CASE AUTH/1824/4/06 *NO BREACH OF THE CODE*

MEDIA/DIRECTOR v SERVIER

Promotion of Protelos

An article entitled 'Strontium ranelate for osteoporosis' which appeared in the Drug and Therapeutics Bulletin (D&TB) of April 2006 criticised the promotion of Protelos (strontium ranelate) by Servier. In accordance with established practice the matter was taken up by the Director as a complaint under the Code. Protelos was indicated for the treatment of postmenopausal osteoporosis (PMO) to reduce the risk of vertebral and hip fractures.

The authors of the article stated that in their view there was no convincing published clinical evidence to support the claims 'the first dual action bone agent' and 'the only drug to simultaneously increase bone formation and decrease bone resorption'. Although the evidence base for the claims was bone marker data from clinical trials, the authors noted that bone biopsies provided a more definitive assessment of bone formation and resorption and had not shown that Protelos stimulated bone formation or resulted in positive remodelling imbalance.

The Panel noted that Section 5.10 of the Protelos summary of product characteristics (SPC) referred to *in vitro* pharmacodynamic data and concluded that there was a rebalance of bone turnover in favour of bone formation. Non clinical models showed increases in certain parameters which were said to result in an improvement in bone strength. Biopsies obtained after up to 60 months of treatment showed no deleterious effects on bone quality or mineralisation. Phase III studies showed bone mineral density increased from baseline by approximately 4% per year at the lumbar spine and 2% per year at the femoral neck, reaching 13-15% and 5-6% respectively after 3 years, depending on the study. Biochemical markers of bone formation increased and those of bone resorption decreased from the third month of treatment up to 3 years.

With regard to the clinical data the Panel noted that Meunier *et al* studied the effects of Protelos on the risk of vertebral fracture in PMO. Serum biochemical markers of bone formation were statistically significantly increased in the Protelos group compared with placebo; markers showing bone resorption were statistically significantly decreased compared with placebo. The authors stated that the mechanism of action of strontium ranelate was yet to be understood but was probably different from other agents. Most antiresorptive agents prevented bone loss by reducing the rate of bone remodelling as reflected by a decrease in markers of bone resorption and bone formation.

Arlot *et al* assessed the mechanism of action of strontium ranelate at the cell or bone tissue level and evaluated bone safety. Bone biopsies confirmed the positive effects on bone formation. The authors stated that the findings '…indicate the stimulating effects of strontium ranelate on the osteoblastic population and [mineral apposition rate] and a moderate decrease on bone resorption. They are in agreement with the increase of biochemical markers of formation and the decrease of those of resorption shown in clinical studies and confirm the dual mode of action of strontium ranelate, rebalancing the bone metabolism in favor of formation'.

The Panel did not consider that given all the data the basis of the claim that Protelos was a dual action bone agent was sufficiently clinically robust. In relation to the mechanism of action of strontium ranelate, Meunier *et al*, on the basis of biochemical data, used the phrases '…being probably different to other medicines' and 'apparent dissociation between reduced bone resorption and increased bone formation'. The bone biopsy data, Arlot *et al* showed that Protelos had a statistically significant positive effect on bone formation but produced only a trend towards a decrease in bone resorption. Arlot *et al* also stated that at the tissue level there was no significant change in activation frequency. The Panel accepted that there was some data to show that Protelos both increased bone formation and decreased bone resorption but considered that the situation was more complicated than implied by the strong, unequivocal claim 'dual action bone agent'. Readers would assume in the absence of information to the contrary that there was clinical evidence for the claim. In the Panel's view the clinical data, particularly with regard to bone resorption, was not sufficient. The Panel considered that the claim was misleading and not capable of substantiation. Breaches of the Code were ruled. The Panel similarly ruled the claim 'the only drug to simultaneously increase bone formation and

decrease bone resoprtion' to be in breach of the Code.

Upon appeal by Servier the Appeal Board noted that the article in the D&TB had not criticised the context in which the claims had been used, just the claims *per se*.

The Appeal Board considered that there was data to show that, as statements of fact, Protelos was 'the first dual action bone agent' and 'the only drug to simultaneously increase bone formation and decrease bone resorption'. The Appeal Board noted that in this therapy area biochemical markers were well accepted as surrogate markers of clinical action. The biochemical data showed that Protelos increased bone formation and decreased bone resorption. Although the bone biopsy data was less robust it nonetheless mirrored the biochemical data. The Appeal Board noted that it was difficult to obtain bone biopsies, particularly paired biopsies. Such data contributed to the evidence base for the medicine but was only a part of it.

The Appeal Board considered that there was data to support the claims that Protelos was 'the first dual action bone agent' and that it was 'the only drug to simultaneously increase bone formation and decrease bone resorption'. No breach of the Code was ruled.

The Appeal Board noted that its rulings above were based on the claims at issue as statements of fact; it had not ruled on their use in promotional material. The context in which such claims were used, however, was important. The Appeal Board was concerned that the claims, although true in themselves, had been used in such a way in the Protelos promotional material supplied by Servier as to imply clinical superiority over other medicines. There was no data to support this implication. The Appeal Board requested that Servier be advised of its concerns in this regard and should review the context in which the claims were made.

An article entitled 'Strontium ranelate for osteoporosis' which appeared in the Drug and Therapeutics Bulletin of April 2006 criticised the promotion of Protelos (strontium ranelate) by Servier Laboratories Ltd. In accordance with established practice the matter was taken up by the Director as a complaint under the Code.

Protelos was indicated for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures.

COMPLAINT

The authors of the article stated that in their view there was no convincing published clinical evidence to support the claims 'the first dual action bone agent' and 'the only drug to simultaneously increase bone formation and decrease bone resorption'. Although the evidence base for the claims was bone marker data from clinical trials, the authors noted that bone biopsies provided a more definitive assessment of bone formation and resorption and had not shown that Protelos stimulated bone formation or resulted in positive remodelling imbalance.

When writing to Servier, the Authority asked it to respond in relation to Clauses 7.2 and 7.4 of the Code.

RESPONSE

Servier disagreed with the views of the authors and did not agree that the claims 'the first dual action bone agent' and 'the only drug to simultaneously increase bone formation and decrease bone resorption' were not accurate, balanced, fair, objective and unambiguous. Servier considered that the claims did not mislead either directly or by implication and that they could be substantiated.

Overall, Servier was very disappointed with the article for a number of reasons. Servier did not consider that the article was a balanced and fair reflection of all the data for Protelos and there appeared to be a number of crucial factual inaccuracies within it. Additionally, specific opinions of the authors did not seem to be consistent with those of other independent experts as detailed in a number of peer reviewed publications and documents approved by regulatory agencies.

The mode of action of Protelos had been clearly demonstrated and acknowledged to increase bone formation and decrease bone resorption. The summary of product characteristics (SPC) for Protelos, section 5.1, Pharmacodynamic properties, stated:

'*In vitro*, strontium ranelate:
increases bone formation in bone tissue culture as well as osteoblast precursor replication and collagen synthesis in bone cell culture;
reduces bone resorption by decreasing osteoclast differentiation and resorbing activity.
This results in a rebalance of bone turnover in favour of bone formation.

The activity of strontium ranelate was studied in various non-clinical models. In particular, in intact rats, strontium ranelate increases trabecular bone mass, trabeculae number and thickness; this results in an improvement of bone strength.

In phase III studies, as compared to placebo, biochemical markers of bone formation (bone-specific alkaline phosphatase and C-terminal propeptide of type I procollagen) increased and those of bone resorption (serum C-telopeptide and urinary N-telopeptide cross links) decreased from the third month of treatment up to 3 years.'

Additionally, in the patient information leaflet (PIL), approved by the EMEA, in the section titled 'How Protelos works', it was stated 'Protelos works by reducing bone breakdown and stimulating rebuilding of bone and therefore reduces the risk of fracture. The newly formed bone is of normal quality'.

Servier considered that the above text taken directly from the SPC and PIL for Protelos clearly reflected that, from the sum of *in vitro*, *in vivo* and clinical data, Protelos did increase bone formation and decrease bone resorption as claimed.

In the promotion of Protelos Servier simply acknowledged that Protelos had been shown to 'de-couple' the otherwise tightly linked resorption-formation sequence of adult bone remodelling causing

an increase in bone formation and decrease in bone resorption. As no other product had been shown to 'de-couple' bone formation and resorption (on the contrary all other products that increased bone formation also increased bone resorption and all other products that decreased bone resorption also decreased bone formation), Protelos was the only medicine that actually increased bone formation and decreased bone resorption simultaneously.

Servier could therefore justify the claim 'the only drug to simultaneously increase bone formation and decrease bone resorption'.

There were a number of peer-reviewed publications that also supported the dual action of Protelos in humans. Meunier *et al* (2004) stated:

'Most antiresorptive agents prevent bone destruction by reducing the rate of bone remodeling, as reflected by a decrease in both markers of bone resorption (more than 50 percent with bisphosphonates and about 30 percent with raloxifene) and markers of bone formation (about 50 percent with bisphosphonates and 20 percent with raloxifene). Treatment with parathyroid hormone increases both bone formation and bone resorption. When parathyroid hormone and alendronate are combined, there is, unexpectedly, no potentiation of their effects on biochemical bone markers. The mechanism of action of strontium ranelate is probably different from those of these drugs. Each time the patients were evaluated during our study, bone formation had increased in the group assigned to strontium ranelate, on the basis of serum concentrations of bone-specific alkaline phosphatase, and bone resorption had decreased, on the basis of serum concentrations of C-telopeptide cross-links, as compared with the values in the placebo group. The changes in biochemical markers of bone resorption and formation were most pronounced during the first six months; the dissociation between the bone markers was evident throughout the study. The mechanisms for the apparent disassociation between reduced bone resorption and increased bone formation are not yet understood, but they probably differ from the mechanisms of current treatments.'

Reginster *et al* (2003) stated: 'Strontium ranelate (SR) is a new antiosteoporotic agent demonstrated to increase in bone formation and decrease bone resorption in preclinical and clinical studies.'

Drugs in Context (2005) stated: 'Strontium ranelate is an antiosteoporotic agent with a unique mechanism of action, and is indicated for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures.'

'By promoting bone formation and reducing bone resorption, strontium ranelate uncouples the bone remodeling process in a favourable manner.'

Disease Reviews in Primary Care (2005) stated: 'In contrast to agents such as SERMs and bisphosphonates, which act by inhibiting bone resorption and anabolic agents such as parathyroid hormone which increase bone formation, pharmacological studies have demonstrated that strontium ranelate has a novel dual mechanism of action resulting in a decrease in bone resorption and an increase in bone formation, thereby resulting in increased bone mass.'

The authors of the article in The Drug and Therapeutics Bulletin stated 'However, bone biopsies provide a more definitive assessment of bone formation and resorption and have not shown that strontium ranelate stimulates bone formation or results in positive remodelling imbalance.'

This statement was factually incorrect; bone biopsy data for strontium ranelate showed a statistically significant increase in bone formation and a decrease in bone resorption (the latter did not reach statistical significance, Arlot *et al* 2005).

The published bone biopsy data for strontium ranelate considered in isolation without taking into account *in vitro*, animal data and human clinical trial (bone biomarker data) would not provide an accurate, balanced, fair, objective and unambiguous assessment of bone formation and resorption or be an up-to-date evaluation of all the evidence. Arlot *et al* performed a limited number of biopsies only five of which were paired biopsies. The second biopsies in the pairs were taken at varying time points, 1 to 5 years, and the results pooled. Clearly this data should not be used in isolation to support or oppose the dual action of strontium ranelate.

Interestingly Arlot *et al* concluded that 'These results demonstrate that the primary mineralization rate is not impaired, but on the contrary stimulated by SR [strontium ranelate]. All these findings indicate the stimulating effects of strontium ranelate on the osteoblastic population and MAR [mineral apposition rate] and a moderate decrease in bone resorption. They are in agreement with the increase of biochemical markers of formation and the decrease of those of resorption shown in clinical studies and confirm the dual mode of action of strontium ranelate, rebalancing the bone metabolism in favour of formation.'

In summary, it had been clearly demonstrated and acknowledged that Protelos was 'The first dual action bone agent' and 'the only drug to simultaneously increase bone formation and decrease bone resorption'. Servier considered that these claims in its materials complied with the requirements of Clauses 7.2 and 7.4 of the Code.

PANEL RULING

The Panel noted that Protelos was indicated for the treatment of postmenopausal osteoporosis (PMO) to reduce the risk of vertebral and hip fractures. Information was given in Section 5.1 of the SPC regarding pharmacodynamics. This referred to *in vitro* data which concluded that there was a rebalance of bone turnover in favour of bone formation. Non clinical models showed increases in certain parameters which were said to result in an improvement in bone strength. Biopsies obtained after up to 60 months of treatment at 2g per day showed no deleterious effects on bone quality or mineralisation. Phase III studies showed bone mineral density increased from baseline by approximately 4% per year at the lumbar spine and

2% per year at the femoral neck, reaching 13-15% and 5-6% respectively after 3 years, depending on the study. Biochemical markers of bone formation increased and those of bone resorption decreased from the third month of treatment up to 3 years.

With regard to the clinical data the Panel noted that Meunier *et al* studied the effects of Protelos on the risk of vertebral fracture in PMO. Serum biochemical markers of bone turnover were measured. Markers showing bone formation were statistically significantly increased in the Protelos group compared with placebo. Markers showing bone resorption were statistically significantly decreased in the Protelos group compared with placebo. The authors stated that the mechanism of action of strontium ranelate '… is probably different from ...' antiresorptive agents, bisphosphonates, raloxifene and parathyroid hormone. Most antiresorptive agents prevented bone destruction by reducing the rate of bone remodelling as reflected by a decrease in both markers of bone resorption (more than 50% with bisphosphonates and about 30% with raloxifene) and bone formation (about 50% with bisphosphonates and 20% with raloxifene).

Meunier *et al* also stated that the mechanisms for the apparent dissociation between reduced bone resorption and increased bone formation were not yet understood but they probably differed from those of current treatments.

Reginster *et al* stated that strontium ranelate demonstrated an increase in bone formation and a decrease bone resorption in preclinical and clinical studies but did not produce any primary data in support of that statement.

Arlot *et al* assessed the mechanism of action of strontium ranelate at the cell or bone tissue level and evaluated bone safety. Bone biopsies were obtained in a subset of patients from SOTI, TROPOS and STRATOS studies (49 treated and 87 untreated). The positive effects on bone formation were confirmed by a significant higher osteoblastic surfaces in treated compared with untreated (+38% p=0.047) and by a significantly greater Mineral Apposition Rate in cancellous and cortical bone. (+8% p=0.008 and +11% p=0.033 respectively). At the tissue level there was no significant change in activation frequency. The effects on resorption consisted of a trend towards lower endosteal eroded surfaces, endosteal and cancellous osteoclast surfaces and osteoclast number (–14, –6% –9%, –9% NS respectively). The authors stated that with the higher osteoblastic surfaces in treated patients it was expected to also observe higher osteoclast surfaces, which was not the case, confirming the dual mode of action of strontium ranelate.

The authors stated that the findings '…indicate the stimulating effects of strontium ranelate on the osteoblastic population and MAR and a moderate decrease on bone resorption. They are in agreement with the increase of biochemical markers of formation and the decrease of those of resorption shown in clinical studies and confirm the dual mode of action of strontium ranelate, rebalancing the bone metabolism in favor of formation'.

The Panel noted that the Drugs and Therapeutic Bulletin stated that bone biopsies provided a more definitive assessment of bone formation and resoprtion and these had not shown that strontium ranelate stimulated bone formation or resulted in positive remodelling imbalance. It was not clear to which data the article was referring to in this regard. The article had not cited Arlot *et al* which had been presented in late September 2005 and was available as an abstract. It was thus unclear whether the authors of the Drugs and Therapeutics Bulletin article had considered Arlot *et al*.

Servier stated that Arlot *et al* performed a limited number of biopsies only five of which were paired biopsies with the second biopsies taken at varying time points, 1 to 5 years, and the results pooled. Servier stated that this data should not be used in isolation to support or oppose the dual action of Protelos.

The Panel noted the claims highlighted by the Drugs and Therapeutic Bulletin were 'dual action bone agent' and 'the only drug to simultaneously increase bone formation and decrease bone resorption'.

On examining the promotional material provided by Servier, the Panel noted that the claim 'a dual action bone agent' was made in for example a GP fact file (05PR335) and the claim 'the first dual action bone agent' was made on post it notes (05PR288) and a detail aid (05PR294).

The Panel did not consider that given all the data the basis of the claim that Protelos was a dual action bone agent was sufficiently clinically robust. In relation to the mechanism of action of strontium ranelate, Meunier *et al*, on the basis of biochemical data, used the phrases '…being probably different to other medicines' and 'apparent dissociation between reduced bone resorption and increased bone formation'. The bone biopsy data was not as described in the Drug and Therapeutics Bulletin; Arlot *et al* showed that Protelos had a statistically significant positive effect on bone formation but produced only a trend towards a decrease in bone resorption. Arlot *et al* also stated that at the tissue level there was no significant change in activation frequency. The Panel accepted that there was some data to show that Protelos both increased bone formation and decreased bone resorption but considered that the situation was more complicated than implied by the strong, unequivocal claim 'dual action bone agent'. Readers would assume in the absence of information to the contrary that there was clinical evidence for the claim. In the Panel's view the clinical data, particularly with regard to bone resorption, was not sufficient. The Panel considered that the claim was misleading and not capable of substantiation. Breaches of Clauses 7.2 and 7.4 of the Code were ruled.

The claim 'the only drug to simultaneously increase bone formation and decrease bone resoprtion' appeared in the GP fact file (O5PR11) and a leavepiece 05PR386 referenced to Arlot *et al* and Marie *et al* (2001). The Panel considered its ruling with regard to the claim 'dual action bone agent' was relevant. The clinical data, particularly with regard to bone

resorption, was not as equivocal as the impression given by the claim now at issue. Thus the Panel ruled breaches of Clauses 7.2 and 7.4 of the Code.

APPEAL BY SERVIER

Servier submitted that healthy human bone was maintained by a constant turnover of bone tissue. Bone was constantly being broken down (or resorbed) and new bone was constantly being laid down (or formed); formation and resorption were tightly linked and in balance in healthy bone. After the menopause there was an increase in bone resorption and a decrease in bone formation. This led to a decrease in bone mass and caused bone thinning resulting in reduced bone strength and increased fracture risk.

Servier submitted that all anti-osteoporotic agents on the market in the UK worked by having a beneficial effect either on bone formation or on bone resorption. As formation and resorption were tightly linked, all agents also had a negative feedback effect opposite to their single beneficial mode of action. Therefore antiresorptive therapies also reduced bone formation. Likewise bone-forming therapies also increased bone resorption. The beneficial effect of all anti-osteoporotic agents either on resorption or formation was greater than the complementary negative effect and hence restored the overall ratio of formation:resorption in a positive manner (Meunier *et al*).

Servier submitted that in medical practice all anti-osteoporotic treatments were classified and referred to relative to their mode of action. For example bisphosphonates were known as antiresorptives (or inhibitors of bone resorption) and teriparatide was known as a bone-forming agent (or a stimulator of bone formation). This terminology was widely accepted in medical practice and in only one product (teriparatide) was there definitive histomorphometric (bone biopsy) data. For all other anti-osteoporotic agents this terminology was based solely on biochemical markers of bone turnover from clinical trials.

Servier submitted that the importance of biochemical markers of bone turnover as clinical data to evaluate the mode of action of anti-osteoporotic agents could not be overstated. It was widely accepted not only in medical practice but also by the regulatory authorities that biochemical markers of bone turnover provided clinically robust evidence to support the mode of action of medicines used in the treatment of PMO. Servier noted that biochemical markers of bone turnover were surrogate markers but they were surrogate markers of fracture/bone mineral density (BMD) not of bone biopsy data. Even though biochemical markers of bone turnover were surrogate markers for fracture/BMD they were also used directly to establish the mode of action of anti-osteoporotic agents.

Servier submitted that the EMEA note for guidance on PMO (adopted by the CPMP January 2001), which was intended to provide guidelines for the evaluation of new medicines in the prevention and treatment of PMO stated in Section 4.3 'Criteria of efficacy and their assessment 4.3.4 Biochemical Markers' that 'Biochemical markers of bone turnover are used to evaluate the mechanism of action of drugs and the integrated effect on bone'. Thus from a regulatory perspective biochemical markers of bone turnover were used to categorise anti-osteoporotic agents as either inhibitors of bone resorption or stimulators of bone formation. The only mention of histomorphometry (bone biopsies) in the EMEA guideline was in Section 4.4 entitled 'Criteria of safety and their assessment'. Here it was clearly recommended that bone biopsies should be taken 'with the aim to disclose any potentially negative effects of the drug on bone remodelling as well as in an attempt to characterise its effects on bone remodelling balance or mineralization'. In summary, from a regulatory perspective, biochemical markers of bone turnover were used to evaluate the mechanism of action of anti-osteoporotic agents. Bone biopsies should primarily be taken to assess safety on bone but also in an attempt to characterize effects on bone remodelling.

Protelos was studied in two large phase III clinical trials SOTI (The Spinal Osteoporosis Therapeutic Intervention Trial) (Meunier *et al*) and TROPOS (Treatment of Peripheral Osteoporosis) (Reginster *et al* 2005). Strontium ranelate was studied in over 1700 patients in these two trials, patient numbers far in excess of any other phase III osteoporosis program to date. In both clinical trials strontium ranelate simultaneously had statistically significant effects on markers of bone formation and bone resorption.

Marker	*SOTI*	*TROPOS*
Bone alkaline phosphatase (formation)	($p < 0.005$)	($p < 0.012$)
C-terminal propeptide of type 1 procollagen (formation)	($p < 0.001$)	($p < 0.001$)
Serum N-terminal cross-linked telopeptide (resorption)	($p < 0.001$)	Not measured
Urinary N-terminal cross-linked telopeptide (resorption)	Not measured	($p < 0.001$)

Data in both studies using the ITT population, from 0-36 months, compared to placebo,
n = 1649 in SOTI, n = 5091 in TROPOS.

Servier submitted that strontium ranelate clearly had a beneficial effect on both bone formation and bone resorption in humans. This was different to all other anti-osteoporotic agents as detailed above (an increase in formation would normally be accompanied by an increase in resorption and vice versa). Strontium ranelate therefore uncoupled the otherwise tightly linked formation: resorption process, having a positive effect on both aspects of the bone remodelling process. As a result, strontium ranelate could not be classified simply as an antiresorptive agent or a bone-forming agent as this would clearly be misleading.

Servier noted that in the promotion of Protelos it was not making any comparisons to any other therapies or

any claims around the magnitude of increase in bone formation or decrease in bone resorption. Servier simply stated that Protelos had been shown to 'uncouple' the otherwise tightly linked resorption-formation sequence of adult bone remodeling causing an increase in bone formation and decrease in bone resorption. All data to date supported this dual mode of action.

Servier submitted that the limited bone biopsy data (Arlot *et al*) for strontium ranelate (only 5 paired biopsies) demonstrated a statistically significant increase in bone formation and a decrease in bone resorption. Whilst the decrease in bone resorption did not reach statistical significance there was a decrease. As described previously, due to the tightly linked process of bone formation and bone resorption it would be expected to see an increase in bone resorption as well as bone formation from biopsy data. This was not the case with strontium ranelate. Whilst the biopsy data, in relation to bone resorption did not reach statistical significance it had demonstrated a reduction in bone resorption and therefore was consistent with the *in vitro*, animal and human biochemical markers of bone turnover data supporting the dual mode of action of strontium ranelate.

Servier submitted that all the data considered above (biochemical markers of bone turnover and histomorphometric data) were available and submitted to the EMEA and evaluated during the licensing procedure. There were no new data that might alter any conclusions reached by the EMEA after evaluation of the data for strontium ranelate and therefore this was an up-to-date evaluation of all the evidence.

Servier submitted that as strontium ranelate had a positive effect on bone formation and a positive effect on bone resorption it had two actions. Because no other anti-osteoporotic agent had a positive effect on both aspects of bone remodeling, strontium ranelate was the only osteoporosis treatment to have these two actions and therefore was the 'only dual action bone agent' which 'simultaneously increases bone formation and decreased bone resorption' as claimed.

Servier stated again that there were a large number of independent peer-reviewed publications that had also assessed the data for strontium ranelate and described the 'dual mode of action'. Furthermore both the BNF and MIMS described strontium ranelate as a 'dual action bone agent'.

Servier submitted that in addition to the large number of independent, peer-reviewed publications and widely accepted independent medical publications which described the 'dual mode of action' of strontium ranelate, there were two independent reviews commissioned by the National Institute for Health and Clinical Excellence (NICE) during the Health Technology Appraisal of strontium ranelate in 2005. The first review stated:

'Strontium ranelate is a dual action bone agent, which reduces bone resorption and increases bone formation. Biochemical markers of bone turnover suggest that the antiresorptive effect of strontium is less than observed with bisphosphonate treatment, whereas the anabolic action is weaker than seen with teriparatide. Nevertheless, this uncoupling of bone resorption and formation is not seen with other osteoporosis treatments and might be expected to improve bone mineral density (BMD) and architecture, thereby decreasing the risk of fracture'.

The second review, stated:

'It is different in its mode of action by being a dual action bone agent (DABA) with properties of increasing bone formation and reducing bone resorption. These actions are in contrast to commonly used antiresorptive agents such as the bisphosphonates and selective estrogen receptor modulators …'.

Servier submitted that in summary, biochemical markers of bone turnover were used scientifically, in medical practice and by regulatory authorities as an appropriate and accepted evaluation of the mechanism of action of anti-osteoporotic agents. In extensive phase III clinical trials strontium ranelate had demonstrated statistically significant increases in biochemical markers of bone formation and statistically significant decreases in biochemical markers of bone resorption. Servier considered that this data, consistent with all other data for strontium ranelate demonstrated an increase in bone formation and a decrease in bone resorption, was sufficiently clinically robust to support the claims that Protelos was 'The first dual action bone agent' and 'the only drug to simultaneously increase bone formation and decrease bone resorption'. Servier submitted that data presented above supported the reasons why these claims were accurate, balanced, fair, objective and unambiguous and based on an up-to-date evaluation of all the evidence and reflected that evidence clearly. The evidence presented demonstrated that the claims in question did not mislead either directly or by implication, by distortion, exaggeration or undue emphasis and that they were capable of substantiation.

Therefore, Servier submitted that the claims in question complied with the requirements of Clauses 7.2 and 7.4 of the Code.

COMMENTS FROM DRUG AND THERAPEUTICS BULLETIN

The Drug and Therapeutics Bulletin (D&TB) stated that it had concerns about the self regulation process and consequently did not in general take complaints to the Authority and rarely commented on appeals. It however wanted to take the opportunity of restating the D&TB position on the promotion of Protelos.

The D&TB noted that the article stated 'In our view, there is no convincing published evidence to support promotional claims that the drug simultaneously stimulates bone formation and reduces bone resorption. Such claims should, therefore, be treated with scepticism and should not sway decisions on whether or not to use the drug'. In reaching this view, the D&TB stated that it had considered the available data on biochemical markers of bone formation and bone resorption and this evidence was cited and discussed in its article. The D&TB accepted that such

evidence was useful in helping to classify the mechanism of action of medicines in osteoporosis. However, as the article indicated, the D&TB considered that data on biochemical markers alone were insufficient and that bone biopsies provided a more definitive assessment of bone formation and resorption, particularly where a wholly new mechanism of action was being suggested. The D&TB found no fully published data to confirm that strontium ranelate simultaneously increased bone formation and reduced bone resorption. The D&TB stated that it had assessed the bone biopsy data (Arlot *et al*) but had not cited it in the article because the study was published only as an abstract and its general policy was to base conclusions primarily on data that had been published in full in peer-reviewed journals. In addition, the study was small. Even if these key limitations were overlooked, the data did not provide convincing confirmatory evidence of a 'dual action' for strontium ranelate, given that it did not find a statistically significant reduction in bone resorption.

The D&TB noted that Servier had widely publicised on a European news release the idea that Arlot *et al* 'provided scientific proof that the novel anti-osteoporotic agent [strontium ranelate] had a dual mechanism of action that was completely different from existing treatments'. The notion that bone-biopsy data would 'provide scientific proof' of the mechanism of action seemed entirely in keeping with the D&TB's view that 'bone biopsies provide a more definitive assessment of bone formation and resorption'. The D&TB submitted that this fact, and the described limitations of Arlot *et al*, made it difficult to see on what basis Servier could question its opinion about the place of and need for bone-biopsy evidence without contradicting its own publicly expressed view on this topic. This view was echoed in Servier's appeal, which stated 'in only one product was there definitive histomorphometric (bone biopsy) data'. Servier's use of the word 'definitive' in describing bone biopsy data was very similar to its suggestion that such evidence would represent 'scientific proof' of strontium ranelate's mechanism of action. It therefore followed that the lack of such 'proof' must be legitimate grounds for questioning the promotional claims of a dual action for strontium ranelate.

The D&TB stated that while it continued to question the evidential basis for the claims about Protelos, it was important to note that these doubts were not, in fact, the main problem associated with the promotion. The key issue was how these claims had been used and could easily be misinterpreted, regardless of whether or not the medicine had been proven to have a dual mechanism of action. The use of the claims 'the first dual action bone agent' and the 'the only drug to simultaneously increase bone formation and decrease bone resorption' in the promotional material more than merely indicated a new mechanism of action in osteoporosis. In particular, 'first' and 'only' obviously marked a contrast with other medicines; and in this context, the repeated, unqualified emphasis of dual action suggested that Protelos offered definite therapeutic advantages over, 'single-action', therapies. This was unhelpful and served only to obscure a key question: how the clinical efficacy (and not simply the mechanism of action) of Protelos compared with that of other, longer-established treatments for osteoporosis. Given the absence of any published randomised comparisons between Protelos and other treatments, the claimed dual action of Protelos had no proven relevance in terms of the absolute and comparative magnitude of Protelos's clinical benefit, as the company appeared to accept in its appeal. This was the basis of the D&TB's view that the claims about the mechanism of action of Protelos should not be allowed to sway clinical decisions on whether to use the medicine.

In summary, D&TB alleged that there was a lack of convincing bone-biopsy data to confirm that Protelos both stimulated bone formation and reduced bone resorption. Since Servier had publicly labelled this type of evidence as 'scientific proof' of Protelos' claimed mechanism of action, the company was now poorly placed to downgrade the need for such confirmatory information. Also, promotional claims that Protelos was the first and only dual-action medicine for osteoporosis should not masquerade as, or hide the absence of, published evidence that the treatment's clinical efficacy matched, let alone exceeded, that of other longer-established therapy.

APPEAL BOARD RULING

The Appeal Board noted that the article in the D&TB, which had formed the basis of the complaint, had stated that there was no convincing published clinical evidence to support the claims 'the first dual action bone agent' and 'the only drug to simultaneously increase bone function and decrease bone resorption'. The article had not criticised the context in which the claims had been used, just the claims *per se*. The Appeal Board noted that although in its response to the appeal, the D&TB had expressed concerns about the way in which the claims had been used, these concerns could not be considered as part of the appeal as they had not been raised in the original article.

The Appeal Board considered that there was data to show that, as statements of fact, Protelos was 'the first dual action bone agent' and 'the only drug to simultaneously increase bone formation and decrease bone resorption'. The Appeal Board noted that in this therapy area biochemical markers were well accepted as surrogate markers of clinical action. The biochemical data showed Protelos increased bone formation and decreased bone resorption. Although the bone biopsy data was less robust it nonetheless mirrored the biochemical data. The Appeal Board noted that it was difficult to obtain bone biopsies, particularly paired biopsies. Such data contributed to the evidence base for the medicine but was only a part of it.

The Appeal Board considered that there was data to support the claim that Protelos was 'the first dual action bone agent' and thus ruled no breach of Clauses 7.2 and 7.4 of the Code. The appeal on this point was successful.

The Appeal Board similarly considered that there was data to support the claim that Protelos was 'the only drug to simultaneously increase bone formation and

decrease bone resorption' and thus ruled no breach of Clauses 7.2 and 7.4 of the Code. The appeal on this point was successful.

The Appeal Board noted that its rulings above were based on the claims at issue as statements of fact; it had not ruled on their use in promotional material. The context in which such claims were used, however, was important. The Appeal Board was concerned that the claims, although true in themselves, had been used in such a way in the Protelos promotional material supplied by Servier as to imply clinical superiority over other medicines. There was no data to support this implication. The Appeal Board requested that Servier be advised of its concerns in this regard and should review the context in which the claims were made.

Proceedings commenced **6 April 2006**

Case completed **21 June 2006**