information to the public, should be sent to the Director of the Prescription Medicines Code of Practice Authority, 12 Whitehall, London SW1A 2DY
(telephone 020 7930 9677
facsimile 020 7930 4554)
By email to: complaints@pmcpa.org.uk.