PRIMARY CARE TRUST PRESCRIBING ADVISOR v ROCHE and GLAXOSMITHKLINE

Bonviva leavepiece

A primary care trust prescribing advisor complained about a Bonviva (ibandronic acid) leavepiece issued jointly by Roche and GlaxoSmithKline. Bonviva 150mg (one tablet) once a month was indicated for the treatment of osteoporosis in postmenopausal women at increased risk of fracture.

A page of the leavepiece headed 'Efficacy' featured a box headed 'Bonviva: reduction in risk of vertebral fracture over 3 years'. A large downward arrow with 62% on it appeared to the left of a statement 'Data adapted from a randomised, double-blind, placebo-controlled, three-year study, involving postmenopausal women, of whom 977 received Bonviva 2.5mg daily, and 975 received placebo' referenced to Chesnut *et al* 2004.

The complainant noted that the study cited did not use once-monthly Bonviva and alleged that it was unacceptable and unethical to use data from a daily formulation to promote a monthly formulation of the same medicine. The vertebral fracture efficacy of once-monthly Bonviva had not been demonstrated in clinical trials, therefore the promotional material was very misleading.

The Panel noted Roche and GlaxoSmithKline's comments about the regulatory guidance for the use of bridging studies when applying for a marketing authorization for medicines that had already demonstrated anti-fracture efficacy for a specific dose. From the Bonviva 150mg summary of product characteristics (SPC) it was clear that Bonviva once-monthly reduced the risk of vertebral fractures.

The Panel noted that every page of the leavepiece, except the one at issue, referred specifically to Bonviva once-monthly. The page at issue referred only to Bonviva. In the Panel's view most readers would not note this difference and assume that everything in the leavepiece was about Bonviva once-monthly which was not so. The claim that there was a 62% reduction in the risk of vertebral fractures over 3 years related to data for patients on once-daily Bonviva. There was no direct clinical data to support a 62% reduction in the risk of vertebral fractures for patients on Bonviva once-monthly. Although a qualification was included next to the risk reduction claim, the Panel considered that in the context of the leaflet as a whole it was not sufficiently clear that the 62% risk reduction claim applied to the once-daily dose. The leaflet was misleading in this regard and a breach of the Code was ruled.

Upon appeal, the Appeal Board noted that the SPC referred to a study looking at bone mineral density (BMD) which had concluded that Bonviva 150mg once monthly was at least as effective as Bonviva 2.5mg daily at increasing BMD in a two year study. The Bonviva 150mg SPC also stated that based on those results Bonviva 150mg once monthly was expected to be at least as effective in preventing fractures as Bonviva 2.5mg daily. In addition the SPC included details of a study in which Bonviva 2.5mg daily had been shown to reduce the relative risk of fracture by 62% over 3 years. It was by bridging data from one formulation to another in this way that Bonviva 150mg once monthly had obtained its marketing authorization. The Appeal Board considered it acceptable to use such data in promotional material for Bonviva 150mg but noted that care should be taken to ensure that it was made clear that the source data was from the 2.5mg daily dose. In the Appeal Board's view the page in question did make it sufficiently clear that the data was adapted from a study on 2.5mg Bonviva daily. No breach of the Code was ruled.

A prescribing advisor to a primary care trust (PCT) complained about a leavepiece (ref P117551) for Bonviva (ibandronic acid). Bonviva was co-promoted by Roche Products Limited and GlaxoSmithKline UK Ltd and the matter was taken up with both companies. According to its summary of product characteristics (SPC) Bonviva 150mg was indicated for the 'treatment of osteoporosis in postmenopausal women at increased risk of fracture (see Section 5.1). A reduction in the risk of vertebral fractures has been demonstrated, efficacy on femoral neck fractures has not been established'. The recommended dose was one tablet (150mg) once a month.

Page three of the leavepiece was headed 'Efficacy' followed by 'Bonviva offers proven vertebral fracture efficacy'. Underneath this was a box headed 'Bonviva: reduction in risk of vertebral fracture over 3 years', a large downward arrow with 62% on it appeared to the left of a statement 'Data adapted from a randomised, double-blind, placebo-controlled, three-year study, involving postmenopausal women, of whom 977 received Bonviva 2.5mg daily, and 975 received placebo' referenced to Chesnut *et al* (2004).

COMPLAINT

The complainant stated that the data quoted was from the BONE study which did not use once-monthly Bonviva. The complainant alleged that it was unacceptable and unethical to use data from a daily formulation to promote a monthly formulation of the same medicine. The vertebral fracture efficacy of once-monthly Bonviva had not been demonstrated in

clinical trials, therefore the promotional material was very misleading.

When writing to the companies, the Authority asked them to respond in relation to Clause 7.2 of the Code.

RESPONSE

The companies disagreed that the leavepiece was misleading and therefore denied a breach of Clause 7.2 of the Code.

Currently there were three licensed formulations of Bonviva: Bonviva 2.5mg tablets (daily) (this formulation was not marketed or promoted in the UK); Bonviva 150mg tablets (monthly) and Bonviva 3mg/3ml solution for intravenous injection (every 3 months).

The indication for Bonviva 150mg tablets, as described in the SPC was 'Treatment of osteoporosis in postmenopausal women at increased risk of fracture (see Section 5.1). **A reduction in the risk of vertebral fractures has been demonstrated**, efficacy on femoral neck fractures has not been established' (emphasis added).

Therefore, from a regulatory perspective, the vertebral fracture efficacy of once-monthly Bonviva had been demonstrated (the indication being issued as part of the marketing authorization). For Bonviva 150mg (monthly formulation) the licensed indication relating to vertebral fracture reduction was, at least in part, based on data from clinical trials for the daily formulation. This extrapolation of clinical data from the daily to the monthly formulation, otherwise known as 'bridging', was fully accepted in the therapy area of osteoporosis by regulatory authorities and was widely accepted in medical practice largely as a result of ethical considerations in clinical research.

Bridging concept

In osteoporosis, regulatory authorities had recognised that it was unethical to perform additional, large, placebo-controlled studies to assess anti-fracture efficacy for compounds that had already demonstrated anti-fracture efficacy and been granted the indication of 'Treatment of osteoporosis in postmenopausal women at high risk of fracture' in relation to a new dose, formulation or route of administration. This concept was part of the European Medicines Evaluation Agency's (EMEA's) Guideline on the Evaluation of Medical Products in the Treatment of Primary Osteoporosis (CPMP/EWP/552/95, 2006) which stated (paragraph 5.3.3):

> 'Alternative surrogate endpoints like biochemical markers of bone turnover should be used in bridging studies after a thorough analysis of historical studies showing a good correlation between pharmacokinetic exposures, the pharmacodynamic response and the reduction in fracture risk. **To avoid having to conduct separate fracture studies, the time-course of changes in surrogate markers should recapitulate the time-course observed for the original dosing regimen. This should apply to any surrogate endpoint that is known to be associated with fracture risk, such as BMD and/or a biochemical marker.'**(emphasis added)
>
> 'Equivalence or non-inferiority can be tested in a bridging study...'

In line with guidance from the EMEA, data from the 2.5mg daily formulation of Bonviva was 'bridged' in order to obtain the marketing authorization for the 150mg monthly formulation.

Presenting the vertebral fracture data for the daily dose of Bonviva ensured that the leavepiece was 'sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine' and that the reader was clear on the origin of the data and the claims associated with it.

The text directly adjacent to the downward arrow on page three of the leavepiece clearly stated that the vertebral efficacy data was derived from a study in which patients received Bonviva 2.5mg daily or placebo. This was presented in an accurate, balanced, fair, objective and unambiguous manner. The way in which the data was presented was not misleading.

Summary

i) The vertebral fracture efficacy of once-monthly Bonviva had been demonstrated (based on the bridging concept) and was reflected in the wording of the licensed indication as described in the SPC;
ii) in osteoporosis it was acceptable and ethical to use fracture efficacy data from a daily formulation to promote a monthly formulation of the same medicine as long as it was made clear from which dose and formulation the clinical data was derived;
iii) the bridging concept in osteoporosis was acknowledged and accepted by regulatory agencies and medical practice and allowed the extrapolation of fracture data, in this case, from a daily to a monthly formulation of the same compound;
iv) it was clearly stated in the leavepiece that the data supporting the vertebral fracture efficacy claims was from patients who received Bonviva 2.5mg daily (this was also clearly described by the complainant).

In conclusion, for the reasons detailed above, the companies submitted that the leavepiece was accurate, balanced, fair, objective and unambiguous and based on an up-to-date evaluation of all the evidence and reflected the evidence clearly. It did not mislead either directly or by implication, by distortion, exaggeration or undue emphasis. Additionally, the material was sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine and was therefore not in breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted Roche and GlaxoSmithKline's comments about the regulatory guidance for the use of bridging studies when applying for a marketing authorization for medicines that had already demonstrated anti-fracture efficacy for a specific dose. From the Bonviva 150mg SPC it was clear that Bonviva once-monthly reduced the risk of vertebral fractures.

The Panel noted that every page of the leavepiece, except the one at issue, referred specifically to Bonviva once-monthly. The page at issue, page three, referred only to Bonviva. In the Panel's view most readers would not note this difference and assume that everything in the leavepiece was about Bonviva once-monthly which was not so. The claim that there was a 62% reduction in the risk of vertebral fractures over 3 years related to data for patients on once-daily Bonviva. There was no direct clinical data to support a 62% reduction in the risk of vertebral fractures for patients on Bonviva once-monthly. Although a qualification was included next to the risk reduction claim, the Panel considered that in the context of the leaflet as a whole it was not sufficiently clear that the 62% risk reduction claim applied to the once-daily dose. The leaflet was misleading in this regard and a breach of Clause 7.2 was ruled.

APPEAL BY ROCHE AND GLAXOSMITHKLINE

The companies stated that the basis for appeal was twofold; firstly that the leavepiece was sufficiently clear as to the source of the 62% fracture reduction data and could not be considered misleading under Clause 7.2 and secondly, although the leavepiece had been withdrawn some time ago, and subsequent materials developed, it was not clear from the Panel's ruling what changes would be needed to ensure that no breach of undertaking could be ruled in future.

From the Panel's ruling and a telephone discussion with the Authority the companies submitted that the foundation for the ruling related to the manner in which the data was presented and not with the actual use of it which was the initial allegation in the complaint.

The companies understood that the Panel accepted that the use of the 62% vertebral fracture data from the initial 2.5mg daily Bonviva preparation in the promotion of Bonviva was valid and not misleading per se. The Panel considered however that a health professional would not be expected to read a leavepiece in any great depth and thus as the leavepiece promoted the licensed and marketed dose of Bonviva 150mg the source of the 62% vertebral fracture data needed to be clearer than in a detail aid for example, which would be accompanied by verbal messaging. The companies did not accept this and submitted that to assume so did not recognise the professional standing of the reader.

The companies submitted that the Panel had considered that the repeated reference to the 150mg dose throughout the leavepiece meant that the qualification next to the arrow displaying the percentage fracture reduction was not sufficient to allow the health professional to make a balanced determination of the value of Bonviva in the management of postmenopausal women. This was considered, by the Panel, to be especially pertinent given that the information was contained in a leavepiece which the reader would not be expected to read in any great depth. The companies submitted that the qualification within the leavepiece was unambiguous, based on up-to-date data, which was also included in the Bonviva 150mg SPC. The data were presented clearly and were not inconsistent with the SPC and were the basis for efficacy upon which the licence was granted; so this, in no way, misled the reader.

The companies submitted that the dosage used in the study, 2.5mg daily, was positioned directly next to the arrow within the same box and was in a font similar to the other bullet points in the leavepiece. The companies had not used an asterix and placed the qualification away from the arrow in a smaller text.

The companies submitted that if the 2.5mg dose was given the same prominence as the 150mg dose within the leavepiece, in terms of placement and font size, this could confuse health professionals as to what to prescribe. The only available oral dose of Bonviva was 150mg monthly.

The companies submitted that whilst it appeared that the Panel had accepted that the use of bridging data across doses was acceptable in promotional material, if this finding of a breach were to be upheld it would have wide reaching consequences on how bridging data was presented across many different disease and therapy areas and potentially confuse health professionals as to the doses available to prescribe. There had to be a balance between being clear as to the source of the original efficacy data and not over-emphasising doses or preparations that were not actually available irrespective of whether the presentation of the data was a leavepiece, detail aid or advertisement.

The companies submitted that there seemed to be a possible misunderstanding about the relevance of bridging data. It was fundamentally wrong to imply that because fracture data was available for the 2.5mg dose and not for the 150mg dose that this suggested inferiority of the latter. Bonviva 150mg was indicated for prevention of vertebral fracture. The indication in the SPC was not qualified by any statement regarding the dose used to obtain that indication. Clause 3.2 stated that promotion of a medicine, *inter alia*, must not be inconsistent with the particulars listed in its SPC.
A ruling that implied that claims about fracture reduction must always be accompanied by a statement that this was based only on data for 2.5mg was not consistent with the marketing authorization and indeed undermined the legitimacy of that marketing authorization when the same data was used as a basis for that approval.

The complainant's initial concern was not that it was not sufficiently clear that the source of the 62% vertebral fracture data was from a trial carried out with 2.5mg daily Bonviva, rather that it was used at all. Indeed it was sufficiently clear to the complainant that the data was from the 2.5mg daily dose as opposed to the 150mg dose for her to conclude that, it was unethical to use daily data when promoting a monthly dose.

The companies noted that in its ruling the Panel stated that given the context of the material it considered that the leavepiece was not sufficiently clear that the 62% risk reduction claim applied to the daily dose. As previously stated, one of the reasons that the companies had appealed was that it was unclear what 'sufficiently clear' meant in this context and thus it was not clear from the Panel's ruling what changes would be needed to ensure that no breach of undertaking could be ruled in future. Any finding would be equally attributable irrespective of the type of material in which these data were presented and thus to determine what was likely and not likely to be read for each type of material was not evident from the correspondence received.

In summary the companies submitted that the leavepiece was not misleading in its presentation of the vertebral fracture data on the following points and was therefore not in breach of Clause 7.2:

- Therapeutic equivalence had been demonstrated by the use of the accepted practice of bridging data between the daily and monthly dose of Bonviva.
- The data presented was consistent with data presented in the Bonviva 150mg SPC
- The qualification relating to the vertebral fracture data claim was directly next to the percentage arrow, was in the same size font as the other bullet points within the leavepiece and was complete in its explanation.
- To further emphasise the 2.5mg dose, which was unavailable in the UK could mislead health professionals as to the oral doses available and therefore impact on patient care. It could also be considered inconsistent with the prescribing information used on Bonviva materials and thus open to challenge.
- A leavepiece was not designed to be skim read and to assume so was incorrect. The clarity as to the source of the data was sufficiently clear in the leavepiece and sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine.

COMMENTS FROM THE COMPLAINANT

The complainant made no further comment regarding the use of bridging data.

APPEAL BOARD RULING

The Appeal Board noted that the SPC referred to a study looking at bone mineral density (BMD) which had concluded that Bonviva 150mg once monthly was at least as effective as Bonviva 2.5mg daily at increasing BMD in a two year study. The Bonviva 150mg SPC also stated that based on those results Bonviva 150mg once monthly was expected to be at least as effective in preventing fractures as Bonviva 2.5mg daily. In addition the SPC included details of a study in which Bonviva 2.5mg daily had been shown to reduce the relative risk of fracture by 62% over 3 years. It was by bridging data from one formulation to another in this way that Bonviva 150mg once monthly had obtained its marketing authorization. The Appeal Board considered it acceptable to use such data in promotional material for Bonviva 150mg but noted that care should be taken to ensure that it was made clear that the source data was from the 2.5mg daily dose. In the Appeal Board's view the page in question did make it sufficiently clear that the data was adapted from a study on 2.5mg Bonviva daily. No breach of Clause 7.2 was ruled. The appeal was successful.

Complaint received 18 December 2006

Case completed 22 February 2007