CASES AUTH/1971/3/07 and AUTH/1972/3/0

SERVIER LABORATORIES v ROCHE and GLAXOSMITHKLINE

Promotion of Bonviva

Servier Laboratories alleged that a leavepiece and a journal advertisement for Bonviva (ibandronic acid), issued by Roche and GlaxoSmithKline, were, *inter alia*, misleading. Both pieces featured the claim 'Building bones' which Servier considered, in the context of promotion of a medicine licensed to treat osteoporosis, implied it had a positive action on bone formation, a bone-forming effect; a doctor would assume that Bonviva was a medicine which positively encouraged growth of bone and not one which might prevent further deterioration of osteoporotic bone. Servier noted that Bonviva, a biophosphonate, actually had a negative impact on bone formation and could not therefore be considered to be 'building bones'.

The summary of product characteristics (SPC) for Bonviva 150mg stated that it acted selectively on bone tissue and specifically inhibited osteoclast activity without directly affecting bone formation. Rodan *et al* (1996) stated that regarding the mechanism of action of bisphosphonates 'there is a reduction in bone turnover', 'evidenced by a decrease in both bone resorption and bone formation'. Furthermore the authors stated that 'besides resorption, formation is decreased too, as evidenced by a reduction in the bone formation surface'.

Servier thus considered that 'building bones' was not an appropriate term to describe a treatment which stopped bone resorption as well as reducing bone formation and as such it was inconsistent with the particulars listed in the Bonviva SPC, misleading and incapable of substantiation.

The Panel noted from the SPC that Bonviva acted selectively on bone tissue and specifically inhibited osteoclast formation (ie bone resorption) without directly affecting bone formation. Bonviva led to progressive net gains in bone mass and a decreased incidence of fractures through the reduction of elevated bone turnover towards premenopausal levels in postmenopausal women. Bonviva, however, did not build bone per se; its principal pharmacodynamic action was to inhibit bone resorption. The Panel noted that bone resorption and bone formation were coupled such that if bone resorption was decreased then bone formation was also decreased.

Delmas *et al* (2004) measured the biochemical markers of bone turnover in postmenopausal women with osteoporosis. Patients were randomized to receive placebo or Bonviva dosed either daily or intermittently. Both Bonviva regimens resulted in persistent levels of suppressed bone resorption (53-68%; p<0.0001 vs placebo) and bone formation (36-41% for serum osteocalcin; p<0.0001 vs placebo). The Panel noted that the biochemical markers showed that although bone resorption was suppressed rapidly (within 3 months), the markers for bone formation did not reach a plateau until within approximately 6 months' treatment. The delay in the decrease of the markers of bone formation compared with those of resorption could be explained by the normal coupling between formation and resorption, since bisphosphonates did not have a direct inhibitory effect on osteoblastic bone formation. The net reduction in bone turnover led to significant increases in spinal and hip BMD (p <0.0001 vs placebo) relative to baseline and a marked reduction in the incidence of vertebral fracture.

The Panel considered that although, as stated in the SPC, treatment with Bonviva led to progressive net gains in bone mass, such gains were not as a direct result of 'Building bones'. Increased bone mass was a result of a decrease in bone turnover with bone resorption being suppressed and then as a consequence of that, but not due to direct action of Bonviva, bone formation being suppressed to a lesser degree. In the Panel's view 'Building bones' implied that Bonviva had a positive effect on bone formation and that in some way it might stimulate osteoblasts which was not so. Any increase in bone mass, as a result of Bonviva therapy, was as a consequence of its main pharmacodynamic action, ie inhibition of bone resorption.

The Panel considered that 'Building bones' was a misleading claim which could not be substantiated; it implied that Bonviva had a direct bone-forming action which was not so. Breaches of the Code were ruled. This ruling was appealed.

Although noting its ruling above, the Panel did not consider that the claim was inconsistent with the Bonviva SPC which stated that therapy led to progressive net gains in bone mass. No breach of the Code was ruled in that regard.

Upon appeal by Roche and GlaxoSmithKline, the Appeal Board noted from its SPC that Bonviva acted selectively on bone tissue and specifically inhibited osteoclast formation (ie bone resorption) without directly affecting bone formation. Bonviva led to progressive net gains in bone mass and a decreased incidence of fractures through the reduction of elevated bone turnover towards premenopausal levels in postmenopausal women.

The SPC did not refer to 'Building bones' although it

did state that treatment with Bonviva led to progressive net gains in bone mass. The patient information leaflet stated that 'Bonviva prevents loss of bone from osteoporosis, and helps to rebuild bone'. The Appeal Board considered that 'leads to progressive net gains in bone mass' and helping to rebuild bone described an indirect effect of therapy whereas 'Building bones' implied that Bonviva had a positive direct effect on new bone formation and that in some way it might stimulate osteoblasts which was not so. Any increase in bone mass, as a result of Bonviva therapy, was as a consequence of its main pharmacodynamic action, ie inhibition of bone resorption.

The Appeal Board noted the respondents' submissions regarding the net clinical effect of Bonviva but nonetheless considered, on balance, that 'Building bones' was a misleading claim which could not be substantiated. The Appeal Board upheld the Panel's rulings of breaches of the Code.

Servier Laboratories Ltd complained about the promotion of Bonviva (ibandronic acid) by Roche Products Limited and GlaxoSmithKline UK Ltd. The items at issue were a leavepiece (ref BON/LVP/06/25189/1) and an advertisement (ref BON/DPS/06/25931/2). Servier supplied Protelos (strontium ranelate). Bonviva and Protelos were both licensed for the treatment of postmenopausal osteoporosis.

COMPLAINT

Servier noted that both the leavepiece and the advertisement featured the claim 'Building bones'. Servier considered that 'Building bones', in the context of promotion of a medicine licensed to treat osteoporosis, implied it had a positive action on bone formation, a bone-forming effect; a doctor would assume that Bonviva was a medicine which positively encouraged growth of bone and not one which might prevent further deterioration of osteoporotic bone.

Servier noted that Bonviva, a bisphosphonate, actually had a negative impact on bone formation and could not therefore be considered to be 'building bones'.

The summary of product characteristics (SPC) for Bonviva 150mg stated that it belonged to the nitrogen-containing group of bisphosphonates, which acted selectively on bone tissue and specifically inhibited osteoclast activity without directly affecting bone formation. Rodan *et al* (1996) stated that regarding the mechanism of action of bisphosphonates 'there is a reduction in bone turnover', 'evidenced by a decrease in both bone resorption and bone formation'. Furthermore the authors stated that 'besides resorption, formation is decreased too, as evidenced by a reduction in the bone formation surface'.

Servier noted that Roche considered that the effect of increasing bone mass, which was observed with bisphosphonates justified the claim 'Building bones'. However Servier disagreed; increasing bone mass was not the same as 'building bones'. Bone mass could be increased by mechanisms other than increasing formation, for example, relating to the mechanism of action of bisphosphonates. Rodan *et al* stated that 'after the decrease in bone turnover... bone will have more time to complete mineralization…thus "older" bone has a higher mineral content'.

Roche had argued that referenced publications supported its claims, using phrases such as 'bone accrual' (Chesnut *et al*, 2004), 'formation of new bone of normal quality' (Müller *et al*, 2004, Lalla *et al*, 1998, and Smith *et al* 2003) and 'bone gain' (Delmas *et al*, 2004). Servier believed that this response was in line with its belief that 'building bones' implied increasing bone formation. However, inspection of these papers revealed that none of the phrases quoted above were used within the papers and furthermore none would support Bonviva being associated with increased bone formation.

For the reasons outlined above, Servier considered that 'Building bones' was not an appropriate term to describe a treatment which stopped bone resorption as well as reducing bone formation and as such it was inconsistent with the particulars listed in the Bonviva SPC, misleading and incapable of substantiation, in breach of Clauses 3.2, 7.2 and 7.4 of the Code.

RESPONSE

Roche responded on behalf of itself and GlaxoSmithKline. Roche stated that the claim 'Building bones' was not used in isolation but as part of a longer statement. On the leavepiece it appeared as 'Building bones with one tablet, once a month' and in the advertisement it formed part of the claim 'Building bones, month, after month, after month'. The basis for these claims, and in particular references to 'Building bones', was consistent with the Bonviva SPC. It was also supported by a body of peer reviewed evidence.

To explain the rationale for the use of the claim 'Building bones' it was useful to understand the currently accepted mechanism of action of bisphosphonates. It was also pertinent to clarify the difference between direct bone formation and the process of building bone which might be either a direct or indirect consequence depending on the agent's mechanism of action. It was also useful to place this in the context of the overall aim of therapy, which was to reduce the risk of postmenopausal osteoporotic fracture. Section 5.1 of the Bonviva SPC stated under the heading 'Mechanism of action':

> 'Ibandronic acid is a highly potent bisphosphonate belonging to the nitrogen-containing group of bisphosphonates which act selectively on bone tissue and specifically inhibit osteoclast activity without directly affecting bone formation. It does not interfere with osteoclast recruitment. Ibandronic acid leads to progressive net gains in bone mass and a decreased incidence of fractures through the reduction of elevated bone turnover towards premenopausal levels in postmenopausal women.'

Roche noted in particular the statement that 'Ibandronic

acid leads to progressive net gains in bone mass.' It was clear that increasing bone mass required the addition of bone to the existing skeleton and this action was effectively 'Building bones'. This was manifested as a demonstrable increase in bone mineral density (BMD) that was significant both statistically and clinically with regard to its resultant effect on fracture rates.

The SPC was based on the balance of evidence and could not be considered misleading. It reflected the current evidence base and understanding of how bisphosphonates worked and therefore reduced fracture risk in postmenopausal osteoporosis.

The mechanism by which bisphosphonates increased bone mineral density was an indirect one via their inhibitory effect on osteoclasts. Roche noted Rodan *et al* stated that resorption and formation were decreased in the presence of bisphosphonates. However to take this statement alone would be to do so out of context and Rodan *et al* went on to state that 'the reduction in total bone formation surface is secondary to diminished resorption and reflects reduced remodelling'. Rodan *et al* further stated that 'there is no evidence for reduced osteoblastic activity'. The authors' conclusion was that 'the amount of bone formed at each individual basic multicellular unit (BMU) measured by the thickness of the newly formed bone, is not decreased but, if anything, even increased'.

When looking at Bonviva specific data it had been seen that in postmenopausal osteoporotic women treated with daily ibandronic acid (2.5mg), increments in lumbar and hip BMD were observed within 12 months. Bone accrual continued throughout the duration of treatment (Chesnut *et al*). Likewise, intermittent ibandronic acid, administered either as a monthly oral dose, or a quarterly intravenous dose, also induced gains in bone mass (Miller *et al* 2005 and Delmas 2006). These clinical observations were entirely consistent with the findings of preclinical studies which provided further clarification that ibandronic acid increased bone mass through the formation of new bone of normal quality with increased or equal mechanical strength (Müller *et al*, Lalla *et al* and Smith *et al*). This reflected the findings of Rodan *et al* stated above.

Roche acknowledged that the Bonviva SPC stated 'bisphosphonates…specifically inhibit osteoclast activity without directly affecting bone formation'. The key here was the statement 'directly affecting bone formation'. Roche did not suggest that Bonviva directly triggered osteoblastic action and therefore Bonviva was not a bone forming agent like Protelos. However as stated earlier it did effect bone turnover due to its influence on the coupling balance of bone formation and bone resorption. The fact that Bonviva treatment affected both bone formation and bone resorption was evident from the data (Delmas *et al*). These data also illustrated that the effect of upon bone resorption was greater than that upon bone formation. As Bonviva suppressed bone resorption to a greater extent than bone formation, the net effect was one of bone gain (Delmas *et al*). This was the mechanism by which BMD was increased. These data further substantiated the claim 'Building bone'.

Servier noted in its complaint that it was aware of these data, however, as was apparent in intercompany dialogue, it did not recognise that there was a distinction between direct anabolic bone formation and bone building which could be brought about by a number of mechanisms both direct and indirect. Roche considered that to only reserve the term 'Building bone' for directly acting bone forming agents was misleading as bisphosphonates had a huge impact on BMD and had, as highlighted above, been shown to increase bone mass through the formation of new bone of normal quality with increased or equal mechanical strength (Müller *et al*, Lalla *et al* and Smith *et al*).

It was this evidence base that resulted in the regulatory approved Bonviva patient information leaflet stating that 'Bonviva prevents loss of bone from osteoporosis, and helps to rebuild bone. Therefore Bonviva makes bone less likely to break'.

In summary, Bonviva reduced the risk of fracture in postmenopausal osteoporosis through its action on the balance between bone formation and bone resorption on the surface of the bone. This resulted in an increase in bone mass and thus indirectly Bonviva built bone. Roche therefore concluded that the claim 'Building bones' did not breach Clause 3.2, as it was consistent with the terms of the marketing authorization and was not inconsistent with the SPC. Neither did the statement breach Clause 7.2 nor 7.4 as the information was accurate, balanced, fair, objective and unambiguous and reflected the evidence relating to the action of ibandronic acid.

In the eyes of prescribers and patients the essential effect required was to increase BMD. Bisphosphonates, including Bonviva, had this effect. The mechanism was not relevant, and thus by demonstrating an increase in BMD, Roche was confident that the claim 'Building bone' was supportable and not in breach of Clauses 3.2, 7.2 and 7.4.

PANEL RULING

The Panel noted from the SPC that Bonviva acted selectively on bone tissue and specifically inhibited osteoclast formation (ie bone resorption) without directly affecting bone formation. Bonviva led to progressive net gains in bone mass and a decreased incidence of fractures through the reduction of elevated bone turnover towards premenopausal levels in postmenopausal women. Bonviva, however, did not build bone per se; its principal pharmacodynamic action was to inhibit bone resorption. The Panel noted that bone resorption and bone formation were coupled such that if bone resorption was decreased then bone formation was also decreased.

Delmas *et al* measured the biochemical markers of bone turnover in postmenopausal women with osteoporosis. Patients were randomized to receive placebo or Bonviva dosed either daily or intermittently. Both Bonviva regimens resulted in persistent levels of suppressed bone resorption (53-68%; $p<0.0001$ vs placebo) and bone formation (36-41% for serum osteocalcin; $p<0.0001$ vs placebo). The Panel noted that

the biochemical markers showed that although bone resorption was suppressed rapidly (within 3 months), the markers for bone formation did not reach a plateau until within approximately 6 months' treatment. The delay in the decrease of the markers of bone formation compared with those of resorption could be explained by the normal coupling between formation and resorption, since bisphosphonates did not have a direct inhibitory effect on osteoblastic bone formation. The net reduction in bone turnover led to significant increases in spinal and hip BMD ($p < 0.0001$ vs placebo) relative to baseline and a marked reduction in the incidence of vertebral fracture.

The Panel considered that although, as stated in the SPC, treatment with Bonviva led to progressive net gains in bone mass, such gains were not as a direct result of 'Building bones'. Increased bone mass was a result of a decrease in bone turnover with bone resorption being suppressed and then as a consequence of that, but not due to direct action of Bonviva, bone formation being suppressed to a lesser degree. In the Panel's view 'Building bones' implied that Bonviva had a positive effect on bone formation and that in some way it might stimulate osteoblasts which was not so. Any increase in bone mass, as a result of Bonviva therapy, was as a consequence of its main pharmacodynamic action, ie inhibition of bone resorption.

The Panel considered that 'Building bones' was a misleading claim which could not be substantiated; it implied that Bonviva had a direct bone-forming action which was not so. Breaches of Clauses 7.2 and 7.4 were ruled. This ruling was appealed.

Although noting its ruling above, the Panel did not consider that the claim was inconsistent with the Bonviva SPC which stated that therapy led to progressive net gains in bone mass. No breach of Clause 3.2 was ruled.

APPEAL BY ROCHE AND GLAXOSMITHKLINE

Roche appealed the Panel's rulings of breaches of Clauses 7.2 and 7.4 on behalf of itself and GlaxoSmithKline.

Roche explained that bone was in a constant state of flux, a process known as bone remodelling. Bone remodelling was a sum of its two parts, bone resorption and bone formation and these must be considered together in order to understand what was happening to bone ie was bone being broken down, being built or in equilibrium?

In young healthy adults there was a continuous breakdown of bone (removal of bone mass or bone mineral) and at the same time a continuous deposition (formation) of bone mineral or bone mass. If resorption and formation were to be considered in isolation one of two conclusions could possibly be drawn; (i) that bone was being broken down or (ii) bone was being built. After considering the two parts together - essential in order to understand what was happening - it was clear that the net result was neither bone breakdown nor formation but equilibrium. Bone mass was neither increasing nor decreasing.

Roche explained that in postmenopausal osteoporosis the bone remodelling process was out of balance with bone resorption being greater than bone formation. The company noted, however, that in the majority of patients it was not just bone resorption that increased after the menopause; both bone resorption and bone formation increased but with bone resorption increasing to a greater extent than bone formation. The net result was bone breakdown resulting in loss of bone mineral or bone mass. This led to a weakening of the bones that were then susceptible to fracture. It was essential to appreciate that the loss of bone in postmenopausal women was as a result of (or the sum of) combined rates of bone resorption and bone formation.

Roche submitted that the principal mechanism of action of bisphosphonates (including Bonviva) was to reduce bone resorption to premenopausal levels. Indeed bisphosphonates were widely known as, and referred to as, antiresorptives or antiresorptive agents. This reduction in bone resorption rebalanced the bone remodelling process where bone formation occurred at a greater rate than bone resorption thus allowing bone mass or bone mineral to be deposited in bone. Whilst bone formation was also reduced it was reduced by a smaller degree than bone resorption. The overall (or net) result was a deposition of bone mineral or bone mass which resulted in bone being built.

It was inaccurate to consider bone resorption and bone formation in isolation as this would not provide the correct information in relation to bone remodelling ie the overall or net effect. As acknowledged by the Panel, the net effect of treatment with Bonviva was that bone mineral or bone mass was increased. Therefore the net result was that bone was being built.

Roche noted that Servier quoted Rodan *et al* to describe the mechanism of action of bisphosphonates. As stated previously, the companies agreed with these quotations about the mechanism of action of bisphosphonates, specifically that bisphosphonates acted principally to reduce bone resorption. There was also a decrease, albeit a smaller decrease, in bone formation. However, Rodan *et al* referred to the net result of bisphosphonates in the bone remodelling process. For example, when discussing the mechanism of action of bisphosphonates at the tissue level Rodan *et al* stated 'Furthermore, the amount of new bone formed at each individual basic multicellular unit (BMU), measured by the thickness of newly formed bone, is not decreased but if anything, even increased'. Rodan *et al* continued and stated 'Bisphosphonates produce a positive calcium balance in animals and increase the amount of bone in animals and in humans'.

Roche submitted that it was clear that Servier considered that Bonviva worked merely by preventing further deterioration of osteoporotic bone and by stopping bone resorption. However, both of these statements were incorrect as highlighted by Rodan *et al*. Bonviva did not stop bone resorption; it reduced

bone resorption to premenopausal levels. The net effect of Bonviva on bone in terms of statistically significant effects on BMD was highlighted in Section 5.1 of the SPC which stated 'Ibandronic acid leads to progressive net gains in bone mass and a decreased incidence of fractures through the reduction of elevated bone turnover towards premenopausal levels in postmenopausal women' and continued in the section describing the pharmacodynamic effects stating 'Both daily and intermittent (with prolonged dose-free intervals) long-term administration in rats, dogs and monkeys was associated with formation of new bone of normal quality and maintained or increased mechanical strength even at doses in the toxic range. In humans, the efficacy of both daily and intermittent administration with a dose-free interval of 9-10 weeks of ibandronic acid was confirmed in a clinical trial (MF4411), in which Bonviva demonstrated anti-fracture efficacy'. (MF4411 was bioequivalent to the 150mg monthly dose and had been considered to be so in the MAA).

Roche submitted that in addition to the SPC the overall or net effect of treatment with Bonviva was also clearly described in the patient information leaflet reviewed and approved by regulatory authorities which stated 'Bonviva prevents loss of bone from osteoporosis, and helps to rebuild bone'.

Roche submitted that the Oxford English Dictionary defined the word 'build' as 'construct by putting parties of material together' and 'establish, make or accumulate gradually' and defined the words 'build up' as 'increase in size or strength'. Bonviva strengthened bones as a result of a gradual accumulation of bone mineral and bone mass. This fitted correctly with the Oxford English Dictionary definition 'build'. However achieved mechanistically, the fact remained that patients benefited from an increase in bone mass which led to a reduced risk of fracture. This increase in bone mass was, for the patient, building bone.

Medicines in other therapy areas also described the net result of the treatment without specifically referred to the mechanism of action. For example, angiotensin coverting enzyme inhibitors would reduce blood pressure but promotional claims did not specifically refer to the mechanism of action. A similar example might be with a diabetic treatment. The net result of a glitazone was to reduce blood glucose levels. The glitazone might work specifically by reducing insulin resistance but again it was acceptable to claim an effective reduction in blood glucose as this was what would benefit the patient, without referring to the mechanism of action ie the net result of the treatment was described without providing details of exactly how the net result was achieved.

Roche submitted that for all the reasons detailed above it considered that the overall or net effect of Bonviva treatment was that bone would be built and therefore Bonviva did build bone and so the claim 'Building bones' was not misleading and was capable of substantiation and therefore not in breach of Clauses 7.2 and 7.4.

COMMENTS FROM SERVIER

Servier alleged that the claim 'Building bones', in the context of promotion of a medicine licenced to treat osteoporosis, implied the medicine had a positive action on bone formation, a bone-forming effect. The impression given to a doctor reading this claim would be of a medicine that positively encouraged growth of bone with an anabolic effect, such as teriparatide, and not one that prevented resorption of osteoporotic bone.

Servier submitted that Bonviva actually had a negative impact on bone forming cells and could not therefore be considered to be 'Building bones'.

Servier noted that the Bonviva SPC stated that it was a 'bisphosphonate belonging to the nitrogen-containing group of bisphosphonates, which act selectively on bone tissue and specifically inhibit osteoclast activity without directly affecting bone formation'. Indeed, osteoclasts were involved in bone resorption and were inhibited by bisphosphonates as reflected by a reduction in markers of bone resorption; whereas osteoblasts were involved in bone formation and biochemical markers of osteoblastic activity (bone-forming) were also reduced with bisphosphonates.

Servier noted that Rodan *et al*, with reference to the mechanism of action of bisphosphonates, had stated 'there is a reduction in bone turnover', 'evidenced by a decrease in both bone resorption and bone formation'. Furthermore, the authors stated that 'besides resorption, formation is decreased too, as evidenced by a reduction in the bone formation surface'. This effect on bone turnover was determined by measuring biochemical markers of bone formation and bone resorption.

Servier alleged that bisphosphonates, including Bonviva, therefore reduced bone formation and bone resorption as measured by biochemical markers. As Roche had noted, because bone formation was reduced by a smaller degree than bone resorption, the net effect was an increase in bone mass. However, the fact that bisphosphonates had a net effect on increasing bone mass did not justify the claim 'Building bones'. In contrast, a true bone building agent had an anabolic effect as reflected in increases in biochemical markers of bone formation.

Servier stated that a treatment that increased bone mass did not necessarily 'Build bones'. Indeed, bone mass could be increased by other mechanisms. With reference to bisphosphonates, Rodan *et al* stated that 'after the decrease in bone turnover…bone will have more time to complete mineralization … thus "older" bone had a higher mineral content'. This implied therefore that the bone was not new as might be expected from a medicine that built bones.

Servier noted that Roche referred to dictionary definitions of the term 'builds' and 'build up'. However the context of these definitions in terms of medicines was not appropriate especially where the term could easily be confused by the reader to mean an effect such as anabolism. Therefore, as Bonviva did not

have any anabolic action these terms were inappropriate.

Roche and GlaxoSmithKline pointed out that medicines in other therapy areas made promotional claims that described the net result of treatment without specifically referring to the mechanism of action. However, this argument did not apply to here as the claim 'Building bones', in the context of the promotion of a medicine licensed to treat osteoporosis, implied the medicine had a positive bone-forming, or anabolic effect. Following the logic that Roche set out with regard to promotional claims in other therapy areas, the claim 'Bonviva increases bone mass' would be appropriate as it referred to the net effect of Bonviva without specifically referring to its mechanism of action.

In conclusion, Servier stated that bisphosphonates, including Bonviva, increased bone mass by acting as anti-resorptive agents but did not have a positive action on bone formation, such as that expected of an anabolic agent, and therefore could not be claimed to have a 'bone building' effect. Consequently, the claim 'Building bones' was misleading and not capable of substantiation, and therefore was in breach of Clauses 7.2 and 7.4.

APPEAL BOARD RULING

The Appeal Board noted from its SPC that Bonviva acted selectively on bone tissue and specifically inhibited osteoclast formation (ie bone resorption) without directly affecting bone formation. Bonviva led to progressive net gains in bone mass and a decreased incidence of fractures through the reduction of elevated bone turnover towards premenopausal levels in postmenopausal women.

The Appeal Board noted that the SPC did not refer to 'Building bones' although it did state that treatment with Bonviva led to progressive net gains in bone mass. The patient information leaflet stated that 'Bonviva prevents loss of bone from osteoporosis, and helps to rebuild bone'. The Appeal Board considered that 'leads to progressive net gains in bone mass' and helping to rebuild bone described an indirect effect of therapy whereas 'Building bones' implied that Bonviva had a positive direct effect on new bone formation and that in some way it might stimulate osteoblasts which was not so. Any increase in bone mass, as a result of Bonviva therapy, was as a consequence of its main pharmacodynamic action, ie inhibition of bone resorption.

The Appeal Board noted the respondents' submissions regarding the net clinical effect of Bonviva but nonetheless considered, on balance, that 'Building bones' was a misleading claim which could not be substantiated. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2 and 7.4. The appeal was unsuccessful.

Complaint received	**12 March 2007**
Case completed	**14 June 2007**