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**