CASE AUTH/2126/5/08

PROCTER & GAMBLE v SERVIER LABORATORIES

Misleading and disparaging material about bisphosphonates

Procter & Gamble alleged that in a letter to prescribing advisors, a press release and and at its sponsored symposium at the British Geriatrics Society (BGS) meeting, Servier Laboratories had issued misleading and disparaging information about bisphosphonates, including Procter & Gamble's product Actonel (risedronate sodium). Servier had inferred that the anti-fracture efficacy of bisphosphonates was attenuated when co-prescribed with acid suppressants. In addition Servier was sharing these misleading messages as part of a broad strategy including communications with official bodies such as the National Institute for Health and Clinical Excellence (NICE).

This was a concerted effort by Servier to disparage oral bisphosphonates so as to influence the prescribing market in its own favour. This was achieved by urging caution when co-prescribing acid suppressants and bisphosphonates due to the increased fracture risk associated with acid suppressants; this was not only misleading but also raised inappropriate concerns about the safety of the oral bisphosphonates. Procter & Gamble alleged that by doing so, Servier brought discredit upon and reduced confidence in the pharmaceutical industry in breach of Clause 2. (Servier supplied Protelos (strontium ranelate) an alternative to bisphosphonates in osteoporosis).

There were limited and contradictory data available (two papers and one abstract) to support the first message conveyed by Servier that '…acid suppressant medication, including proton pump inhibitors (PPIs) has been associated with an increased risk of fracture'; the authors concluded that further studies were needed to confirm and explain the results. In some cases, some of the results were not statistically significant. Use of PPIs was not currently considered an established risk factor for an osteoporotic fracture. In a review of the data upon which Servier based its claims, commissioned by NICE, the final report concluded that the quality of the evidence regarding any possible association between acid suppressants and increased risk of fracture was generally poor and their design appeared to be prone to confounding.

The second message was that epidemiological data, such as that recently presented at the National Osteoporosis Conference, suggested that the anti-fracture efficacy of bisphosphonates was potentially attenuated when co-prescribed with acid suppressants (de Vries *et al* 2007). Procter & Gamble noted that this analysis, published only as an abstract, was funded by Servier. It was the first and only analysis to have shown this 'association' and the authors suggested that further studies were needed. The review commissioned by NICE concluded that 'No confidence may be placed in the results of the study by de Vries *et al* because of its failure to demonstrate comparability between exposure groups in terms of key prognostic factors, in particular whether bisphosphonates were prescribed for primary or secondary fracture prevention, and for primary or secondary osteoporosis'. The current summaries of product characteristics (SPCs) for Actonel did not caution against co-prescription of acid suppressants nor was such a potential interaction listed. Data was available for risedronate from a retrospective analysis on a subset of 5,454 patients from three phase-III fracture trials who took either placebo or risedronate (5mg daily) and who were classified as either PPI or H_2 antagonist users, or nonusers. This showed that efficacy of risedronate in reducing the risk of new vertebral fractures was not influenced by concomitant PPI and H_2 antagonist use (Roux *et al* 2008).

In conclusion Procter & Gamble believed that the numerous messages communicated by Servier on this topic were not balanced and were misleading. In addition, the inferences made regarding lack of efficacy of bisphosphonates with concomitant PPI use were disparaging.

Procter & Gamble further alleged that the use of misleading claims in a high level promotional campaign which disparaged bisphosphonates as a drug class, brought discredit upon and reduced confidence in the pharmaceutical industry in breach of Clause 2.

The detailed response from Servier is given below.

The Panel noted that when a clinical or scientific issue existed which had not been resolved in favour of one generally accepted viewpoint, particular care must be taken to ensure that the issue was treated in a balanced manner in promotional material.

The Panel noted the data submitted in support of the claims that the use of acid suppressants had been associated with an increased risk of fracture. Yang *et al* (2006) found a significantly increased risk of hip fracture associated with long-term PPI therapy, particularly high dose PPI. The authors, however, stated that further studies were needed to confirm their findings. Yu *et al* (2006) concluded that amongst postmenopausal women, use of acid suppressants *might* (emphasis added) be associated with an increased risk of non-spine fracture. Vestergaard *et al* (2006) concluded that PPIs appeared to be associated with an increased fracture risk in contrast to H_2 antagonists which

seemed to be associated with a decreased fracture risk. The changes in risk estimates were small in all instances and might have limited consequences; further studies were needed. De Vries *et al* concluded that concomitant use of bisphosphonates and acid suppressants was associated with an increased risk of fracture and that possibly acid suppressants attenuated the protective effects of bisphosphonates on fracture risk. The authors stated that given the frequency of co-prescription of bisphosphonates and acid suppressants, the issue required further investigation.

A critique of the evidence suggesting an association between acid suppressants and increased fracture risk stated that the data was generally poor. In its appraisal consultation document on alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women, NICE noted that data indicating that acid suppressants led to a small increase in fracture risk and that co-administration of acid suppressants and bisphosphonates might lead to an increased fracture risk compared with bisphosphonates alone was observational and tentative and different for different fracture sites and different acid suppressants. NICE considered, however, that because various studies showed a trend, caution should be exercised when the co-prescribing of acid suppressants and bisphosphonates was being considered. The committee was not persuaded, however that a change to its recommendations, based on the evidence, was necessary. The Panel noted that the NICE document was an appraisal consultation document and was marked confidential. The document stated that it did not constitute the Institute's formal guidance and its recommendations were preliminary and might change after consultation.

The Panel noted that a template letter to prescribing advisors was headed 'Increased risk of fracture associated with use of acid suppressant medication'. The Panel considered that the quality of the data was such that it could not support such a robust, unqualified claim. Although the reader was told that data *suggested* that the anti-fracture efficacy of bisphosphonates was *potentially* attenuated when co prescribed with acid suppressants (emphasis added) the Panel nonetheless considered that the letter implied that acid suppressants had been unequivocally proven to attenuate the anti-fracture efficacy of biphosphonates. The letter went on to refer to this growing body of evidence and assessment of the implications of the data, in particular the potential effect on health outcomes and healthcare budgets. It appeared that the data had proven clinical implications and this was not so. In that regard the Panel considered the letter was not balanced and did not reflect the data accurately. A breach of the Code was ruled. The implication that bisphosphonates were less effective if co-prescribed with acid suppressants was disparaging given the current data. Breaches of the Code were ruled and upheld on appeal by Servier.

The press release was headed 'Servier welcomes revised draft NICE guidance'. The third paragraph began 'Servier also welcomes the acknowledgement by NICE in its draft guidance that caution should be exercised when considering the co-prescription of acid suppressants and bisphosphonates'. Readers were also told that NICE had previously failed to address the increased risk of fractures associated with the use of acid suppressants, in particular PPIs, which were commonly co-prescribed with bisphosphonates. The Panel considered that the quality of the data was such that it could not substantiate such robust unqualified claims. The tentative nature of the data acknowledged by NICE, was not referred to in the press release. The Panel considered that the press release was not balanced and did not reflect the data accurately. A breach of the Code was ruled. The Panel also considered that the implication that bisphosphonates were less effective if co-prescribed with acid suppressants was disparaging given the current data. Breaches of the Code were ruled and upheld on appeal by Servier.

The Panel noted that Servier's sponsored symposium at the BGS meeting had included a presentation entitled 'Acid Suppressant Medication and Fractures'. The speaker's briefing notes stated that the objective was to communicate on the use of PPIs in osteoporotic patients and the associated risks. Then to give a primary care perspective on how to manage patient cases not covered by NICE guidance. Points to include in the presentation were, *inter alia*: acid suppressants and increased risk of fracture; attenuation of bisphosphonate efficacy when acid suppressants were co-prescribed; how to identify patients at risk of PPIs if prescribed an oral bisphosphonate and the conclusion was to consider prescribing an appropriate agent for these patients – eg strontium ranelate [Servier's product Protelos]. The speaker was further advised that the tone of the presentation should cause delegates to think about their current medical practice and then provide them with a simple solution to the problem.

The final slide of the presentation was headed 'Summary: overview of evidence' and detailed the findings of Yang *et al* and Vestergaard *et al*. In the Panel's view the results of the two studies were presented on the slide as if the findings had been unequivocal; the authors' comments as noted above had not been included. There was no transcript of the presentation although the speaker had provided an overview of what he had said. With regard to the last slide the speaker stated that he had said that there might be a reduction in the effect of a bisphosphonate with PPI usage; this needed further study. The Panel considered, however, that the tentative nature of the data was not reflected in the slides and in its view delegates would be left with the impression that acid

suppressants, particularly PPIs, had been unequivocally proven to attenuate the anti-fracture efficacy of bisphosphonates with proven clinical implications. In that regard the Panel considered that the slides were not balanced and did not reflect the data accurately. A breach of the Code was ruled. The implication that bisphosphonates were less effective if co-prescribed with acid suppressants was disparaging given the current data. A breach of the Code was ruled.

The Panel noted its rulings above but nonetheless did not consider that there had been a breach of Clause 2 of the Code which was reserved for use as a sign of particular censure. This ruling was not appealed

The Appeal Board noted Servier's submission that the slides used at the BGS presentation were not intended to stand alone. The company had emphasised that attendees had not been given copies of the presentation. In the Appeal Board's view, however, a company could not rely on a speaker to qualify or explain otherwise misleading slides and in that regard it was irrelevant as to whether they were given to the attendees.

Servier's sponsored symposium at the BGS was entitled 'Trips, slips and fractured hips'. The title of the speaker's presentation in question was given as 'Global risk management' although the title slide of his presentation read 'Acid Suppressant Medication and Fractures'. The company had specifically briefed the speaker to talk about the potential attenuation of bisphosphonate anti-fracture efficacy when acid suppressants were co-prescribed. The Appeal Board was extremely concerned about the speaker's briefing notes. Although the notes correctly cited the title of the talk ('Global risk management') the objective was much narrower and was to talk about the use of PPIs in osteoporotic patients and the associated risks. Then to give a primary care perspective on how to manage patient cases not covered by NICE guidance. Points Servier briefed the speaker to include in the presentation were, *inter alia*: acid suppressants and increased risk of fracture and attenuation of bisphosphonate efficacy when acid suppressants were co-prescribed. These points echoed Servier's views as expressed in the letter and press release discussed above. The tentative nature of the data was not reflected in the briefing notes. The speaker was further asked to discuss identification of patients at risk of PPIs if prescribed an oral bisphosphonate and the conclusion was to consider prescribing an appropriate agent for these patients – eg strontium ranelate [Servier's product Protelos]. The speaker was further advised that the tone of the presentation should cause delegates to think about their current medical practice and then provide them with a simple solution to the problem. In the Appeal Board's view the briefing notes essentially instructed the speaker to raise concerns amongst the delegates about the co-prescription of bisphosphonates and acid suppressants and to get them to consider prescribing Protelos instead of bisphosphonates in at risk patients. In the Appeal Board's view, to include such a direct and promotional call to action in a brief to an independent speaker was wholly unacceptable and gave a very poor reflection of the company's procedures.

The Appeal Board considered that the presentation at the BGS had exaggerated the clinical importance of the data regarding bisphosphonates and acid suppressants. The presentation was not an accurate or balanced reflection of the data in that regard. The Appeal Board upheld the Panel's ruling of a breach of the Code. The Appeal Board also considered that the implication that bisphosphonates were less effective if co-prescribed with acid suppressants was disparaging given the existing data. The Appeal Board upheld the Panel's ruling of a breach of the Code.

Procter & Gamble Pharmaceuticals UK, Limited complained about the activities of Servier Laboratories Ltd in relation to alleged misleading and disparaging information about bisphosphonates, including Procter & Gamble's product Actonel (risedronate sodium). Servier supplied Protelos (strontium ranelate).

At issue were a letter to prescribing advisors (ref 07MKA0006), a press release 'Servier welcomes revised NICE Guideline…' (ref 08MC0026) and Servier's sponsored symposium at the British Geriatrics Society (BGS) meeting in Glasgow on 24 April.

Inter-company dialogue between the companies had proved unsuccessful.

COMPLAINT

Procter & Gamble alleged that materials/activities which inferred that the anti-fracture efficacy of bisphosphonates was attenuated when co-prescribed with acid suppressants were in breach of Clauses 7.2 and 8.1 of the Code.

In addition Servier was sharing these misleading messages as part of a strategy that was not limited to promotional activities but extended to communications with official bodies such as the National Institute for Health and Clinical Excellence (NICE). Although such communications did not necessarily fall under the remit of the Code, it illustrated that Servier was sharing these messages as part of a broader strategy.

In summary, this was a concerted effort by Servier to disparage oral bisphosphonates so as to influence the prescribing market in its own favour. This was achieved by portraying messages that caution should be exercised when co-prescribing acid suppressants and bisphosphonates due to the increased fracture risk associated with acid suppressants, which was not only misleading but also raised inappropriate concerns about the safety

of the oral bisphosphonates. Procter & Gamble alleged that by doing so, Servier brought discredit upon and reduced confidence in the pharmaceutical industry in breach of Clause 2.

The messages conveyed by Servier were:

1 **'…acid suppressant medication, including proton pump inhibitors (PPIs) has been associated with an increased risk of fracture.'**

It was important to note that there were limited and contradictory data available (two papers and one abstract) to support this claim and the authors concluded that further studies were needed to confirm and explain the results. In some cases, some of the results were not statistically significant.

- Yang *et al* (2006) '…Thus, further studies are urgently needed to confirm our findings and clarify the underlying mechanism.'
- Vestergaard *et al* (2006), '…In conclusion, PPIs [proton pump inhibitors] appear to be associated with an increased fracture risk, in contrast to histamine H_2 antagonists (H_2 antagonists), which seem to be associated with a decreased fracture risk. The changes in risk estimates were small in all instances and may have limited clinical consequences. However, further studies in the field are needed.'
- Yu *et al* (2006) (abstract), '…There was also a non-significant increase risk of hip fracture among PPI/H_2 antagonists users.' (There was, however, an increased in the risk of non-spine fracture among users of acid suppressants.)

Use of PPIs was not currently considered an established risk factor for an osteoporotic fracture. Established risk factors included a prevalent vertebral fracture, maternal hip fracture, corticosteroid use etc.

NICE had asked the School of Health and Related Research (ScHARR), to view the data upon which Servier made its claims. The ScHARR report stated: 'Servier claim that acid-suppressing medication significantly reduces, if not completely negates, the anti-fracture benefits of bisphosphonate treatment'. The ScHARR report concluded however, that the quality of the evidence regarding any possible association between acid suppressants and increased risk of fracture was generally poor and their design appeared to be prone to confounding.

Procter & Gamble was not asking the Panel to rule on the scientific validity of these data or the clinical interpretation. However it considered that given the uncertain nature of these findings, use in such a high level promotional way by Servier was not consistent with the letter or spirit of the Code and in breach of Clause 7.2.

2 **Epidermiological data, as eg recently presented at the National Osteoporosis Conference, suggested that the anti-fracture efficacy of bisphosphonates was potentially attenuated when co-prescribed with acid suppressants. (de Vries *et al* 2007)**

Procter & Gamble noted the following:

- This analysis, published only as an abstract, was funded by Servier.
- This was the first and only analysis to have shown this 'association' and the authors suggested that further studies were needed.
- ScHARR concluded that 'No confidence may be placed in the results of the study by de Vries *et al* because of its failure to demonstrate comparability between exposure groups in terms of key prognostic factors, in particular whether bisphosphonates were prescribed bisphosphonates for primary or secondary fracture prevention, and for primary or secondary osteoporosis'.

ScHARR also stated, '…. It is possible that the findings are invalidated by imbalances between the groups in the proportions of patients receiving bisphosphonates for primary or secondary fracture prevention, and for primary or secondary osteoporosis'.

- de Vries was also not consistent with the current labelling for risedronate. The current summaries of product characteristics (SPCs) for risedronate did not caution against co-prescription of acid suppressants in Section 4.4 nor was such a potential interaction listed in Section 4.5.
- Data was available for risedronate from a retrospective analysis on a subset of 5,454 patients from three phase-III fracture trials who took either placebo or risedronate (5mg daily) and who were classified as either PPI or H2 antagonist users, or nonusers. This showed that efficacy of risedronate in reducing the risk of new vertebral fractures was not influenced by concomitant PPI and H2 antagonist use (Roux *et al* 2008).
- Procter & Gamble alleged that the claim made by Servier was in breach of Clause 7.2. In addition, the intention was to disparage not only risedronate but all oral bisphosphonates in breach of Clause 8.1.

In conclusion Procter & Gamble believed that the numerous messages communicated by Servier on this topic were not balanced and were misleading and in breach of Clause 7.2. In addition, the inferences made regarding lack of efficacy of bisphosphonates with concomitant PPI use were disparaging, in breach of Clause 8.1.

Procter & Gamble further alleged that the use of misleading claims in a high level promotional campaign which disparaged a drug class, brought

discredit upon and reduced confidence in the pharmaceutical industry in breach of Clause 2.

RESPONSE

Servier vigorously refuted that the activities/materials at issue were misleading or that they disparaged bisphosphonates, including Actonel, as alleged. The company therefore denied breaches of Clauses 7.2 and 8.1. It also did not agree that it had brought discredit upon and reduced confidence in the pharmaceutical industry and so there was no breach of Clause 2.

As the marketing authorization holder for Protelos Servier had participated in the development of the Health Technology Appraisals: 'Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women' and 'Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women'. As part of this process Servier had submitted data to NICE demonstrating an association between use of acid suppressants (PPIs and H_2 antagonists) and increased fracture risk as well as evidence of an attenuation of the bisphosphonate anti-fracture efficacy with use of concomitant acid suppressants. Communication regarding these data had taken place via the formal NICE consultation process and fell outside the scope of the Code.

Acid suppressants (PPIs and H_2 antagonists) were commonly prescribed, particularly in patients with postmenopausal osteoporosis. Therefore, Servier considered that it was important that the demonstrated association between use of acid suppressants and increased fracture risk, as well as evidence that this effect was also apparent in patients taking concomitant acid suppressants and oral bisphosphonates compared with bisphosphonate alone was communicated appropriately to prescribers and bodies such as NICE. Indeed, this was even more important due to differences in acid suppressant use between osteoporotic agents, which could be explained by class differences between these agents in their upper gastro-intestinal (GI) profiles (see below).

Materials/activities related to the complaint

1 Letter to prescribing advisors dated 14 February 2008 (ref 07MKA0006)

This was a mailing sent by Servier's healthcare development managers to tell prescribing advisors about the increased risk of fractures associated with the use of acid suppressants and in particular its possible relevance to the treatment of patients with bisphosphonates. The healthcare development managers reported into the Department of Medical & Corporate Affairs and were responsible for informing budget holders on matters related to healthcare outcomes and healthcare budgets.

2 Press release: 'Servier welcomes revised NICE guidance on postmenopausal osteoporosis but urges NICE to go further …' dated 4 April 2008

Servier issued this press release to the medical press and also placed the document on the UK corporate website in the 'Health Care Professionals' section under Protelos articles. The press release outlined Servier's position regarding the latest NICE draft guidance on the management of osteoporosis. The press release submitted by Procter & Gamble was based on 08MCA0026.

3 Servier's sponsored symposium at the BGS meeting

Servier's sponsored symposium took place at the BGS meeting in Glasgow on 24 April from 7.15am-8.30am. The symposium was entitled 'Trips, slips and fractured hips' and was attended by approximately 100 health professionals. Topics covered at the meeting were: introduction and demonstration of FRAX; the impact of hip fractures; evidence based interventions in the elderly and global risk management.

The speaker for the session 'Global risk management' was asked to speak on the association between acid suppressants and increased risk of fracture, and on the potential attenuation of bisphosphonate anti-fracture efficacy when acid suppressants were co-prescribed. The objective of this session was to appropriately inform geriatricians on this topic relevant to the management of their elderly patients suffering from osteoporosis.

Claim '…acid suppression medication, including proton pump inhibitors (PPIs) has been associated with an increased risk of fracture'

Servier noted that Procter & Gamble had stated that 'there are limited and contradictory data available' to support this claim, however a number of independent studies had now demonstrated a consistent association between acid suppressants, particularly for PPIs, and an increased risk of fracture. These studies employed both retrospective and prospective observational study designs and examined various populations, whilst controlling for a wide range of potential confounding factors. The ScHARR report, undertaken at the request of NICE, summarised the evidence to date and acknowledged that these 'studies are controlled observational studies. This is appropriate: most RCTs are too small to detect adverse events which are either rare or take a long time to develop'.

Procter & Gamble referred to the fact that the authors of two of these papers recommended that further studies were needed in this area. However, it was important to note that three of these studies reported in the same year, and so the various authors were likely to have been unaware of the

growing body of evidence on this topic when their respective studies were published. The evidence base was further supported by additional studies showing similar findings.

The key studies were:

Yang *et al* (2006): This was a retrospective nested case-control study, published in the Journal of the American Medical Association, which used the UK General Practice Research Database (GPRD) to examine the association between PPIs and H_2 antagonist and hip fracture risk. The study cohort comprised patients aged 50 years and older and included 13,556 hip fracture cases and 135,386 controls. One to ten controls per case were drawn from the same cohort as the cases, using incidence density sampling and matching for sex, index date, year of birth, and both calendar period and duration of follow-up before the index date. A comprehensive list of potential confounders that were risk factors for osteoporosis or risk of falling were controlled for in the analysis: body mass index (BMI), smoking history, alcoholism, congestive heart failure, cerebral vascular accident, dementia, impaired mobility, myocardial infarction, chronic obstructive pulmonary disease or asthma, peptic ulcer disease, peripheral vascular disease, rheumatoid arthritis, vision loss, celiac sprue, Paget's disease, osteomalacia, chronic renal failure, Cushings disease, inflammatory bowel disease, seizure disorder and prior history of fracture (> 3 months before the index date). Exposure to various classes of medications were also considered: anxiolytics, antidepressants, antiparkinsonian medicines, thiazide diuretics, statins, corticosteroids, hormone therapy, bisphosphonates, calcitonin, nonsteroidal anti-inflammatory medicines, anticonvulsants, thyroxine and calcium and vitamin D supplements.

This study found an increase in the risk of hip fracture for patients with more than one year of cumulative PPI (Adjusted Odds Ratio (AOR) 1.44; 95% CI 1.30-1.59) or H_2 antagonist use (AOR 1.23, 95% CI 1.14-1.39), compared with acid suppression non-users. The association between hip fracture risk and PPI use was also found to be duration dependent, with risk of hip fracture increasing with duration of PPI use, compared to acid suppression non-users [AOR: 1 year, 1.22 (95% CI 1.15-1.30); 2 years, 1.41 (95% CI, 1.28-1.56); 3 years, 1.54 (95% CI, 1.37-1.73); and 4 years, 1.59 (95% CI 1.39-1.80]. A dose-dependent relationship for PPI and hip fracture risk was also observed, with the risk increasing with higher doses, from AOR 1.40 (95% CI 1.26-1.54) for those receiving ≤1.75 average daily dose of PPI, to AOR 2.65 (95% CI 1.80-3.90) for those receiving more than 1.75 average daily dose, compared to acid suppression non-users.

Vestergaard *et al* (2006): The association between fracture risk and PPIs was also demonstrated in a case-control study using Danish medical records. This study examined the association between the use of PPIs, H_2 antagonist and other acid suppressants and the risk of fracture in 2000 (n = 124,655) and matched controls (n=373,962). Use of a PPI during the year prior to fracture was associated with an increase in overall fracture risk compared with matched controls (AOR 1.18, 95% CI 1.12-1.43), as well as an increase in hip (AOR 1.45, 95% CI 1.28-1.65) and vertebral fracture risk (AOR 1.60, 95% CI 1.25-2.04). There was no increased risk of fracture in patients who had used PPIs in the past, but not in the year before their fracture.

In contrast, H_2 antagonists were associated with a decreased fracture risk. This might be because H2 antagonists had a lower level of acid suppression than PPIs. On average, H_2 antagonists blocked approximately 70% of gastric acid production whilst PPIs suppressed up to 97% (see also below for further discussion on possible mechanism of action). In addition, the decrease in fracture risk was observed regardless of temporal duration of H_2 antagonist exposure, being evident for patients who had not received a H_2 antagonist for more than a year, suggesting that this reduction in fracture risk was not related to drug exposure *per se*.

Grisso *et al* (1997): This was a case-control study designed to identify risk factors for hip fracture in men. It comprised 365 men (aged 45 years and older) admitted to hospital with a radiologically confirmed first hip fracture, and 402 controls matched by age and zip code/telephone exchange, and found that use of the H_2 antagonist cimetidine was associated with an increased risk of hip fracture (OR 2.5, 95% CI 1.4-4.6).

Yu *et al* (2006): The association between PPI and/or H_2 antagonist use and adverse skeletal outcomes in postmenopausal women (n=3,432) was also assessed as part of the Study of Osteoporotic Fractures. After a mean of 4.9 years follow-up and adjustment for potential confounding factors (including age, ethnicity, BMI, calcium intake, health status, exercise, alcohol intake, and use of oestrogens or corticosteroids), an increase in the risk of non-spine fracture was observed among acid suppressant users (Adjusted Relative Hazard (ARH) 1.18, 95% CI 1.01-1.39), and a non-significant increase in the risk of hip fracture (ARH 1.15, 95% CI 0.86-1.52), the latter being potentially under-powered due to the small number of hip fractures observed in this study.

Briot *et al* (2007): Six year data from the prospective multi-centre study, OPUS, (Osteoporosis and Ultrasound Study), examining clinical risk factors for incident vertebral fractures, had also assessed the effects of PPIs. This study included 2,409 postmenopausal women aged between 55-81 years. A variety of baseline clinical risk factors (age, weight, current smoking, personal or familial previous fracture, corticosteroids, medical diseases, physical activity), and bone mineral density (BMD) measurements were included in the analysis. In the age-adjusted multivariate analysis, several clinical factors were significantly associated with incident vertebral fractures (radiologically confirmed),

independently of BMD value, namely age (per 10 years) (sOR=1.7; 95% CI, 1.0-2.7; p<0.04), previous fall (sOR=1.4; 95% CI, 1.0-1.9; p<0.04), previous paternal hip fracture (sOR=3.0; 95% CI, 1.5-5.9; p<0.002), and current intake of PPI therapy (omeprazole) (sOR=1.9; 95% CI, 1.2-2.9; p<0.006). Therefore, this 6-year prospective study provided further evidence of the association between PPI therapy and increased risk of vertebral fracture.

In conclusion, these studies, performed by a variety of research groups utilising different study designs and populations, provided clear evidence for an association between acid suppressants and increased fracture risk.

Servier explained that the potential mechanism underpinning the observed association between acid suppressants and increased fracture risk was that of reduced calcium absorption, secondary to decreased acidity in the stomach and proximal duodenum. Recker (1985) demonstrated that absorption of calcium was impaired in fasting achlorhydric patients. Furthermore, a randomised placebo controlled cross-over trial in healthy postmenopausal women (aged 65–89 years old) found that omeprazole significantly reduced fractional intestinal calcium absorption (O'Connell *et al* 2005). Such a reduction in calcium absorption might consequently lead to an increase in fracture risk.

Servier noted Procter & Gamble's statement that use of PPIs was not currently considered an established risk factor for an osteoporotic fracture. However, as outlined above, there was now a significant body of published evidence demonstrating an association between the use of acid suppressants and fracture risk, and therefore it was entirely appropriate for Servier to refer to this association as it was an important consideration in the management of postmenopausal osteoporosis.

Procter & Gamble also referred to analysis of the data by ScHARR following a request by NICE. Several of the studies discussed above were considered as well as de Vries *et al* (see below) in the development of the latest NICE appraisal consultation documents in osteoporosis (issued 25 March 2008). Based on a consideration of this evidence, NICE concluded that 'caution should be exercised when considering the co-prescription of acid-suppressive medication and bisphosphonates' (Section 4.3.33 and 4.3.34 of the primary and secondary prevention appraisal consultation documents respectively).

Therefore, it was clear that there was a significant body of evidence to support the claim that '…acid suppression medication, including proton pump inhibitors (PPIs) has been associated with an increased risk of fracture' and as such, Servier considered this claim to be fair and balanced and not misleading. Consequently, Servier did not agree that this claim was in breach of Clause 7.2.

Epidemiological data, as eg recently presented at the National Osteoporosis Conference, suggested that the anti-fracture efficacy of bisphosphonates was potentially attenuated when co-prescribed with acid suppressants.

The above statement referred to a study conducted using the GPRD, which was funded by Servier, conducted by the GPRD research team, and undertaken in collaboration with leading experts in the fields of epidemiology and osteoporosis (de Vries *et al*). This was a retrospective cohort study assessing the fracture risk of patients taking concomitant bisphosphonate and PPIs or H_2 antagonist vs those taking bisphosphonates alone. Patients were aged 40 years or older starting treatment with PPIs (n = 234,144), H_2 antagonists (n = 166,798) or bisphosphonates (n = 67,309).

The analysis adjusted for an extensive list of potential confounders including age, gender, BMI, smoking status, a history of any fractures, diabetes mellitus, rheumatoid arthritis, inflammatory bowel disease, heart failure, cardiovascular disease, chronic obstructive pulmonary disease, hysterectomy/early menopause, and use in the six months before of anticonvulsants, anxiolytics, hypnotics, antidepressants, anti-Parkinson medication, HRT, thiazide diuretics, systemic glucocorticoids, inhaled corticosteroids/ bronchodilators, aluminium/magnesium containing acid suppressants, and calcium/vitamin D supplements. The analyses were also adjusted for the number of non-steroidal anti inflammatories (NSAIDs) in the year before each acid suppressant prescription (none, 1-4, >4).

This study found that concomitant use of bisphosphonates and PPIs was associated with a statistically significant increased risk of any fracture (Adjusted Relative Rate (ARR) 1.08; 95% CI 1.01-1.15) and hip fracture (ARR 1.21; 95% CI 1.05-1.38), but not vertebral fracture (ARR 1.11; 95% CI 0.94-1.31), compared with bisphosphonate use alone. The results suggested that PPIs might attenuate the anti-fracture efficacy of bisphosphonates on fracture risk.

The fact that the study was funded by Servier, as noted by Procter & Gamble, did not invalidate the results. The study was conducted by the respected GPRD Research team (part of the MHRA), which had an extensive heritage in undertaking studies examining medicine-induced fracture risk and were widely published in this area. Furthermore, abstracts from this study had been peer-reviewed and deemed to be of sufficient scientific merit to be worthy of oral presentations at both the 2007 National Osteoporosis Society Conference in Edinburgh and the 2008 European Congress on Clinical and Economical Aspects of Osteoporosis and Osteoarthritis.

Servier noted that Procter & Gamble had specifically referred to comments from ScHARR regarding the potential for confounding in this

study, particular relating to fracture history. However, as described above, the analysis adjusted for an extensive list of potential confounders, including history of fracture, which ensured that this variable was accounted for in the results.

Procter & Gamble also highlighted that this was the first study examining the effect of concomitant acid suppressants and bisphosphonates vs bisphosphonate use alone on fracture risk. The demonstrated attenuation of anti-fracture efficacy as a result of concomitant PPI use was consistent with the results of the multiple studies reviewed above, that demonstrated an association between the use of acid suppressants and increased fracture risk. This study additionally demonstrated that the excess risk of fracture with PPI use remained, despite concomitant bisphosphonate treatment.

Servier noted that Procter & Gamble referred to the analysis by ScHARR of Yang *et al*, Vestergaard *et al*, Yu *et al* and de Vries *et al*. NICE had taken account of the ScHARR analysis in its assessment of data indicating that acid suppressants increased fracture risk and that co-administration with bisphosphonates might lead to an increased fracture risk compared with bisphosphonates alone. Consequently, in the latest osteoporosis Appraisal Consultation Documents, NICE concluded 'caution should be exercised when considering the co-prescription of acid-suppressive medication and bisphosphonates' (Section 4.3.33 and 4.3.34 of the primary and secondary prevention appraisal consultation documents respectively).

Servier disagreed with Procter & Gamble's submission that de Vries *et al* was inconsistent with the current labelling of Actonel. The special warnings and precautions sections of the SPCs for oral bisphosphonates, including Actonel, stated that bisphosphonates could cause local irritation of the upper GI mucosa such as oesophagitis. This was consistent with evidence from multiple sources demonstrating that the commonly prescribed oral bisphosphonates were associated with upper GI problems such as dyspepsia. This tolerability profile of oral bisphosphonates was also acknowledged in national and regional guidance documents.

In prescription event-monitoring studies conducted by the Drug Safety Research Unit, dyspeptic symptoms were the most commonly reported side effect for oral bisphosphonates, with the incidence in the first month of treatment being four times more common for risedronate (n=13,164) and five times more common for alendronate (n=11,916), than for comparable patients taking non-gastrointestinal medicines. Therefore, based on the special warnings and precautions section of oral bisphosphonate SPCs and the prescription event monitoring data, it was reasonable to expect that patients taking oral bisphosphonates were more likely to require acid suppressants than osteoporotic agents without such a tolerability profile, eg Protelos.

Indeed, several separate data sources demonstrated an increase in acid suppressant prescriptions with bisphosphonate use. Using the Australian GP Research Network, Roughead *et al* (2004) conducted a case-control study and found that 6 weeks after initiation, 2.9% (95% CI 1.8-3.9, n=1,753) of new bisphosphonate users returned to their GP and were prescribed an acid suppressant, usually a PPI, compared to 0.9 per cent of matched control patients (95 %CI 0.5-1.2, n=3,341), representing a 3-fold increase in use (AOR 3.21, 95% CI 2.02-5.11), while controlling for previous NSAID use. These findings were consistent with the upper GI tolerability profile of the oral bisphosphonates outlined in the relevant SPCs.

Further analysis of de Vries *et al* also provided information on the increased use of acid suppressants in patients initiated on bisphosphonates. The use of acid suppressants in women aged 50 years and older who started treatment with bisphosphonates, and who had not received a prescription for a systemic corticosteroid in the 12 months before or 6 months after starting therapy (n = 36,575) was examined. In the 6 months before initiation of bisphosphonates, 15% of patients were prescribed a PPI and 5.9% had received an H_2 antagonist. Analysis of the proportion of women starting acid suppressants after initiating bisphosphonate therapy over time demonstrated an increased use of acid suppressants following initiation with bisphosphonate, such that a greater proportion of patients were prescribed a PPI or H_2 antagonist in the 6 months following bisphosphonate initiation compared to the 6 month prior to bisphosphonate initiation.

Servier also commissioned an analysis using the primary care database, CSD Patient data, to assess whether PPI usage changed in patients following initiation of treatment for osteoporosis. In this analysis, patients were included if they had been initiated on osteoporotic therapy between August 2005-July 2007. The subset of patients who had subsequently received a second consecutive prescription of treatment for osteoporosis were assessed to see whether they had received PPI therapy in the six months prior to the introduction of osteoporotic treatment and then also in the six months post the second prescription. As expected, these data demonstrated a consistent pattern of increased PPI use following commencement of an oral bisphosphonate, but not with Protelos, an osteoporotic therapy that did not contain a special caution regarding local irritation of the upper gastrointestinal mucosa. Furthermore, *post-hoc* analyses of phase III randomised placebo-controlled trials demonstrating the efficacy of Protelos in the treatment of postmenopausal osteoporosis showed no increase in PPI initiation in the Protelos arm compared with placebo. Therefore, these data demonstrated that PPI usage varied with different anti-osteoporotic agents, with increased use being observed for certain classes, such as the oral bisphosphonates, but not for others, such as Protelos.

The pattern of increased use of acid suppressants in patients started on oral bisphosphonates was consistent with the special warnings and precautions relating to the upper GI tolerability of oral bisphosphonates (see SPCs). Various independent studies had demonstrated an association between acid suppressants and increased risk of fracture, and the data from de Vries *et al* showed that this effect was also apparent in patients receiving bisphosphonate therapy. As stated above, the association between acid suppressants and fracture risk was an important consideration in the management of osteoporotic patients and it was therefore appropriate for Servier to refer this data in it materials/activities.

Servier noted that Procter & Gamble also referred to its own *post-hoc* analysis of three phase III placebo-controlled trials of risedronate (5mg daily; n=5,454) to support the statement that the efficacy of risedronate in reducing the risk of new vertebral fractures was not influenced by concomitant use of PPIs or H_2 antagonists. However, this analysis had many limitations (Roux *et al*), which made interpreting the results difficult. This was a *post-hoc* analysis of phase III clinical trials, which were not designed to investigate the interaction between acid suppressants and fracture risk. There was no assessment of the degree of exposure to PPIs or H_2 antagonists. Subjects were classified as PPI or H_2 antagonist users if they used these agents at any point during the trial and therefore could be classed as a user even if they had only taken an acid suppressant once. This was an important point because studies had shown the risk was dependent on dose and duration. There was also no consideration of the temporal relationship between PPI or H_2 antagonist exposure and fracture incidence; it could not be determined from this study whether fractures occurred either before or after exposure to acid suppressants. Finally, as stated in the abstract, the sub-groups were not balanced in terms of confounding factors, and only the number of prevalent vertebral fractures appeared to have been controlled for in the analysis. Together, these issues made it difficult to draw firm conclusions as to the validity of these data.

In conclusion, Servier considered the claim 'Epidemiological data, as e.g. recently presented at the National Osteoporosis Conference, suggest that the anti-fracture efficacy of bisphosphonates is potentially attenuated when co-prescribed with acid suppressant medication' was fair and balanced and not misleading. Consequently, Servier did not agree that this claim was in breach of Clause 7.2 or that it disparaged risedronate or the oral bisphosphonate class, and therefore it did not consider it to be a breach of Clause 8.1. Consequently, Servier did not agree that there was a breach of Clause 2.

PANEL RULING

The Panel noted that the supplementary information to Clause 7.2, emerging clinical or scientific opinion, stated that when a clinical or scientific issue existed which had not been resolved in favour of one generally accepted viewpoint, particular care must be taken to ensure that the issue was treated in a balanced manner in promotional material.

The Panel noted the data submitted in support of the claims that the use of acid suppressants had been associated with an increased risk of fracture. Yang *et al* found a significantly increased risk of hip fracture associated with long-term PPI therapy, particularly high dose PPI. The authors, however, stated that further studies were needed to confirm their findings. Yu *et al* concluded that amongst postmenopausal women, use of acid suppressants *might* (emphasis added) be associated with an increased risk of non-spine fracture. Vestergaard *et al* concluded that PPIs appeared to be associated with an increased fracture risk in contrast to H_2 antagonists which seemed to be associated with a decreased fracture risk. The changes in risk estimates were small in all instances and might have limited consequences; further studies were needed. De Vries *et al* concluded that concomitant use of bisphosphonates and acid suppressants was associated with an increased risk of fracture and that possibly acid suppressants attenuated the protective effects of bisphosphonates on fracture risk. The authors stated that given the frequency of co-prescription of bisphosphonates and acid suppressants, the issue required further investigation.

A critique of the evidence suggesting an association between acid suppressants and increased fracture risk stated that the data was generally poor. In its appraisal consultation document on alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women, NICE noted that data indicating that acid suppressants led to a small increase in fracture risk and that co-administration of acid suppressants and bisphosphonates might lead to an increased fracture risk compared with bisphosphonates alone was observational and tentative and different for different fracture sites and different acid suppressants. NICE considered, however, that because various studies showed a trend, caution should be exercised when the co-prescribing of acid suppressants and bisphosphonates was being considered. The committee was not persuaded, however that a change to its recommendations, based on the evidence, was necessary. The Panel noted that the NICE document was an appraisal consultation document and was marked confidential. The document stated that it did not constitute formal guidance and its recommendations were preliminary and might change after consultation.

The Panel noted that a template letter to prescribing advisors was headed 'Increased risk of fracture associated with use of acid suppressant

medication'. The Panel considered that the quality of the data was such that it could not support such a robust, unqualified claim. Although the reader was told that data *suggested* that the anti-fracture efficacy of bisphosphonates was *potentially* attenuated when co prescribed with acid suppressants (emphasis added) the Panel nonetheless considered that the letter implied that acid suppressants had been unequivocally proven to attenuate the anti-fracture efficacy of biphosphonates. The letter went on to refer to this growing body of evidence and assessment of the implications of the data, in particular the potential effect on health outcomes and healthcare budgets. It appeared that the data had proven clinical implications and this was not so. In that regard the Panel considered the letter was not balanced and did not reflect the data accurately. A breach of Clause 7.2 was ruled. The implication that bisphosphonates were less effective if co-prescribed with acid suppressants was disparaging given the current data. A breach of Clause 8.1 was ruled.

The press release (ref 08MCA0026 April 2008) was headed 'Servier welcomes revised draft NICE guidance'. The third paragraph began 'Servier also welcomes the acknowledgement by NICE in its draft guidance that caution should be exercised when considering the co-prescription of acid suppressants and bisphosphonates'. Readers were also told that NICE had previously failed to address the increased risk of fractures associated with the use of acid suppressants, in particular PPIs, which were commonly co-prescribed with bisphosphonates. The Panel considered that the quality of the data was such that it could not substantiate such robust unqualified claims. The tentative nature of the data acknowledged by NICE, was not referred to in the press release. The Panel considered that the press release was not balanced and did not reflect the data accurately. A breach of Clause 7.2 was ruled. The Panel also considered that the implication that bisphosphonates were less effective if co-prescribed with acid suppressants was disparaging given the current data. A breach of Clause 8.1 was ruled.

The Panel noted that Servier's sponsored symposium at the BGS meeting had included a presentation entitled 'Acid Suppressant Medication and Fractures'. The speaker's briefing notes stated that the objective was to communicate on the use of PPIs in osteoporotic patients and the associated risks. Then to give a primary care perspective on how to manage patient cases not covered by NICE guidance. Points to include in the presentation were, *inter alia*: acid suppressants and increased risk of fracture; attenuation of bisphosphonate efficacy when acid suppressants were co-prescribed; how to identify patients at risk of PPIs if prescribed an oral bisphosphonate and the conclusion was to consider prescribing an appropriate agent for these patients – eg strontium ranelate [Servier's product Protelos]. The speaker was further advised that the tone of the presentation should cause delegates to think about their current medical practice and then provide them with a simple solution to the problem.

The final slide of the presentation was headed 'Summary: overview of evidence' and detailed the findings of Yang *et al* and Vestergaard *et al*. In the Panel's view the results of the two studies were presented on the slide as if the findings had been unequivocal; the authors' comments as noted above had not been included. There was no transcript of the presentation although the speaker had provided an overview of what he had said. With regard to the last slide the speaker stated that he had said that there might be a reduction in the effect of a bisphosphonate with PPI usage; this needed further study. The Panel considered, however, that the tentative nature of the data was not reflected in the slides and in its view delegates would be left with the impression that acid suppressants, particularly PPIs, had been unequivocally proven to attenuate the anti-fracture efficacy of bisphosphonates with proven clinical implications. In that regard the Panel considered that the slides were not balanced and did not reflect the data accurately. A breach of Clause 7.2 was ruled. The implication that bisphosphonates were less effective if co-prescribed with acid suppressants was disparaging given the current data. A breach of Clause 8.1 was ruled.

The Panel noted its rulings above but nonetheless did not consider that there had been a breach of Clause 2 of the Code which was reserved for use as a sign of particular censure. This ruling was not appealed.

APPEAL BY SERVIER

Servier appealed all of the Panel's rulings of breaches of Clauses 7.2 (for misleading claims relating to issues of emerging clinical or scientific opinion) and Clause 8.1 (for disparaging references to the medicines of other pharmaceutical companies).

Servier submitted that it was not the Panel's role to evaluate any scientific data. However, Servier appreciated that for the purposes of the complaint the Panel had to consider whether issues of emerging clinical or scientific opinion had been treated in a balanced manner in the promotional material. Further, the Panel had to consider whether references to competitors' products in the promotional material were disparaging. In order to decide whether the issues had been treated in an appropriately balanced way, the Panel had to assess whether Servier's claims were justifiable on the basis of the data on which they were based. Accordingly, the Panel's consideration of the data informed its rulings in relation to the letter, the press release and the symposium.

It was apparent from the ruling that the Panel's view was that the data did not adequately support Servier's claims that the use of acid suppressants had been associated with an increased risk of

fracture. Servier disagreed with this conclusion.

The Panel placed significant weight on the fact that the authors of the published studies submitted by Servier indicated that further investigation of the association between the use of acid suppressants and the increased risk of fractures was necessary. However, Servier noted that Yang *et al* and Vestergaard *et al* were published in the same year, and so they would likely have been unaware of each other's research when writing their respective papers. The Panel also noted that 'A critique of the evidence suggesting an association between acid suppressants and increased fracture risk stated that the data was **generally poor.'** (emphasis added). However, this critique was contradictory to the substance of each individual study.

Servier submitted that Yang *et al* found that the PPI therapy was associated with a significantly increased risk of hip fractures, with the highest risk seen among patients receiving long-term high-dose PPI therapy (adjusted odds ratio 2.65, 95% CI 1.80-3.90). In addition, Yang *et al* also found that long-term H_2 agonist therapy was associated with a significantly increased risk of hip fracture (AOR 1.23, 95% CI 1.14-1.39), compared to acid suppression non-users.

Servier submitted that de Vries *et al* found that concomitant use of bisphosphonates and PPIs was associated with a statistically significant increased risk of any fracture (Adjusted Relative Rate (ARR) 1.08; 95% CI 1.01-1.15) and hip fracture (ARR 1.21; 95% CI 1.05-1.38), but not vertebral fracture (ARR 1.11; 95% CI 0.94-1.31), compared to bisphosphonate use alone. Furthermore, the increased risk of any and hip fracture showed a dose-dependent trend. The results suggested that PPIs might attenuate the anti-fracture efficacy of bisphosphonates on fracture risk.

Servier submitted that Vestergaard *et al* found that recent use of PPI was associated with an increased risk of hip fracture (AOR 1.45, 95% CI 1.28-1.65), whilst distant use was not (AOR 1.08, 95% CI 0.94-1.23). In contrast, H_2 agonist use was not associated with an increase hip fracture risk.

Servier submitted that whilst the findings relating to H_2 agonists had been contradictory, the dose and duration dependent effects of PPI use and increased fracture risk, seen across these three studies, was indicative of an underlying biological mechanism. This had been also noted by Wright *et al* (2008) who commented on Yang *et al* and Vestergaard *et al* that: 'Despite the conflicting conclusion about the risk of fracture with H2RA use, these two very large, long-term, case controlled studies **both report a strong association of PPI use with fracture.'** (emphasis added)

Servier further noted that in its publication IMPACT, which provided information to prescribers, the Scottish NHS-Grampian Medicines Information Centres stated in January 2007 that **'Long-term use of proton-pump inhibitors (PPI) is associated with an increased risk of hip fracture, according to a large epidemiological study using UK data (JAMA 2006).** Risk was further increased with high-dose PPI use, and with longer duration of treatment. Based on their analysis, the authors conclude that long-term use of PPI may be associated with an increased risk of hip fracture, particularly when high doses are used. They note that there may be confounding factors that they could not adjust for, but suggest that doctors should ensure that the lowest effective dose is used if long term PPI use is required' (emphasis added).

Servier submitted that this publication on behalf of the Scottish NHS indicated that the provided piece of evidence was considered of sufficient clinical significance that doctors should be made aware of the risk that long-term PPI use might be associated with an increased risk of hip fracture. It should be noted that no evidence was provided by Procter & Gamble to justify a conclusion that there was no association between the use of PPIs and the increased risk of hip fractures.

Servier therefore submitted that the Panel failed to make a proper assessment of the scientific data. Whilst the authors of the publications submitted by Servier indicated that further studies were necessary in support of the identified association between the use of acid suppressants and the increased risk of fractures, this circumstance should not be used in itself as a justification for dismissing the data. On balance, the studies performed by a variety of research groups utilising different study designs and populations overwhelmingly supported the claim that the use of acid suppressants was associated with an increased risk of fracture. Servier considered the Panel's rulings were made on the basis of a misconceived interpretation of the scientific issues.

Servier disagreed with the comments made by the Panel in relation to the letter to prescribing advisers. The Panel stated that the letter implied that acid suppressants had been unequivocally proven to attenuate the anti-fracture efficacy of bisphosphonates. Servier did not accept that this statement was made or even implied in the letter. As regards the title of the letter, 'Increased risk of fractures associated with the use of acid suppressant medication', the Panel stated that the data could not support 'such a robust, unqualified claim'. However, the claim was not unqualified. The word 'associated' suggested that there was some link between the increased risk of fractures and the use of acid suppressant medication without implying a definite causal relationship between the two. Further, the first sentence stated 'Epidemiological data recently published at the 2007 National Osteoporosis Society Conference, **suggest** that the anti-fracture efficacy of bisphosphonates is **potentially** attenuated when co-prescribed with acid suppressant medication' (emphasis added).

Servier submitted that the choice of the wording (ie

'suggest' and 'potentially') could not lead the prescribing advisers to conclude that this statement was based on unequivocal evidence.

Additionally, Servier opposed the Panel's statement that the content of the data as mentioned in the third paragraph could be interpreted to mean that they had proven clinical implications. The reference to the 'growing body of evidence' was linked to the second paragraph of the letter which contained appropriate statements referenced to the relevant sections of the published data. In addition, all sentences had been appropriately referenced so the reader would be able to check the source of the information. As explained above in relation to the Panel's assessment of the scientific data, all studies concluded that there was an association between the use of PPIs and increased risk of fracture. Rather than suggesting that the data had proven clinical implications, the letter explained that an investigation of the implications of the data was still to come: '**I will be analysing** the implications of the data...' (emphasis added).

Servier submitted that, in an attempt to protect public health, it had sent the letter to prescribing advisers to alert them of the possible risk in prescribing PPIs for long-term use. This was in accordance with Yang *et al* which concluded that: 'At this point, **physicians should be aware of this potential association when considering PPI therapy and should use the lowest effective dose for patients with appropriate indications.** For elderly patients who require long-term and particularly high-dose PPI therapy, it may be prudent to reemphasize increased calcium intake, preferably from a dairy source, and coingestion of a meal' (emphasis added).

Therefore, Servier submitted that all statements in the letter had treated the existing scientific data in a balanced manner. For this reason, the letter was not misleading in relation to issues of emerging clinical/scientific opinion and therefore it was not in breach of Clause 7.2.

Additionally, Servier submitted its discussion of bisphosphonates (ie risedronate and alendronate) was accurate, balanced, fair and capable of substantiation. The information provided relied on the published literature. In addition, Servier also provided the relevant references so the advisers would be able to confirm the validity of the information. Therefore, the references in the letter to bisphosphonates were not disparaging and Servier therefore disagreed with the Panel's ruling of a breach of Clause 8.1.

Servier submitted that it had issued the press release 'Servier welcomes revised NICE guidance on postmenopausal osteoporosis but urges NICE to go further' on 4 April to the medical press; it was also on the Servier UK corporate website in the health professionals' section under articles. Servier also issued a bulletin with the same code number and content. The only differences identified were the title and the conclusion. These outlined Servier's position regarding the latest NICE draft guidance on the management of osteoporosis. The Panel's comments were based on the bulletin.

Servier submitted that the Panel misconstrued the information derived from the appraisal consultation documents as published in March 2008. The Panel in its general comments about the scientific data noted that that these documents were marked as confidential and did not constitute the NICE's formal guidance since the considerations were preliminary and might change after the consultation. However this did not reflect the precise role of the appraisal consultation documents. In particular, the documents were communicated to Servier in confidence in March 2008 and were published on 4 April on NICE's website. The press release had been published on 4 and 8 April 2008. Therefore, the assumption of the Panel that this document was confidential was incorrect.

Furthermore, Servier submitted that the appraisal consultation documents reflected the latest position of the NICE at that time in relation to primary and secondary prevention of post-menopausal osteoporosis. Servier's press release underlined NICE's findings. In particular, it was mentioned that: 'Servier also welcomes the acknowledgement by NICE in its draft guidance that caution should be exercised when considering the co-prescription of acid-suppressive medication and bishphosphonates'. This statement was a quotation from the latest appraisal consultation documents at that time (Section 4.3.33 and 4.3.34 of the primary and secondary prevention documents respectively).

Additionally, the press release also indicated that NICE had previously failed to address the increased risk of fractures associated with the use of acid suppressants, in particular PPIs, which were commonly prescribed with bisphosphonates. This was again a statement of fact since the original version of the final appraisal determinations did not raise that issue.

However, Servier submitted that it had explicitly mentioned in the press release that its comments were derived from the draft guidance and there was no implication that this was the final position of NICE in relation to the co-prescription of bisphosphonates with acid suppressants. After all, Servier had a direct interest to inform the medical community on any progress in the field, it had already appealed the original version of the final appraisal determinations and had also lodged judicial review proceedings on the same issue.

Servier submitted that its press release relied solely on NICE's latest considerations. Therefore, Servier made statements based on the facts and not on assumptions. For this reason Servier was not in breach of Clause 7.2 as it treated the evidence relating to issues of emerging clinical/scientific opinion in a fair and balanced manner in accordance with Clause 7.2.

Further, for the reasons explained above, Servier denied a breach of Clause 8.1 of the Code because references to the oral bisphosphonates were accurate, balanced, fair and capable of substantiation in accordance with Clause 8.1.

The BGS presentation in Glasgow on 24 April 2008 was attended by health professionals with an interest in elderly care medicine. The abstract book was distributed to the attendees on the day of the symposium but they were not given copies of the presentation at issue. Servier submitted that slides generally only formed the basis of a presentation but they were not self-sufficient and not intended to stand alone. The speaker's comments provided important additional information and emphasis. There were no official transcripts from the symposium. However, the speaker had provided a summary of his speech and confirmed that in his last slide he raised the point that there was significant evidence linking the use of PPIs to the increase of fracture risk, especially at the hip. To support this statement the speaker referred to de Vries *et al* which in addition showed the increased risk of hip fracture in patients taking both PPIs and bisphosphonates. However, the speaker explained that there might be an attenuation of the anti-fracture efficacy of the bisphosphonates with PPI use, but that this required further study. Therefore the data had been presented in an appropriately balanced way.

Servier noted that it had not received any comment on behalf of the attendees that they left with the impression that acid suppressants, particularly PPIs, had been unequivocally proven to attenuate the anti-fracture efficacy of bisphosphonates. Therefore, judging that the presentation in its entirety (slides and speaker's comments) covered any potential 'grey' area in relation to the studies, Servier had presented the issues of emerging clinical/scientific opinion in a balanced manner. For this reason, Servier denied a breach of Clause 7.2.

Further, Servier did not breach Clause 8.1 of the Code because references to the oral bisphosphonates were accurate, balanced, fair and capable of substantiation and thus not disparaging.

In conclusion Servier vigorously refuted the Panel's rulings that the letter, press release and the symposium were in breach of Clause 7.2. Further, Servier did not agree that such messages disparaged the oral bisphosphonates and thus denied breaches of Clause 8.1.

COMMENTS FROM PROCTER & GAMBLE

Procter & Gamble alleged that Servier continued to confuse the issue of clinical interpretation and scientific validity with the issue of treating emerging clinical or scientific data in a balanced manner. This debate was based on limited and contradictory data, hence claims should reflect this and must be balanced, not misleading and not disparaging.

Servier justified the dissemination of these messages in an attempt to protect public health. The Medicines and Healthcare products Regulatory Agency (MHRA), however, was responsible for protecting public health in the UK; it was not for pharmaceutical companies to take unilateral action on decisions as to what constituted a public health matter, or to pre-empt the decisions of health authorities.

Procter & Gamble fully supported the Panel's ruling which it considered was appropriate and illustrated the extent to which this was still an emerging debate.

Procter & Gamble had not asked the Panel to rule on the scientific validity of the data or the clinical interpretation. The Panel was asked to rule whether the data used by Servier were presented in a balanced, non-misleading and non-disparaging way. The Panel ruled Servier in breach of Clauses 7.2 and 8.1.

Procter & Gamble submitted that the fact remained that limited and contradictory data were available (two papers, one abstract, Yang *et al*, Vestergaard *et al* and Yu *et al*) to support the claims and inferences made by Servier that acid suppressants, including PPIs had been associated with an increased risk of fracture and anti-fracture efficacy of bisphosphonates was potentially attenuated when co-prescribed with acid suppressants (one abstract de Vries *et al*). The authors rightly called for further investigation to confirm findings and understand potential mechanisms. In no way did these data overwhelmingly support Servier's claims.

Procter & Gamble appreciated that new data emerged that might or might not change scientific thinking. This was, however, the reason why supplementary information to Clause 7.2, emerging clinical or scientific opinion, stated that where a clinical or scientific issue existed which had not been resolved in favour of one generally accepted viewpoint, particular care must be taken to ensure that the issue was treated in a balanced manner in promotional material. This was not the case with the claims made by Servier, the data as it currently stood did not support robust unqualified claims as ruled by the Panel. This was particularly important in this case since Servier was potentially misleading and disparaging regarding the safety of PPIs, H_2 agonists and bisphosphonates.

Procter & Gamble noted Servier's comment that it had provided no evidence that PPIs did not increase the risk of fracture. This was irrelevant. Procter & Gamble had simply asked that the data that did exist be treated cautiously, consistent with the supplementary information to Clause 7.2 and existing SPCs. Procter & Gamble's overall concern remained that this debate was based on limited and contradictory data, hence claims must be balanced, not misleading and not disparaging.

Procter & Gamble considered that the Panel

correctly interpreted Servier's intent with the prescribing advisor's letter to imply an unequivocal link between acid suppressants and attenuated anti-fracture efficacy of bisphosphonates. In fact, in its appeal Servier again presented data by Yang *et al*, de Vries *et al* and Vestergaard *et al* that Servier concluded overwhelmingly supported its claims. Yet, Servier appeared to consider that adding the words 'suggest' and 'potentially' were necessary in the letter to prescribing advisors and disagreed with the Panel that the letter implied an unequivocal link. Servier could not argue this both ways.

Furthermore, Procter & Gamble alleged that for Servier to state that it would analyse the implications of the data, was intended to acknowledge a tentative link to clinical consequences was also contradictory. The text in the letter was 'potential effect on health outcomes and healthcare budgets'. If Servier acknowledged that the clinical implications were not so concrete, why would one assess budgetary impact?

Servier's response to the Panel illustrated the second major concern of Procter & Gamble. As justification for the dissemination of its messages, Servier stated that, in an attempt to protect public health, it had sent this letter to prescribing advisors to alert them of the possible risk in prescribing PPIs for long-term use. Procter & Gamble considered this justification illustrated a lack of appreciation for the UK regulatory infrastructure and the roles and responsibilities of health authorities, in particular the MHRA.

Procter & Gamble reiterated that the MHRA was responsible for protecting public health. The MHRA executed this responsibility via a number of well established mechanisms such as robust license procedures, structure and content of a product's SPC, the establishment of Pharmacovigilance Advisory Groups to assess data on behalf of the agency and direct communication to health professionals on safety matters.

Procter & Gamble stated that all of its safety data were regularly reviewed by health authorities as part of the licence renewal and, to date, the potential signal of attenuation of risedronate efficacy by acid suppressants has not been raised by any European agency, including the MHRA. The current SPCs for risedronate did not caution against co-prescription of acid suppressants in Section 4.4, nor was such a potential interaction listed in Section 4.5. The MHRA Pharmacovigilance Expert Advisory group (MHRA PEA) met on 12 September 2007 to discuss PPIs and risk of fracture. The conclusion stated: 'on the basis of current evidence and the limitations of these recent studies regulatory action was not warranted at this time'. On 23 July 2008 that statement continued to reflect the current position of the MHRA on the issue of PPIs and risk of bone fracture.

Procter & Gamble stated the MHRA Pharmacovigilance Expert Advisory group regularly reviewed all potential signals on behalf the MHRA, formed part of the UK Commission on Human Medicines and advised the European Committee for Medicinal Products for Human use. The published objectives of this body were to advise the Commission of the public health importance of potential new signals, the confirmation and quantification of risks identified and the appropriate risk minimisation measures including communication. No direct communication to health professionals had been sanctioned by MHRA, for example via 'Dear Doctor' letters, and no direct communication to health professionals had been endorsed by the MHRA Pharmacovigilance Expert Advisory Group.

It was not for pharmaceutical companies to take unilateral action on decisions as to what constituted a public health matter, or to pre-empt the decisions of health authorities; pharmaceutical companies had a duty to support UK regulatory systems not undermine them. Procter & Gamble considered that Servier's justification of its actions as an attempt to protect public health demonstrated a concerning lack of understanding of, and support for, these systems.

Procter and Gamble mentioned Servier's communications with NICE to illustrate that the misleading messages were part of a concerted broad strategy that was not limited to promotional activities. As shown by the Panel's ruling, the messages were misleading and disparaging and thus, the communications by Servier that affected the appraisal consultation documents were an attempt to inappropriately influence subsequent guidance for its own commercial ends. Sections 4.3.37 (primary prevention of osteoporosis) and 4.3.38 (secondary prevention of osteoporosis) of the latest final appraisal determinations by NICE (published online on 8 of July 2008), now stated: 'The Committee was made aware of data indicating that acid-suppressive medication leads to a small increase in fracture risk and that co-administration of acid-suppressive medication and bisphosphonates may lead to an increased fracture risk compared with bisphosphonate administration alone. **The Committee was not persuaded by this evidence**; [emphasis added] it noted that the data are observational and have not been reported in full, and are different for different fracture sites and for different acid suppressors. Furthermore, the Committee was informed, during consultation, of analyses showing that acid-suppressive medication given in addition to risedronate did not increase fracture risk. However, the Committee concluded that **caution should be exercised when considering the evidence about co-prescription of acid-suppressive medication and bisphosphonates.'** (emphasis added).

Procter & Gamble alleged that the above text supported the Panel's initial ruling of breaches of Clauses 7.2 and 8.1 of the Code. Servier, however, appeared to not only disagree with the Panel but also with NICE, as it had appealed the original

version of the final appraisal determinations and had lodged judicial review proceedings on the same issue.

Procter and Gamble noted that Servier stated that slides presented at Servier's symposium held in Glasgow on 24 April 2008, were not self-sufficient and not intended to stand alone. Whilst Procter & Gamble agreed that some clarification could be given verbally, the slides should be sufficiently stand-alone as not to create a misleading impression when presented to the audience. To present bold statements on acid suppressants and fracture risk on slides to be (or not) clarified verbally as requiring further study was not acceptable. Whilst Procter & Gamble disagreed in this instance with the speaker's opinion, it had not challenged his right to share his own perspective. Procter & Gamble expected, however, that Servier briefed its speakers to present in a fair, balanced and non misleading way and ensured that each material presented in promotional activities complied with the Code.

Procter & Gamble therefore considered that the Panel was correct to rule breaches of Clauses 7.2 and 8.1.

APPEAL BOARD RULING

The Appeal Board noted the data upon which the claims implying that the anti-fracture efficacy of bisphosphonates was attenuated when co-prescribed with acid suppressants were based. In particular the Appeal Board noted the conclusions of Vestergaard *et al* ie that 'The changes in risk estimates were small in all instances and may have limited clinical consequences. However, further studies in the field are needed'. In the Appeal Board's view the data provided were not robust enough to support claims such as 'Increased risk of fracture associated with the use of acid suppressant medication' which appeared as the heading on the letter to prescribing advisors and the reference to '… the increased risk of fractures associated with the use of acid suppressive medication …' which appeared in the press release. The Appeal Board further noted the submission by Procter & Gamble at the appeal hearing that the original efficacy trials on bisphosphonates had not excluded patients also taking PPIs and the like. Thus it was very likely that the reported efficacy of bisphosphonates already took some account of patients co-prescribed acid suppressants.

The Appeal Board considered that the letter to prescribing advisors and the press release had exaggerated the clinical importance of the data regarding the consequences of co-prescribing bisphosphonates and acid suppressants. The documents were not balanced and did not accurately reflect the data. The Appeal Board upheld the Panel's rulings of breaches of Clause 7.2. The Appeal Board also considered that the implication that bisphosphonates were less effective if co-prescribed with acid suppressants was disparaging given the existing data. The Appeal Board upheld the Panel's rulings of breaches of Clause 8.1. The appeal on these points was unsuccessful.

The Appeal Board noted Servier's submission that the slides used at the BGS presentation were not intended to stand alone. The company had emphasised that attendees had not been given copies of the presentation. In the Appeal Board's view, however, a company could not rely on a speaker to qualify or explain otherwise misleading slides and in that regard it was irrelevant as to whether they were given to the attendees.

Servier's sponsored symposium at the BGS was entitled 'Trips, slips and fractured hips'. The title of the speaker's presentation in question was given as 'Global risk management' although the title slide of his presentation read 'Acid Suppressant Medication and Fractures'. The company had specifically briefed the speaker to talk about the potential attenuation of bisphosphonate anti-fracture efficacy when acid suppressants were co-prescribed. The Appeal Board was extremely concerned about the speaker's briefing notes. Although the notes correctly cited the title of the talk ('Global risk management') the objective was much narrower and was to talk about the use of PPIs in osteoporotic patients and the associated risks. Then to give a primary care perspective on how to manage patient cases not covered by NICE guidance. Points Servier briefed the speaker to include in the presentation were, *inter alia*: acid suppressants and increased risk of fracture and attenuation of bisphosphonate efficacy when acid suppressants were co-prescribed. These points echoed Servier's views as expressed in the letter and press release discussed above. The tentative nature of the data was not reflected in the briefing notes. The speaker was further asked to discuss identification of patients at risk of PPIs if prescribed an oral bisphosphonate and the conclusion was to consider prescribing an appropriate agent for these patients – eg strontium ranelate [Servier's product Protelos]. The speaker was further advised that the tone of the presentation should cause delegates to think about their current medical practice and then provide them with a simple solution to the problem. In the Appeal Board's view the briefing notes essentially instructed the speaker to raise concerns amongst the delegates about the co-prescription of bisphosphonates and acid suppressants and to get them to consider prescribing Protelos instead of bisphosphonates in at risk patients. In the Appeal Board's view, to include such a direct and promotional call to action in a brief to an independent speaker was wholly unacceptable and gave a very poor reflection of the company's procedures.

The Appeal Board considered that the presentation at the BGS had exaggerated the clinical importance of the data regarding bisphosphonates and acid suppressants. The presentation was not an accurate

or balanced reflection of the data in that regard. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2. The Appeal Board also considered that the implication that bisphosphonates were less effective if co-prescribed with acid suppressants was disparaging given the existing data. The Appeal Board upheld the Panel's ruling of a breach of Clause 8.1. The appeal on these points was unsuccessful.

Complaint received **9 May 2008**

Case completed **23 September 2008**