ROCHE and GLAXOSMITHKLINE v PROCTER & GAMBLE and SANOFI-AVENTIS

Disparagement of Bonviva

Roche complained on behalf of itself and GlaxoSmithKline about a slide kit produced by Procter & Gamble and Sanofi-Aventis, acting as the Alliance for Better Bone Health. The slide kit presented data on Roche's product, Bonviva (ibandronate). Procter & Gamble and Sanofi-Aventis jointly promoted Actonel (risedronate).

Roche drew attention to supplementary evidence to support a previous complaint made by it and GlaxoSmithKline (Cases AUTH/1885/8/06 and AUTH/1886/8/06) in respect of activities undertaken by Procter & Gamble and Sanofi-Aventis which misled clinicians about the licensed indication for Bonviva and disparaged it and the existing evidence base.

The slide kit entitled 'Do all bisphosphonates have the same fracture efficacy? Non-vertebral Fracture Risk in Ibandronate Clinical Trials' was being proactively used as a promotional item and distributed to clinicians by Procter & Gamble and Sanofi-Aventis for use at speaker meetings. Its content was formed from the same data set used in the claim that ibandronate increased non-vertebral fracture in a subset of patients made at a Procter & Gamble and Sanofi-Aventis sponsored symposium in June 2006 and considered in Cases AUTH/1885/8/06 and AUTH/1886/8/06.

Roche and GlaxoSmithKline believed that because the slide kit was prepared in May, ie before the symposium in June, it contradicted the companies' contention in Cases AUTH/1885/8/06 and AUTH/1886/8/06 that the data presented was unknown to them and represented the speaker's opinion alone.

Roche alleged that the content of the slide kit was disparaging and was taken out of context from materials supplied to the Food and Drug Administration (FDA) as part of the original licence submission and thus breached the Code. This slide set and the slide used at the symposium purported to reflect analyses carried out by or endorsed by the FDA. In fact the link to the FDA website led only to a summary prepared by the FDA reviewers of clinical data submitted by Roche for licence approval in the US. This summary included a short section which examined a subgroup of patients in one of the pivotal studies who were at high risk of non-vertebral fracture and in which treatment with ibandronate led to a 69% decrease in fracture rate. An FDA annotation in this summary noted that the information was of academic interest but would not be included in the package insert. Procter & Gamble and Sanofi-Aventis however had included this analysis plus tables and other data in the clinical summary to construct a slide set designed to disparage Bonviva. Thus one of the slides was a construct which showed a higher fracture rate in patients with T score < -3 which was similar to the bar chart shown at the company sponsored symposium. The FDA reviewers did not perform this analysis although the slides misled the viewer to believe that they had. Indeed the juxtaposition of genuine FDA slide copies with slides constructed by Procter & Gamble and Sanofi-Aventis further misled as to the origin of the analysis especially as all the slides were referenced to the website. The way in which Procter & Gamble and Sanofi-Aventis were proactively distributing these data undermined confidence in the pharmaceutical industry in breach of Clause 2.

The Panel noted that the previous cases, Cases AUTH/1885/8/06 and AUTH/1886/8/06 concerned a slide headed 'Beware subgroup analyses!' used by an independent speaker at a symposium organized by Procter & Gamble and Sanofi-Aventis. The slide featured two bar charts: the first showed that in patients with a femoral neck bone mineral density (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 was used to illustrate the dangers of sub-group analysis and 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 authorization 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 had been ruled.

Turning to the present complaint, Cases AUTH/1911/11/06 and AUTH/1912/11/06, the Panel noted that the slide kit at issue, entitled 'Do all bisphosphonates have the same fracture efficacy? Non-vertebral Fracture Risk in Ibandronate Clinical Trials', similarly presented analysis based on data from the FDA website. The material was, however, different to that considered in Cases AUTH/1885/8/06 and AUTH/1886/8/06. The Panel noted that there was no allegation of a breach of undertaking and that the slide kit had, in any event, been withdrawn pursuant to the earlier cases.

Slide 14 of the set featured a table headed 'Non-vertebral fractures in women with femoral neck T-score above and below -3.0 SD' which was 'Deduced from

tables presented on pages 25 and 26 of the FDA report'. The number of non-vertebral osteoporotic fractures for the ITT population subjects with femoral neck T-score above -3SD was 47 for placebo and 68 for Bonviva 2.5mg. This data was reproduced in graphs on two subsequent slides, one of which showed that patients with a baseline femoral neck BMD T-score ≥ - 3 SD represented 87% of the patient population (ITT). The Panel also noted that some slides featured tables headed 'FDA Medical Review of Ibandronate' and cited the relevant report page. Some slides featured graphs which were not similarly headed but featured the relevant FDA website address in the bottom right-hand corner. Two tables explained data was 'deduced' from tables in the FDA report. Other slides did not refer to the FDA.

The Panel considered that the data showing increased fracture risk disparaged Bonviva as alleged. A breach of the Code was ruled. Further, the Panel considered that juxtaposing FDA data with material created by Procter & Gamble and Sanofi-Aventis, and slides which gave no indication of the material's origin were such that the origin of the analyses was not sufficiently clear. Readers might gain the impression that data regarding the increased fracture risk in patients with a baseline femoral neck BMD T-score ≥ - 3 SD was consistent with the relevant FDA report which was not so. The material was misleading in this regard. A breach of the Code was ruled.

The Panel did not consider that use of material was in breach of Clause 2 of the Code which was used as a sign of particular censure and reserved for such use.

Roche Products Limited complained on behalf of itself and GlaxoSmithKline UK Ltd about a slide kit (ACT 3206) produced by Procter & Gamble Pharmaceuticals UK Ltd and Sanofi-Aventis, acting as the Alliance for Better Bone Health. The slide kit presented data on Roche's product, Bonviva (ibandronate). Procter & Gamble and Sanofi-Aventis jointly promoted Actonel (risedronate).

COMPLAINT

Roche drew attention to supplementary evidence to support the complaint made by it and GlaxoSmithKline (Cases AUTH/1885/8/06 and AUTH/1886/8/06) in respect of activities undertaken by Procter & Gamble and Sanofi-Aventis which misled clinicians about the licensed indication for Bonviva and disparaged it and the existing evidence base.

The slide kit entitled 'Do all bisphosphonates have the same fracture efficacy? Non-vertebral Fracture Risk in Ibandronate Clinical Trials' was being proactively used and distributed as a promotional item by Procter & Gamble and Sanofi-Aventis. Its content was formed from the same data set used in the claim that ibandronate increased non-vertebral fracture in a subset of patients made at the symposium sponsored by Procter & Gamble and Sanofi-Aventis at the National Osteoporosis Society meeting held in Harrogate (25-28 June). This was originally considered in Cases AUTH/1885/8/06 and AUTH/1886/8/06.

Roche and GlaxoSmithKline believed that because the preparation date of the slide kit (May 2006) preceded the symposium (June 2006) it contradicted the companies' contention in Cases AUTH/1885/8/06 and AUTH/1886/8/06 that the data presented was unknown to them and represented the speaker's opinion alone.

Roche also alleged that the slide kit was being actively used as a promotional item and proactively distributed to clinicians for use at speaker meetings. The content was clearly disparaging and was taken out of context from materials supplied to the Food and Drug Administration (FDA) as part of the original licence submission and thus breached Clauses 8.1 and 7.2 of the Code. This slide set and the slide used at the symposium were used as if they reflected analyses carried out by or endorsed by the FDA. In fact the link to the FDA website led only to a summary prepared by the FDA reviewers of clinical data submitted by Roche for licence approval in the US. Included in this summary of clinical data was a short section which examined a subgroup of patients in one of the pivotal studies who were at high risk of non-vertebral fracture and in which treatment with ibandronate led to a 69% decrease in fracture rate. An FDA annotation in this summary noted that the information was of academic interest but would not be included in the package insert. Procter & Gamble and Sanofi-Aventis however had included this analysis plus tables and other data in the clinical summary to construct a slide set designed to disparage the evidence base for effectiveness of Bonviva at non-vertebral sites and to disparage Bonviva effectiveness in general. Thus one of the slides was a construct which showed a higher fracture rate in patients with T score < -3 which was similar to the bar chart shown at the company sponsored symposium. The FDA reviewers did not perform this analysis although the slides misled the viewer to believe that they had. Indeed the juxtaposition of genuine FDA slide copies with slides constructed by Procter & Gamble and Sanofi-Aventis further misled as to the origin of the analysis especially as all the slides were referenced in the same manner to the website. The manner in which Procter & Gamble and Sanofi-Aventis was proactively distributing these data undermined confidence in the pharmaceutical industry in breach of Clause 2.

Whilst the original complaint relating to the inappropriate statistical analysis did not claim that Procter & Gamble and Sanofi-Aventis' activities breached Clause 2, Roche and GlaxoSmithKline now believed that the activities had reduced confidence in the pharmaceutical industry. This was based on the concerted campaign to disparage Bonviva in combination with the abuse of Paragraph 5.2 of the Constitution and Procedure evidenced by the complete denial that they neither knew of the data presented at the symposium referred to in the original complaint or its active promotion via a slide kit thereafter despite direct questioning.

RESPONSE

Procter & Gamble and Sanofi-Aventis explained that the

slide kit in question 'Do all bisphosphonates have the same fracture efficacy?' was designed to provide scientific information on the non-vertebral fracture efficacy of Bonviva to thought leaders in osteoporosis. The 16 slides captured the evidence base on the ibandronate non-vertebral fracture efficacy. All efforts were taken to include all the data available in the public domain regarding the non-vertebral fracture efficacy of ibandronate. That was without making interpretations, performing analysis and omitting relevant fracture data.

Chesnut et al (2004), and study MF4411 (which was shared in the Medical Review of the FDA report and currently mentioned in section 5.1 of the Bonviva summary of product characteristics (SPC)) were shared accurately and were fairly represented. The allegations that the data had been altered, or misrepresented were untrue. Furthermore the data provided was sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine. If any more information was available the companies would welcome this input from Roche and GlaxoSmithKline. The companies denied breaches of Clauses 8.1 and 7.2.

The slides faithfully led the reader through the data starting with Chesnut *et al*, and clearly stated that there was no significant difference for the non-vertebral fracture levels between the placebo and active arms of the study. When depicting study MF4411 the slides clearly showed where the data was presented in the FDA website, and clearly stated that data was deduced. It was not claimed that ibandronate increased non-vertebral fracture in a subset of patients, nor was it implied that any analysis was performed by the FDA. The companies stressed that it would never intentionally bring discredit upon, or reduce confidence in, the pharmaceutical industry, and thus refuted any breach of Clause 2.

The companies noted that this data led to the Bonviva SPC revisions (Section 5.1) and was not only of academic interest as previously dismissed by Roche.

The companies acknowledged the ruling in Cases AUTH/1885/8/06 and AUTH/1886/8/06 and had withdrawn the slide kit.

PANEL RULING

The Panel noted that the previous cases, Cases AUTH/1885/8/06 and AUTH/1886/8/06 concerned a slide headed 'Beware subgroup analyses!' used by an independent speaker at a symposium organized by Procter & Gamble and Sanofi-Aventis. The slide featured two bar charts: the first showed that in patients with a femoral neck bone mineral density (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 authorization 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 had been ruled.

Turning to the present complaint, Cases AUTH/1911/11/06 and AUTH/1912/11/06, the Panel noted that the slide kit at issue, entitled 'Do all bisphosphonates have the same fracture efficacy? Non-vertebral Fracture Risk in Ibandronate Clinical Trials', similarly presented analysis based on data from the FDA website. The material was, however, different to that considered in Cases AUTH/1885/8/06 and AUTH/1886/8/06. The Panel noted that there was no allegation of a breach of undertaking and that the slide kit had, in any event, been withdrawn pursuant to the earlier cases.

The Panel noted that slide 14 of the set featured a table headed 'Non-vertebral fractures in women with femoral neck T-score above and below -3.0 SD' which was 'Deduced from tables presented on pages 25 and 26 of the FDA report'. The number of non-vertebral osteoporotic fractures for the ITT population subjects with femoral neck T-score above -3SD was 47 for placebo and 68 for Bonviva 2.5mg. This data was reproduced in two subsequent graphs on slides 15 and 16, one of which showed that patients with a baseline femoral neck BMD T-score ≥ - 3 SD represented 87% of the patient population (ITT). The Panel also noted that some slides featured tables headed 'FDA Medical Review of Ibandronate' and cited the relevant report page. Some slides featured graphs which were not similarly headed but featured the relevant FDA website address in the bottom right-hand corner. Two tables explained data was 'deduced' from tables in the FDA report. Other slides did not refer to the FDA.

The Panel considered that the data showing increased fracture risk disparaged Bonviva as alleged. A breach of Clause 8.1 was ruled. Further, the Panel considered that the juxtaposing of FDA data with material created by Procter & Gamble and Sanofi-Aventis, and slides which gave no indication of the material's origin were such that the origin of the analyses was not sufficiently clear. Readers might gain the impression that data regarding the increased fracture risk in patients with a baseline femoral neck BMD T-score ≥ - 3 SD was consistent with the relevant FDA report which was not so. The material was misleading in this regard. A breach of Clause 7.2 was ruled.

The Panel did not consider that use of material was in breach of Clause 2 of the Code which was used as a sign of particular censure and reserved for such use.

Complaint received 7 November 2006

Case completed 5 March 2007