ROCHE v PROCTER & GAMBLE and SANOFI-AVENTIS

Disparagement of Bonviva

Roche complained that, in a concerted campaign, Procter & Gamble and Sanofi-Aventis (the Alliance for Better Bone Health) had consistently misled clinicians about the indication for Roche's product Bonviva (ibandronate) and disparaged the product and the existing evidence base. Procter & Gamble and Sanofi-Aventis supplied Actonel (risedronic acid).

Roche explained that the companies had agreed that the claim 'Only 18% of osteoporotic fractures are vertebral…' was potentially misleading, however the revised claim 'Only 14% of symptomatic osteoporotic fractures are vertebral' (which appeared in a leavepiece and on exhibition panels for Actonel) was also misleading and an unbalanced representation of the data. By only referring to symptomatic vertebral fractures, the burden of vertebral osteoporosis and attendant fractures was grossly underestimated. The vast majority of vertebral fractures were un-diagnosed and yet could have serious clinical consequences at a later date. The lifetime risk of spinal and hip fractures in women was 29% and 14% respectively and in the UK the annual incidence of spinal fractures was 810,000 compared to 400,000 hip fractures (Harvey *et al* 2005). Although the immediate impact of these fractures varied, with 100% of hip fractures, but only 2-10% of vertebral fractures requiring hospitalization, the relative survival rates were similar (0.82 to 0.83).

Whilst the claim might be substantiable, it placed undue emphasis upon a subset of vertebral fractures (those that were symptomatic and came to medical attention), despite the fact that the treatment of the condition depended on diagnosis of osteoporosis, whether or not it was symptomatic. This was unbalanced and misled by implication.

The Panel noted that the claim at issue was referenced to a NICE technology appraisal document on, *inter alia*, alendronate and risedronate for the secondary prevention of osteoporosis fragility fractures in postmenopausal women. This described osteoporosis and noted that fragility fractures occurred most often at the vertebrae, hips and wrists although many vertebral fractures were asymptomatic. Of the estimated 180,000 symptomatic osteoporotic fractures annually in England and Wales, 39% were of the hip, 14% were vertebral fractures and 23% were fractures of the wrist. In women over 50 years of age, the lifetime risk of vertebral fracture was estimated to be about one in three (including asymptomatic vertebral fractures), and approximately one in six for hip fracture. Postmenopausal women with an initial fracture were at much greater risk of subsequent fractures.

The page of the leavepiece at issue included the claim 'Patients would want their osteoporosis treatment to protect them from hip fracture…'. The Panel considered that the page implied symptomatic fractures were either vertebral or hip. No mention was made of wrist fractures (23%). The Panel noted that although the incidence of symptomatic vertebral fractures was less than that of hip fracture, women over 50 were twice as likely to sustain a vertebral fracture (including asymptomatic vertebral fractures) than a hip fracture. The Panel considered that the claim 'Only 14% of symptomatic osteoporotic fractures are vertebral' was misleading as alleged. It minimised the impact of vertebral fractures and implied that they were not very common which was not so. A breach of the Code was ruled.

Roche complained that at a symposium sponsored by Procter & Gamble and Sanofi-Aventis, a slide used by one of the presenters asserted that ibandronate increased the risk of non-vertebral fractures in a subset of patients. This conclusion had been reached by using an inappropriate method of analysis. A more appropriate statistical method revealed that ibandronate did not increase the risk of such fractures. Further, regulatory authorities granted marketing authorization on the basis of anti-fracture efficacy at one skeletal site, and no detrimental effect upon other sites. Thus this claim was not consistent with the Bonviva summary of product characteristics (SPC) and hence disparaged the product.

The Panel noted that the slide in question, headed 'Beware of subgroup analyses!' had been used by an independent speaker at a symposium organized by the Alliance for Better Bone Health. The slide featured two bar charts; the first showed that in patients with a femoral neck BMD > –3.0, ibandronate increased fracture risk by 44% compared with placebo. The second bar chart showed a 64% decreased fracture risk compared with placebo in patients with a femoral neck BMD of < –3.0.

The slide illustrated the dangers of sub-group analysis. The Panel understood that the results shown, if true, might have been such as to prevent Bonviva obtaining a marketing authorisation for the treatment of osteoporosis at least in a subgroup of patients. The Panel acknowledged the very limited use of the data and the context in which the slide was shown but nonetheless considered that Bonviva had been disparaged as alleged. A breach of the Code was ruled.

Roche noted that a telephone survey conducted on behalf of Procter & Gamble and Sanofi-Aventis asked patients to choose between a weekly bisphosphonate with efficacy against both hip and vertebral fractures, and a monthly bisphosphonate with only vertebral fracture efficacy. As Bonviva was the only monthly bisphosphonate, this survey unambiguously referred to ibandronate. The options presented to participants were unbalanced and misleading in that they failed to highlight the fact that both Bonviva and Actonel had similar licences for the treatment of postmenopausal osteoporosis (although different evidence bases) and that there was clinical efficacy for Bonviva at the hip represented by the BMD and bone marker data.

In real life (as opposed to the choices in the questionnaire) Bonviva patients would be given a

patient information leaflet (PIL) which stated 'Bonviva is prescribed to you to treat osteoporosis. Osteoporosis is a thinning and weakening of the bones which is common in women after the menopause…'. There was no warning in the PIL about lack of effect at the hip. The PIL also stated that Bonviva 'prevents loss of bone from osteoporosis and help to rebuild bone. Therefore Bonviva makes bone less likely to break'. To therefore imply in the questionnaire that ibandronate had only vertebral efficacy contradicted the position of the regulatory authorities and prior rulings by the Panel, as well as the general understanding of osteoporosis, the mechanism of action of bisphosphonates and Bonviva's licensed indication. Furthermore, one could only imagine how disquieting such suggestions might be for participants.

Roche alleged that the survey was misleading and disparaging and constituted disguised promotion. It was particularly worrying that this information went directly to patients who were unlikely, unless already treated with Bonviva, to be fully informed of the facts about the efficacy of the medicine. Roche alleged that the survey brought discredit upon, and reduced confidence in, the pharmaceutical industry in breach of Clause 2.

The Panel noted that in the screening questionnaire, all patients currently taking, *inter alia*, Bonviva, were ineligible to take part in the main survey. Thus no patients taking a monthly bisphosphonate would take part.

The main survey sought to elicit perceptions of bisphosphonates with different characteristics. First of all patients had to choose between product R and product I. Product R was to be taken once weekly and had clinical data to show that it reduced fracture at the hip and spine. Product I was to be taken once a month and had clinical data to show that it reduced fracture at the spine but no such data for the hip. Participants were then asked to rate product E, which was a once monthly bisphosphonate which had clinical data to show that it reduced fracture at the spine and hip, and compare it with product R.

The Panel noted that the only requirement in the Code with respect to market research was that such activities must not be disguised promotion. Although the Panel assumed that products I and R were ibandronate (Bonviva) and risedronate (Actonel) respectively, the public would not generally make such an assumption. The Panel did not consider that the questionnaire was disguised promotion of a medicine. No breach of the Code was ruled.

Roche Products Limited complained that Procter & Gamble Pharmaceuticals UK Ltd and Sanofi-Aventis, acting as the Alliance for Better Bone Health, had misled clinicians about the indication for ibandronate (Roche's product Bonviva) and disparaged the product and the existing evidence base. The consistency of this theme across several promotional items and at a recent satellite symposium at the National Osteoporosis Society meeting led Roche to conclude that these actions represented a concerted campaign. Procter & Gamble and Sanofi-Aventis supplied Actonel (risedronic acid).

General Comments by Roche

Roche contended that these efforts undertaken by the Alliance were contrary to the fact that Bonviva had been licensed for the treatment of postmenopausal osteoporosis. This position also contradicted the rulings in Cases AUTH/1779/11/05, AUTH/1780/11/05 and AUTH/1790/1/06. Roche had been satisfied that claims relating to the definition of osteoporosis and the interpretation of the licences of bisphosphonates had been clarified at the completion of these cases. However, the Alliance persisted in claiming, implying and suggesting that Bonviva possessed a restricted licence in osteoporosis that limited its efficacy only to one skeletal area. The Alliance was involved in two of these appeals and thus would know about the Appeal Board's rulings.

Roche noted that Bonviva was licensed for the treatment of osteoporosis in postmenopausal women, in order to reduce the risk of vertebral fractures. Demonstration of a reduction in the rate of femoral neck fractures was not a requirement for the licence of treatment of postmenopausal osteoporosis. Osteoporosis was a generalised disease of bone. Bisphosphonates acted on all bones. In addition section 5.1 of the Bonviva summary of product characteristics (SPC) under the heading of 'Clinical efficacy' showed that Bonviva increased bone mineral density (BMD) at the whole hip, the femoral neck and trochanter. In addition this section stated that Bonviva produced 'clinically meaningful reductions in markers of bone resorption'.

Roche had detailed in the above cases that the EU requirements for obtaining an osteoporosis licence took account of the problems involved in carrying out placebo-controlled studies for new bisphosphonates. These guidelines also stated that a licence for osteoporosis would only be granted if anti-fracture efficacy had been demonstrated at a minimum of one site, with no deleterious effect upon other sites. The same guidelines indicated that licences were issued for either the treatment or prevention of postmenopausal osteoporosis. Marketing authorization for the treatment of osteoporosis was not granted in a site-specific manner. A claim that Bonviva reduced fracture rates at the hip would not be consistent with the SPC. Conversely claims that Bonviva had no effect at the hip (ie ignoring the BMD data) or that its pharmacodynamic effect was restricted to vertebral bone were misleading, unbalanced, unfair and inaccurate.

These matters had previously been addressed through inter-company dialogue and with the Authority. Nevertheless, the Alliance continued to disparage the efficacy and safety profile of ibandronate. Despite inter-company communication, Roche was unable to reach a consensus, and thus was obliged to refer the matter to the Authority.

1 Claim 'Only 14% of symptomatic osteoporotic fractures are vertebral'

This claim appeared as the heading to an Actonel

leavepiece (A2925) and also on exhibition panels.

COMPLAINT

Roche noted that during inter-company discussion, it had been agreed that the claim 'Only 18% of osteoporotic fractures are vertebral…' was potentially misleading. However Roche considered that the revised claim 'Only 14% of symptomatic osteoporotic fractures are vertebral' was also misleading and an unbalanced representation of the data. By only referring to vertebral fractures which presented to medical attention symptomatically, the burden of disease imposed by vertebral osteoporosis and attendant fractures was grossly underestimated. It was well known that the vast majority of vertebral fractures were un-diagnosed and yet could have serious clinical consequences at a later date. In contrast, Harvey *et al* (2005) revealed that the lifetime risk of spinal and hip fractures in women was 29% and 14% respectively. The authors also reported that in the UK, the annual incidence of spinal fractures was 810,000 compared to 400,000 hip fractures. Although the immediate impact of these fractures varied, with 100% of hip fractures, but only 2-10% of vertebral fractures requiring hospitalization, the relative survival rates were similar (0.82 to 0.83).

All information in promotional material must be accurate and balanced. Whilst the claim might be capable of substantiation, the statement placed undue emphasis upon a subset of vertebral fractures (ie those that were symptomatic and came to medical attention), despite the fact that the treatment of the condition depended on diagnosis of osteoporosis, whether or not it was symptomatic. This was unbalanced and misleading by implication and in breach of Clause 7.2.

RESPONSE

Procter & Gamble and Sanofi-Aventis stated that they had talked to Roche about a related claim, 'In established osteoporosis only 18% of osteoporotic fractures are vertebral', and as a conciliatory gesture had offered to amend it. Roche had not discussed the revised claim with the companies, which was not in the spirit of the process described above.

The 14% cited in this leavepiece was derived from, and thus substantiated by, data published by the National Institute for Health and Clinical Excellence (NICE). The leavepiece was intended for doctors who based the diagnosis of osteoporosis on clinical evidence. Procter & Gamble and Sanofi-Aventis agreed that the treatment of the condition depended on the diagnosis of osteoporosis. Current NICE guidance referred to women who had sustained a clinically apparent osteoporotic fracture, thus emphasizing the role of the symptomatic osteoporotic fracture in treatment decisions. In the Appraisal Consultation Document issued by NICE on the primary prevention of osteoporotic fragility fractures, treatment decisions were guided by the result of BMD measurement and additional risk factors, none of which included un-diagnosed vertebral fractures. Thus when talking to physicians it made sense to refer to clinical/symptomatic vertebral fractures specifically, as these were the fractures that came to clinical attention, resulting in consultations and subsequent costs to the NHS.

In addition, Roche had referred to the review by Harvey *et al*; some of the data cited by Roche from that paper was from 1992. The 29% lifetime risk of spinal fracture cited by Roche was actually 28% in the paper and the annual incidence of spinal fracture of 810,000 and of hip fracture of 400,000 did not appear in the paper. While Procter & Gamble and Sanofi-Aventis agreed that the amount of un-diagnosed vertebral fractures was of academic interest, the figure relevant to doctors was the number of fractures coming to clinical attention (namely 14%), which was specifically highlighted in the documents from NICE.

Procter & Gamble and Sanofi-Aventis therefore disagreed that the claim was misleading. The leavepiece was a balanced view of scientific and promotional communication of current data. The companies denied a breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted that the claim 'Only 14% of symptomatic osteoporotic fractures are vertebral' was referenced to NICE. The NICE document in question was a technology appraisal document on, *inter alia*, alendronate and risedronate for the secondary prevention of osteoporosis fragility fractures in postmenopausal women (January 2005). Section 2, 'Clinical need and practice', described osteoporosis and noted that fragility fractures occurred most often at the vertebrae, hips and wrists although many vertebral fractures were asymptomatic. Of the estimated 180,000 symptomatic osteoporotic fractures annually in England and Wales 39% were hip fractures, 14% were vertebral fractures and 23% were fractures of the wrist. In women over 50 years of age, the lifetime risk of vertebral fracture was estimated to be about one in three (including asymptomatic vertebral fractures), and approximately one in six for hip fracture. Postmenopausal women with an initial fracture were at much greater risk of subsequent fractures.

The page of the leavepiece at issue included the claim 'Patients would want their osteoporosis treatment to protect them from hip fracture…'. The Panel considered that the page implied symptomatic fractures were either vertebral or hip. No mention was made of wrist fractures (23%). The Panel noted that although the incidence of symptomatic vertebral fractures was less than that of hip fracture, women over 50 were twice as likely to sustain a vertebral fracture (including asymptomatic vertebral fractures) than a hip fracture. The Panel considered that the claim 'Only 14% of symptomatic osteoporotic fractures are vertebral' was misleading as alleged. It minimised the impact of vertebral fractures and implied that they were not very common which was not so. A breach of Clause 7.2 was ruled.

2 Use of inappropriate statistical analysis

COMPLAINT

Roche stated that Procter & Gamble and Sanofi-Aventis had been responsible for the claim that

ibandronate increased non-vertebral fracture risk in a subset of patients. At a symposium sponsored by the two companies at the National Osteoporosis Society, a slide used by one of the presenters asserted that ibandronate increased the risk of non-vertebral fractures in a subset of patients from the pivotal BONE study with a femoral neck BMD T-score > –3. This misleading and inaccurate claim would inevitably raise concerns about ibandronate's safety profile.

To arrive at this conclusion, chi-square analyses were applied to data that appeared on the FDA website. Whilst such tests were useful for elucidating differences between groups, this analysis was inappropriate when examining drug effects, which must take 'time to event' into account. To determine drug efficacy therefore, the FDA proposed that Kaplan-Meier tests were performed. This appropriate analysis revealed that ibandronate did not increase the risk of non-vertebral fractures in a subset with femoral neck BMD T-scores > –3.0. Further, it should be acknowledged that the regulatory authorities granted marketing authorization on the basis of anti-fracture efficacy at one skeletal site, and no detrimental effect upon other sites. Thus this claim was not consistent with the Bonviva SPC and hence disparaged the product.

Procter & Gamble and Sanofi-Aventis contended that all the data represented the speaker's opinion. However, it was the sponsor's responsibility to ensure that all materials relating to a sponsored conference symposium were accurate, fair, balanced and neither misleading or disparaging. Furthermore, the supplementary information to Clause 7.2 indicated that there were precedents wherein claims were based upon publications quoting incorrect statistical methodology. Thus, the supplementary information to Clause 7.2 required that 'before statistical information is used … it must be subjected to statistical appraisal'.

RESPONSE

Procter & Gamble and Sanofi-Aventis submitted that the slide was developed by the speaker, in this case an international thought leader in the field of osteoporosis and a former officer of the European Calcified Tissue Society, the key European society for osteoporosis research, who was not an employee of either of the two companies. The two companies had not provided any materials showing a proportional analysis figure of the sub-population in question and the speaker confirmed in his letter to the Authority, that Roche had misrepresented what was actually presented.

The above presentation reflected an independent opinion and in addition conveyed a fair and balanced view of the data supporting ibandronate. Roche had not fairly represented what occurred at the symposium, so Procter & Gamble and Sanofi-Aventis therefore disagreed with the opinion that there had been a breach of Clause 8.1 of the Code.

PANEL RULING

The Panel noted that the slide in question, headed 'Beware of subgroup analyses!' had been used by an independent speaker at a symposium organized by the Alliance for Better Bone Health. The slide featured two bar charts; the first showed that in patients with a femoral neck BMD > –3.0, ibandronate increased fracture risk by 44% compared with placebo. The second bar chart showed a 64% decreased fracture risk compared with placebo in patients with a femoral neck BMD of < –3.0.

The Panel noted that the slide was shown to delegates at a company-sponsored symposium and used to illustrate the dangers of sub-group analysis. The slide featured clinical results about a product which was a direct competitor to that of the sponsor company. The Panel queried why other data could not have been used to illustrate the point. The Panel understood that the results shown, if true, might have been such as to prevent Bonviva obtaining a marketing authorisation for the treatment of osteoporosis at least in a subgroup of patients. The Panel acknowledged the very limited use of the data and the context in which the slide was shown but nonetheless considered that Bonviva had been disparaged as alleged. A breach of Clause 8.1 was ruled.

3 Market research telephone survey

COMPLAINT

Roche alleged that a patient preference survey conducted on behalf of Procter & Gamble and Sanofi-Aventis disparaged Bonviva. The telephone questionnaire asked patients to choose between a weekly bisphosphonate with efficacy against both hip and vertebral fractures, and a monthly bisphosphonate with only vertebral fracture efficacy. As Bonviva was the only monthly bisphosphonate, this survey unambiguously referred to ibandronate. The options presented to participants were unbalanced and misleading in that it failed to highlight the fact that both Bonviva and Actonel had similar licences for the treatment of postmenopausal osteoporosis (although different evidence bases) and that there was clinical efficacy for Bonviva at the hip represented by the BMD and bone marker data.

In real life (as opposed to the choices in the questionnaire) Bonviva patients would be given a patient information leaflet (PIL) which stated 'Bonviva is prescribed to you to treat osteoporosis. Osteoporosis is a thinning and weakening of the bones which is common in women after the menopause…'. There was no warning in the PIL about lack of effect at the hip. The PIL also stated that Bonviva 'prevents loss of bone from osteoporosis and help to rebuild bone. Therefore Bonviva makes bone less likely to break'. To therefore imply in the questionnaire that ibandronate had only vertebral efficacy contradicted the position of the regulatory authorities and prior rulings by the Panel, as well as the general understanding of osteoporosis, the mechanism of action of bisphosphonates and Bonviva's licensed indication. Furthermore, one could only imagine how disquieting such suggestions might be for participants in the survey if they, or someone known to them, were prescribed Bonviva.

Roche alleged that the survey was misleading and

disparaging in breach of Clauses 7.2 and 8.1 and constituted disguised promotion in breach of Clause 10.2. Roche considered that the survey was irresponsible and deliberately disparaged the only available monthly bisphosphonate by implication. It was particularly worrying that this information went directly to patients who were unlikely, unless already treated with Bonviva, to be fully informed of the true facts about the efficacy of the medicine. Roche believed therefore that this activity brought discredit upon, and reduced confidence in, the pharmaceutical industry, and therefore alleged a breach of Clause 2.

RESPONSE

Procter & Gamble and Sanofi-Aventis submitted that the market research was non-promotional and did not contravene the Code.

Procter & Gamble and Sanofi-Aventis noted Roche's allegation that the survey failed to highlight that the licences had similar indications but different evidence bases. The wording in the questionnaire 'The product does not have information based on clinical studies to support that it is effective at reducing the risk of a broken hip bone' referred to the difference in this evidence base.

Roche had also claimed that Actonel and Bonviva had similar licences. Rulings from the Appeal Board clearly stated that the Bonviva indications were not similar to the indications for once weekly bisphosphonates: Cases AUTH/1779/11/05 and AUTH/1780/11/05. In addition the Appeal Board went on to state 'given the context of the page readers would assume that alendronate and Bonviva had the same indication and this was not so'. In Cases AUTH/1790/1/06 and AUTH/1791/1/06, the Appeal Board stated '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 fracture had not been established whilst Fosamax was specifically licensed to reduce the risk of hip fracture'.

Roche went on to quote the Bonviva PIL and stated that 'there is no warning in the PIL about lack of effect at the hip'. It was not common practice to include warnings of lack of efficacy in the PIL and this could not be accepted as the position of the regulatory authorities that ibandronate had shown efficacy in hip fracture reduction. On the contrary the regulatory authorities had clearly stated in the indication section of the Bonviva SPC: 'Efficacy on femoral neck fractures has not been established'.

Roche mentioned how disquieting this survey might have been to subjects if they or someone known to them were prescribed ibandronate. In the screening document it was outlined that only subjects currently on a weekly bisphosphonate were eligible to participate. It was also very unlikely that the subjects would be aware that only one monthly treatment existed as promotion direct to consumers was prohibited under the Code.

Based on the above Procter & Gamble and Sanofi-Aventis denied that the telephone survey was in breach of Clauses 2, 7.2 and 10.2. The telephone survey was conducted as pure market research and was not promotional or disparaging to Bonviva.

PANEL RULING

The Panel noted the parties' references to previous cases and was concerned about some of Procter & Gamble and Sanofi-Aventis' comments about the rulings. The previous cases had all involved material directed at health professionals. The matter now under consideration involved material for patients. Each case under the Code had to be considered on its own merits.

The Panel noted that in the screening questionnaire, all patients currently taking, *inter alia*, Bonviva, were ineligible to take part in the main survey. Thus no patients taking a monthly bisphosphonate would take part in the survey.

The main survey sought to elicit patients' perceptions of bisphosphonates with different characteristics. First of all patients had to choose between product R and product I. Product R was to be taken once weekly and had clinical data to show that it reduced fracture at the hip and spine. Product I was to be taken once a month and had clinical data to show that it reduced fracture at the spine but no such data for the hip. Participants were then asked to rate product E, which was a once monthly bisphosphonate which had clinical data to show that it reduced fracture at the spine and hip, and compare it with product R.

The Panel noted that the only requirement in the Code with respect to market research was that such activities must not be disguised promotion. Although the Panel assumed that products I and R were ibandronate (Bonviva) and risedronate (Actonel) respectively, the public would not generally make such an assumption. The Panel did not consider that the questionnaire was disguised promotion of a medicine. No breach of Clause 10.2 was ruled. It thus followed that there was no breach of Clauses 7.2, 8.1 and 2 of the Code.

Complaint received **22 August 2006**

Case completed **8 December 2006**