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**