CASE AUTH/2191/12/08

NOVARTIS v ROCHE

Bondronat detail aid

Novartis complained about a Bondronat (ibandronic acid) hospital detail aid produced by Roche. Novartis marketed Zometa (zoledronic acid). Both Zometa and Bondronat were bisphosphonates which could be used to prevent skeletal events in patients with breast cancer and bone metastases.

The detailed response from Roche is given below.

Novatis alleged that the claim 'Innovative, multi-targeted bone protection' which appeared as an integral part of the product logo was misleading and incapable of substantiation. Health professionals would believe that Bondronat had a mechanism of action or benefit not previously seen with regard to bone protection.

In the Panel's view most readers would assume that innovative was a description of the multi-targeted bone protection and that somehow Bondronat was a different approach to therapy which was not so. The Panel considered the claim ambiguous, misleading and incapable of substantiation as alleged. Breaches of the Code were ruled.

The claim appeared on the front page and on many other pages of the detail aid and would be read in light of the data on the relevant page. The Panel considered that on the front cover, which featured the phrase 'Time for a change?' the claim would be seen as comparative ie it would encourage doctors to change from their current therapy choice to one which offered innovative, multi-targeted bone protection. The Panel considered that such a comparison was misleading. A breach of the Code was ruled.

Page 8 of the detail aid, headed 'Time to compare tolerability', compared oral Bondronat with iv zoledronic acid. Beneath the claim 'Oral Bondronat has a better tolerability profile than zoledronic acid' a bar chart, adapted from Body *et al* (2005), compared the percentage of patients with adverse events throughout the study (Bondronat 65%, zoledronic acid 76%) and with pyrexia and flu-like symptoms during the first 3 days (Bondronat 1%, zoledronic acid 27%). No p values were given.

Novartis stated that a reasonable comparison could not be made between iv and oral formulations given over different time lines without any statistical statement. This point in itself was misleading. In addition it was not stated that zoledronic acid had been administered intravenously; it was not immediately clear from the graph that an oral preparation was being compared with an iv preparation.

The detail aid promoted iv Brondronat and oral Bondronat; such a comparison was alleged to be unbalanced in the absence of data on the iv formulation of Bondronat. Since this adverse drug reaction (ADR) was also seen with iv Bondronat a similar statement could quite fairly be made for iv Bondronat. Novartis therefore contended that to suggest this statement was a product specific ADR was disingenuous and clearly disparaged zoledronic acid.

Novartis alleged that use of Body *et al* (2005) demonstrated cherry picking data, not allowing fair and balanced review of the data which was also borne out by Roche's view that the juggling skeleton on the front page of the detail aid suggested that patients might be able to change between the two formulations of Bondronat, where clinically relevant. But this data did not allow for the choice between the two Roche formulations.

In Novartis' view, a lack of comparative data for iv Bondronat [to oral ibandronate or comparing iv Bondronat to iv zoledronic acid] should preclude the use of this study in the detail aid.

The Panel noted Roche's submission that oral Bondronat and iv zoledronic acid were the two most frequently prescribed bisphosphonates in UK hospitals for the treatment of bone disease in metastatic breast cancer. The detail aid was for use in hospitals. Both companies agreed that most clinicians knew that zoledronic acid was given iv. Two bullet points beneath the bar chart clearly stated the infusion rate of zoledronic acid and thus made its iv presentation clear although these were much less prominent than the preceding bar chart and heading which made no mention of zoledronic acid's presentation. Nonetheless on balance the Panel did not consider the page misleading or disparaging because it failed to make the iv presentation of zoledronic acid sufficiently clear as alleged. Given the intended audience, readers would know that zoledronic acid was administered intravenously. No breaches of the Code were ruled. The Panel did not consider that the page suggested that adverse reactions were product specific or that in that regard zoledronic acid had been disparaged. Nor did the Panel consider it misleading to fail to mention comparable data for iv Bondronat as alleged. Further, the Panel did not consider that the use of Body *et al* (2005) represented unfair cherry picking as alleged. No breach of the Code was ruled.

The claim 'No evidence for any treatment-related deterioration in renal function was seen for any patient – as assessed by change from baseline in

[serum creatinine], calculated [creatinine clearance rate] or in the urinary excretion of markers of glomerular and tubular function' outlined the results and conclusions of von Moos *et al* (2006), a comparison of the renal safety of iv Bondronat 6mg infused over 15 (n=101) or 60 minutes (n=26). A graph on page 10 showed changes in calculated creatine clearance rate over time for both treatment groups. 'Time not to exclude patients due to renal dysfunction' was the heading on page 11 which set out the dosage and administration of iv Bondronat including that for patients with moderate or severe renal impairment.

Novartis explained that it raised both points (the claim and the heading cited above) simultaneously because individually and together they gave an unbalanced and misleading view of Bondronat's safety profile in terms of renal toxicity, and therefore did not support rational prescribing. Breaches of the Code were alleged.

The Panel noted that Novartis had not provided any reasons to support its allegation that the two claims at issue were in breach of the Code.

The Panel noted that pages 9 and 10 of the detail aid were tagged 'Safety' and together gave details of a study by von Moos *et al* which evaluated the renal safety of Bondronat 6mg infused over 15 or 60 minutes every 3-4 weeks for 6 months. The study concluded that a 15 minute infusion was well tolerated with a safety profile consistent with that of the 60 minute infusion. The study authors noted, however, that in the 15 minute group 3% of patients (n=3) had an increase in serum creatine levels over the limit established by the primary endpoint. In one of these patients Bondronat was listed as one of three possible causes and serum creatinine returned to normal levels after the study end. The Panel noted that section 4.8, Undesirable Effects of the iv Bondronat summary of product characteristics (SPC) detailed the adverse reactions from a phase III study with Bondronat 6mg (n=152); an increase in creatinine occurred more often in Bondronat patients (2%) than in placebo treated patients (0.6%). Renal and urinary disorders were listed as uncommon. The oral Bondronat SPC listed renal and urinary disorders as uncommon.

The Panel noted that on page 10 two bullet points referred to the 3 patients in the 15 minute group who had a serum creatinine increase over the primary endpoint limit. These details preceded and were of equal prominence to the bullet point detailing the study conclusions including the claim at issue 'No evidence for any treatment-related deterioration in renal function was seen for any patient – as assessed by change from baseline in [serum creatinine], calculated [creatinine clearance] or in the urinary excretion of markers of glomerular and tubular function'. The Panel considered that the claim was misleading; the authors had cited Bondronat as a possible cause for increased serum creatinine in one patient. A breach of the Code was ruled. The Panel did not consider that the claim failed to encourage rational prescribing. No breach of the Code was ruled.

The claim 'Time not to exclude patients due to renal dysfunction' headed page 11 of the detail aid which was tagged 'IV Dosing'. The Panel noted that the page reproduced the iv Bondronat dosing regimen for patients with varying degrees of renal function and showed that even patients with severe renal impairment could be treated with Bondronat albeit at a reduced dose with an infusion time of 1 hour. Thus impaired renal function was not a contraindication to Bondronat. The Panel thus did not consider the claim was either misleading or that it did not encourage rational prescribing. No breach of the Code was ruled.

Page 13 headed 'Time to review bisphosphonates in hospital' discussed a clinical audit (Barrett-Lee *et al* 2006) which captured data on the whole patient experience of receiving iv bisphosphonate therapy. A diagram depicted the total mean patient time spent on a hospital unit for iv pamidronate as 2 hours 36 minutes and iv zoledronic acid 1 hour 38 minutes. A pie chart overleaf on page 14 showed the reasons for attending hospital for breast cancer patients receiving iv bisphosphonates; 77% of them attended a hospital unit for that therapy alone whereas 23% at the same time also received chemotherapy and/or a clinic appointment.

Novartis stated that there was no explanation of how these findings related to either Bondronat formulation. In the absence of data for either formulation this lack of comparison alone was misleading and disparaging as it seemed only to question whether patients should be switched from pamidronate or zoledronic acid as highlighted by the use of the phrase 'Time to review bisphosphonates in hospitals'.

Furthermore, the conclusions on page 14 did not reflect the aim of the study to 'provide insight into the intravenous administration of bisphosphonates and how this impacts on hospital resources and patient experiences'. Novartis alleged that the conclusions 'IV bisphosphonate administration involved time, cost and inconvenience for patients' and 'IV bisphosphonate administration involved substantial resource use for clinics and staff' were all-embracing as there was no data for iv Bondronat.

Novartis stated that iv Bondronat would sit somewhere between iv zoledronic acid and iv pamidronate in terms of overall time, cost and inconvenience for patients, and that for hospitals these would therefore be equally applicable arguments for substantial resource use for iv Bondronat for clinics and staff. Therefore by explicitly highlighting these requirements only for competitor products Roche had unfairly disparaged zoledronic acid and pamidronate.

The Panel noted that the audit was designed to quantify the current time involved in the

administration of iv bisphosphonates and how this might impact on patient experience and cancer unit capacity. The Panel considered that the objective of the audit was clear. The audit was not designed to detect differences between specific bisphosphonates; however page 13 stated that the audit findings were that on average iv pamidronate patients spent 2 hours 36 minutes on a hospital unit and iv zoledronic acid patients spent 1 hour 38 minutes. The Panel considered that in the detail aid in question, and in the absence of a statement to the contrary, these times would be taken as an implied comparison with Bondronat. Barrett-Lee *et al*, however, had noted these times only in order to show that the preparation of bisphosphonates infusion was not the main driver for the time that patients spent on a unit and once the infusion was started they were, on average, completed in a similar time to the manufacturers' recommendations of 90 minutes for pamidronate and 15 minutes for zoledronic acid. This was not made clear in the detail aid. The Panel considered that some readers might assume that the infusion time for zoledronic acid was 1 hour 38 minutes which was not so. Similarly the recommended infusion time for pamidronate was 90 minutes and not the 2 hours and 36 minutes referred to in the detail aid. The Panel noted Barrett-Lee's view that it appeared use of an iv bisphosphonate with a shorter infusion time might not release as much capacity for a day care unit as might be expected. The Panel noted the emphasis throughout the detail aid of a 15 minute infusion time for Bondronat. It considered that without any information as to how long patients might spend on a unit in addition to the time receiving Bondronat iv and/or to not give the recommended infusion times for zoledronic acid and pamidronate created a misleading impression and exaggerated the differences between the products which could not be substantiated and was disparaging. Breaches of the Code were ruled.

The Panel noted that page 14 only referred to the iv administration of bisphosphonates and the time, cost and inconvenience for patients and the staff and clinic resources needed. In that regard the Panel did not consider that the lack of data for Bondronat meant that the claims were all embracing as alleged. No breach of the Code was ruled.

'Time to consider resources' headed page 15 which detailed the UK interim analysis of a pharmacoeconomic study (Wardley *et al* 2004). A bar chart compared the average resource time burden per patient of several aspects involved in the administration of iv zoledronic acid and oral Bondronat; preparation of the infusion, infusion duration, and time spent by the clinician, nurse, laboratory technician and pharmacist. Oral Bondronat was described as a cost-effective choice compared with zoledronic acid. 'Time to save resources' headed page 16 which compared the additional clinician and nurse time required with zoledronic acid iv administration vs oral Bondronat over 12 months.

Novartis alleged that there was no substantiation that this pharmacoeconomic study (n=9) reflected the average resource and time burden; no reasonable conclusions could realistically be drawn from the very small population. Its use in promotional material was an unfair, scientifically invalid comparison and misleading. Novartis alleged that these findings were all-embracing and would be equally applicable to iv Bondronat which was not represented.

The Panel noted that Wardley *et al* was an interim analysis of the UK data from an open label sub-study of a clinical trial which assessed medical care utilization of iv zoledronic acid (4mg infusion every four weeks (n=5)) and oral Bondronat (50mg daily (n=4)).

The Panel did not consider that data from such a small interim analysis, for which no statistical analysis was reported, was sufficiently robust to support the claims made from it. The Panel was particularly concerned about the claim 'Bondronat – a cost effective choice'. The Panel queried the validity of extrapolating clinician and nursing minutes saved per patient per infusion from a data set of 5 to the saving of 16 hours/patient/year to 200 days per 100 patients per year. The Panel considered the material on pages 15 and 16 were misleading as alleged. Breaches of the Code were ruled.

Page 17 headed 'Time for flexibility and consistency of care' summarised the data in the detail aid in a series of bullet points. Novartis stated that Roche was unable to give specific assurances on points highlighted above which included unfair comparisons between the products.

The Panel noted Novartis alleged that unfair comparisons between the products were covered by the rulings above. No specific clauses of the Code had been cited in relation to this page but Novartis had referred to matters highlighted above. The Panel noted that one comparative claim was featured 'Time for a cost-effective approach to resources. 16 hours time saved per patient per year with oral Bondronat vs zoledronic acid'. The Panel considered that this claim was covered by its ruling above. Breaches of the Code were ruled.

Finally, Novartis alleged that Roche's use of the American Society of Clinical Oncology (ASCO) guidelines to support the claims 'Time to initiate …' and 'Time to maintain …' was misleading as Bondronat was not licensed in the US for the prevention of skeletal related events in patients with breast cancer and bone metastases and therefore had not been reviewed within the guidelines.

The Panel noted that the heading 'Time to initiate with IV Bondronat 15 minute infusion (for the majority of patients)' introduced the bullet point

'ASCO Guidelines 2003 – Bisphosphonates should be given to women with lytic destruction on X-ray and receiving systemic treatment for [metastatic bone cancer]'. The heading 'Time to maintain treatment with oral Bondronat' introduced the bullet point 'ASCO Guidelines 2003 – Bisphosphonates should continue until decline in patients performance status'.

The Panel noted that the ASCO Guideline 2003 did not include data from ongoing phase III studies of oral and iv Bondronat as they had not been fully published. The two bullet points in question, however, were included on a page which summarised the whole of the Bondronat detail aid and in that context readers would assume the ASCO Guidelines reviewed Bondronat data and that was not so. The bullet points were misleading and incapable of substantiation as alleged. Breaches of the Code were ruled.

Novartis Pharmaceuticals UK Ltd complained about a Bondronat (ibandronic acid) hospital detail aid (P116402) produced by Roche Products Limited. The date of preparation for the detail aid was March 2007 and so the 2006 Code applied. However the clauses cited by Novartis (7.2, 7.3, 7.4, 7.8, 7.10 and 8.1) were the same in the 2006 Code as in the 2008 Code. The case was therefore considered under the 2008 Code.

Roche explained that although the detail aid was withdrawn in mid 2008 many of the claims it contained had been used in subsequent materials.

Inter-company dialogue had not been successful. Novartis marketed Zometa (zoledronic acid). Both Zometa and Bondronat were bisphosphonates which could be used to prevent skeletal events in patients with breast cancer and bone metastases.

Bisphosphonates were available in both intravenous (iv) and oral formulations. Overall in UK hospitals in 2007 3% of patients with metastatic bone disease due to breast cancer received oral clodronate, 15% iv pamidronate, 23% oral Bondronat and 59% iv zoledronic acid. In addition, oral clodronate and oral Bondronat were also prescribed in primary care for metastatic bone disease, following initial prescriptions in secondary care. Thus oral Bondronate and iv zoledronic acid were the agents with the greatest UK hospital usage in the treatment of metastatic bone disease in breast cancer in 2007. Intravenous Bondronat and iv clodronate were only used in 2% and less than 1% respectively, of breast cancer patients treated with iv bisphosphonates in 2007.

The detail aid was entitled 'Time for a change?' The front page featured a red banner 'Now with 15 minute infusion' and a visual of a skeleton juggling what appeared to be an infusion pack, a clock and a pill blister pack of tablets. The detail aid discussed various features of oral and iv Bondronat including mechanism of action, efficacy, tolerability, safety, iv dosing and clinical audit.

1 Claim 'Innovative, multi-targeted bone protection'

This claim appeared as an integral part of the product logo on the front page and on several other pages throughout the detail aid.

COMPLAINT

Novartis alleged that the claim was misleading and incapable of substantiation in breach of Clauses 7.2, 7.3 and 7.4 of the Code. Health professionals would believe that Bondronat had a mechanism of action or benefit not previously seen with regard to bone protection.

Roche had contended in inter-company dialogue that 'innovative' referred to the fact that Bondronat was the only amino-bisphosphonate available in both oral and iv formulation which thus offered health professionals the flexibility to treat patients with the same molecule in the formulation most suited to their particular circumstances.
Novartis contended that:

- Roche did not explain its interpretation of innovation within the detail aid to allow the health professional to form a judgement on whether they agreed that this was a credible claim.
- Novartis believed that suggesting the presentation was an innovative feature for an amino-bisphosphonate gave it undue emphasis, and the compound would be perceived as having greater superiority whereas 'innovative' was meaningless in terms of clinical significance, or mechanism of action. The non-nitrogen containing bisphosphonate, clodrondate had long been available as an oral and iv preparation. In this clinical setting nitrogen containing bisphosphonates had the same mechanism of action regardless of formulation.
- 'Multi-targeted bone protection' could not be considered innovative because in the prevention of skeletal events nitrogen containing bisphosphonates all had the same mechanism of action (Roelofs *et al* 2006).
- Novartis believed Roche had confused innovation with flexibility of use. Novartis was confident that a health professional would recognise this statement as a claim for flexibility rather than innovation, but in the absence of all the facts this was misleading.

RESPONSE

Roche stated that the claim 'Innovative, multi-targeted bone protection' referred to several proven features of Bondronat. 'Multi-targeted' referred to its mode of action which, in common with other amino-bisphosphonates, had a number of mechanisms which might be responsible for the prevention of skeletal events in metastatic bone disease. 'Bone protection' referred to the prevention

of skeletal related events by Bondronat therapy.

'Innovative' referred to the availability of Bondronat not only as an iv preparation, but also as an effective oral preparation for the treatment of metastatic bone disease. The amino-bisphosphonates, eg pamidronate, zoledronic acid and Bondronat, had a different mode of action from earlier non nitrogen-containing bisphosphonates such as clodronate and this had led to greater efficacy in the prevention of skeletal related events and pain in metastatic bone disease. However, as a consequence of this novel mode of action, the amino-bisphosphonates might also induce gastrointestinal side effects (Suri *et al* 2001) which could limit patient acceptability and thus efficacy of oral formulations. For example, oral pamidronate had greater efficacy against skeletal morbidity at 600mg/day than at 300mg/day, but patients could not tolerate the 600mg/day dose due to gastrointestinal side effects (Diener 1996). As a result, oral pamidronate was not marketed. Bondronat was the only amino-bisphosphonate which could be given orally in a sufficiently large dose to be highly effective against the skeletal complications of malignancy, while having gastrointestinal tolerability sufficient to allow patients to comply with daily oral dosing (Bondronat oral summary of product characteristics (SPC), Diel 2004).

Thus 'innovative' referred to the fact that Bondronat was the only amino-bisphosphonate available as an oral formulation for the treatment of metastatic bone disease which allowed patients a choice in how and where their bisphosphonate care was delivered, added to which the availability of both oral and iv formulations allowed health professionals to treat patients with the same molecule in the formulation most suited to their particular circumstances.

Thus all elements of the claim 'Innovative, multi-targeted bone protection' were capable of substantiation, were not misleading and were not in breach of Clauses 7.2, 7.3, and 7.4.

PANEL RULING

The Panel did not consider that many readers would interpret the claim 'Innovative, multi-targeted bone protection' as submitted by Roche. In the Panel's view most readers would assume that innovative was a description of the multi-targeted bone protection and that somehow Bondronat was a different approach to therapy which was not so. The Panel considered the claim ambiguous, misleading and incapable of substantiation as alleged. Breaches of Clauses 7.2 and 7.4 were ruled.

The claim appeared on the front page and on many other pages of the detail aid and would be read in light of the data on the relevant page. The Panel considered that on the front cover, which featured the phrase 'Time for a change?' the claim would be seen as comparative ie it would encourage doctors to change from their current therapy choice to one which offered innovative, multi-targeted bone protection. Similarly on other pages of the detail aid where Bondronat was compared with other bisphosphonates a comparison would be implied. The Panel considered that such a comparison was misleading. A breach of Clause 7.3 was ruled.

2 Comparison of oral Bondronat with iv zoledronic acid

Page 8 of the detail aid, headed 'Time to compare tolerability', compared oral Bondronat with iv zoledronic acid in metastatic breast cancer. Beneath the claim 'Oral Bondronat has a better tolerability profile than zoledronic acid' a bar chart, adapted from Body *et al* (2005), compared the percentage of patients with adverse events throughout the study (Bondronat 65%, zoledronic acid 76%) and with pyrexia and flu-like symptoms during the first 3 days (Bondronat 1%, zoledronic acid 27%). No p values were given.

COMPLAINT

Novartis stated that a reasonable comparison could not be made between iv and oral formulations given over different time lines without any statistical statement and in itself was misleading.

Novartis also noted that it was not stated that zoledronic acid had been administered intravenously and so it was not immediately clear that an oral preparation was being compared with an iv preparation. The page did not state very clearly that it was not a comparison of like with like, but of an oral vs an iv bisphosphonate. Furthermore, it would not be immediately obvious from the graph that two different formulations were being compared. Whilst most clinicians would know that zoledronic acid was administered as an iv infusion this sentence and accompanying graph were the most prominent on the page and both were incomplete.

The detail aid promoted iv Brondronat and oral Bondronat; such a comparison was alleged to be unbalanced in the absence of data on the iv formulation of Bondronat. Since this adverse drug reaction (ADR) was also seen with iv Bondronat a similar statement could quite fairly be made for iv Bondronat (ie oral Bondronat had a better tolerability profile than iv ibandronic acid). Novartis therefore contended that to suggest this statement was a product specific ADR in promotional material was disingenuous and clearly disparaged 4mg zoledronic acid.

Novartis alleged that use of Body *et al* (2005) demonstrated cherry picking data, not allowing fair and balanced review of the data was also borne out by Roche's inter-company correspondence wherein it stated that the juggling skeleton on the front page

of the detail aid suggested that patients might be able to change between the two formulations of Bondronat, where clinically relevant. But this data did not allow for the choice between the two Roche formulations.

Roche maintained that '… consistency of care' (used as a strapline on page 17) related to the potential to maintain treatment on the same compound but different formulations. The ability to use the same compound in its various presentations was Roche's defence for the 'Innovation' strapline. Novartis alleged, in the light of these facts, that to not include iv Bondronat was unbalanced, misleading and disparaging.

Roche's contention was that this was a study which compared these two formulations at the time and it had presented the comparison as reported. However, in Novartis' view, a lack of comparative data for iv ibandronate [to oral ibandronate or comparing iv Bondronat to iv zoledronic acid] should preclude the use of this study in this promotional material.

Roche's offer to amend the claim 'Oral Bondronat has a better tolerability profile than zoledronic acid' did not meet all of Novartis' concerns. Novartis strongly believed that the use of this study as well as the strapline was in breach of Clauses 7.2, 7.3, 7.8 and 8.1.

RESPONSE

Roche stated that with regards to the data from a comparative study of oral Bondronat and iv zoledronic acid, this was a comparison of medicines for the same intended purpose as required by Clause 7.3, which showed material, relevant, substantiable and representative features of those medicines. The two bisphosphonates most frequently prescribed in UK hospitals for the treatment of bone disease in metastatic breast cancer were oral Bondronat and iv zoledronic acid. It was therefore relevant to UK clinical practice to compare these two agents. Tolerability data was an important element in the prescribing decision/choice for any medicine. This study gave clinicians a view of the most common adverse effects that their patients might experience with each medicine. The large study was conducted as a multi-centre randomised trial, which added weight to its findings. The graph on page 8 was relevant to the comparison being made and had been faithfully reproduced, as in the original publication. Thus the graph provided an accurate, clear, fair, balanced view, substantiated by the cited reference, and thus was not misleading or disparaging.

The iv status of zoledronic acid had not been omitted from the page even though Novartis agreed that most clinicians knew that zoledronic acid was given iv. The page stated that zoledronic acid was given iv as 4mg infused over 15 minutes every 4 weeks. This statement was shown in larger type than that used on the graph and was placed below the graph so that readers could not miss it. The page in question did not state or imply that pyrexia and flu-like symptoms were a product specific ADR of zoledronic acid.

As shown above, iv Bondronat was only prescribed to 2% of UK breast cancer patients given iv bisphosphonate in 2007. To include this medicine in a comparison of the two most commonly used bisphosphonate therapies for this disease would therefore give it an undue and unsuitable prominence and it would provide an incorrect comparator for the study shown on page 8. However, data for the tolerability of both iv Bondronat vs placebo and oral Bondronat vs placebo were shown on the two preceding pages of the detail aid. This allowed any clinician who wished to learn of the tolerability of iv Bondronat to be readily informed by the sales representative. Roche had been very careful not to include any comparison between the iv Bondronat and zoledronic acid data, as it was not valid to make such cross-study comparisons.

Roche rejected Novartis' concerns that page 8 was disingenuous, misleading, or disparaging to 4mg zoledronic acid and it was not in breach of Clauses 7.2, 7.3, 7.8, and 8.1, nor was it incapable of substantiation.

PANEL RULING

The Panel noted Roche's submission that oral Bondronat and iv zoledronic acid were the two most frequently prescribed bisphosphonates in UK hospitals for the treatment of bone disease in metastatic breast cancer. The detail aid was for use in hospitals. Both companies agreed that most clinicians knew that zoledronic acid was given iv. Two bullet points beneath the bar chart clearly stated the infusion rate of zoledronic acid and thus made its iv presentation clear although these were much less prominent than the preceding bar chart and heading which made no mention of zoledronic acid's presentation. Nonetheless on balance the Panel did not consider the page misleading or disparaging because it failed to make the iv presentation of zoledronic acid sufficiently clear as alleged. Given the intended audience, readers would know that zoledronic acid was administered intravenously. No breach of Clauses 7.2, 7.4, 7.8 and 8.1 was ruled. The Panel did not consider that the page suggested that adverse reactions were product specific or that in that regard zoledronic acid had been disparaged. No breach of Clause 8.1 was ruled. Nor did the Panel consider it misleading to fail to mention comparable data for iv Bondronat as alleged. No breach of Clauses 7.2, 7.3, 7.8 and 8.1 was ruled on this point. Further, the Panel did not consider that the use of Body *et al* (2005) represented unfair cherry picking as alleged. No breach of Clause 7.2 was ruled.

During its consideration of this case the Panel noted

that the claim 'Oral Bondronat has a better tolerability profile than zoledronic acid' was a strong unequivocal claim which contained no reference to time. It preceded a bar chart adapted from Body *et al* (2005) which was a 12 week study comparing the safety profiles of Bondronat and iv zoledronic acid (n=254). The chart showed that in the first 3 days of the study 1% and 27% of patients had pyrexia and flu-like symptoms in the Bondronat and zoledronic acid groups respectively. The authors stated that these symptoms were probably or possibly treatment related. Throughout the trial (overall) the percentage of patients reporting adverse events was 65% in the Bondronat group and 76% in the zoledronic acid group. No p value was given for either the 3 day or the overall comparison and so there was no way of knowing if the results, which favoured Bondronat, represented a statistically significant difference between the products. The Panel was concerned that the data presented was insufficient to support the claim and asked that both parties be advised of its concerns.

3 Claims 'No evidence for any treatment-related deterioration in renal function …' (page 10) and 'Time not to exclude patients due to renal dysfunction' (page 11)

The claim 'No evidence for any treatment-related deterioration in renal function was seen for any patient – as assessed by change from baseline in [serum creatinine], calculated [creatinine clearance rate] or in the urinary excretion of markers of glomerular and tubular function' was a bullet point on page 10 which outlined the results and conclusions of von Moos *et al* (2006) which was a comparison of the renal safety of iv Bondronat 6mg infused over 15 (n=101) or 60 minutes (n=26). A graph showed changes in calculated creatine clearance rate over time for both treatment groups.

'Time not to exclude patients due to renal dysfunction' was the heading on page 11 which set out the dosage and administration of iv Bondronat including that for patients with moderate or severe renal impairment.

COMPLAINT

Novartis explained that both of these points were raised simultaneously because individually and together they gave an unbalanced and misleading view of Bondronat's safety profile in terms of renal toxicity, and therefore did not support rational prescribing. Breaches of Clauses 7.2 and 7.10 were alleged.

RESPONSE

Roche submitted that renal safety was a particular issue in metastatic patients treated with bisphosphonates, Roche therefore presented data to address this issue. However, the two points cited by Novartis described different aspects of the data for Bondronat.

In the past, rapid infusion of bisphosphonates led to renal damage. The claim 'No evidence for treatment-related deterioration in renal dysfunction' appeared on a page designed to reassure clinicians that a 15 minute iv infusion of Bondronat had shown adequate renal safety in this setting. The claim was a conclusion from a clinical trial specifically designed to investigate renal safety in 102 breast cancer patients with bone metastases receiving iv Bondronat infused over 15 minutes every 3-4 weeks for 6 months. This was accepted by the European Medicines Evaluation Agency (EMEA) as evidence of renal safety in the registration filing for the 15 minute infusion. The claim on page 10 clearly showed that renal function was assessed by four, well accepted, parameters. However, in order not to mislead the reader, Roche had also referred to the three patients who had an increase in serum creatinine above primary endpoint in the study. The investigators assigned those to non-permanent or treatment unrelated changes, as shown in the reference. Roche noted that section 4.4 of the SPC for Bondronat stated that 'Clinical studies have not shown any evidence of deterioration in renal function with long term Bondronat therapy'.

The claim 'Time not to exclude patients due to renal dysfunction' headed page 11 which showed the iv Bondronat dosing schedule for different levels of renal impairment. As shown, the rate of infusion and the dose must be modified with declining renal function, but it was possible to use Bondronat in patients with impaired renal function. Roche believed that such data should appear prominently in the detail aid and should not be restricted to the prescribing information, to encourage responsible prescribing of Bondronat.

The claims at issue neither individually nor in combination gave an unbalanced and misleading view of Bondronat's safety profile in terms of renal toxicity. Furthermore, both efficacy and safety data for iv Bondronat were reported in the detail aid thereby presenting the risk/benefit profile of the medicine to enable health professionals to form their own opinion of the therapeutic value of Bondronat. Roche denied breaches of Clauses 7.2 and 7.10.

PANEL RULING

The Panel noted that Novartis had alleged that the two claims at issue 'No evidence for any treatment-related deterioration was seen for any patient…' and 'Time not to exclude patients due to renal dysfunction' individually and together gave an unbalanced and misleading view of Bondronat's safety profile in terms of renal toxicity, and therefore did not support rational prescribing. No reasons for this allegation were given.

The Panel noted that pages 9 and 10 of the detail

aid were tagged 'Safety' and together gave details of a study by von Moos *et al* which evaluated the renal safety of Bondronat 6mg infused over 15 or 60 minutes every 3-4 weeks for 6 months. The study concluded that a 15 minute infusion was well tolerated with a safety profile consistent with that of the 60 minute infusion. The study authors noted, however, that in the 15 minute group 3% of patients (n=3) had an increase in serum creatine levels over the limit established by the primary endpoint (an increase in serum creatinine from baseline of ≥ 44.2_mol/L at any point in the study). In one of these patients Bondronat was listed as one of three possible causes and serum creatinine returned to normal levels after the study end. The Panel noted that section 4.8, Undesirable Effects of the iv Bondronat SPC detailed the adverse reactions from a phase III study with Bondronat 6mg (n=152); an increase in creatinine occurred more often in Bondronat patients (2%) than in placebo treated patients (0.6%). Renal and urinary disorders were listed as uncommon. The oral Bondronat SPC listed renal and urinary disorders as uncommon.

The Panel noted that on page 10 two bullet points referred to the 3 patients in the 15 minute group who had a serum creatinine increase over the primary endpoint limit. These details preceded and were of equal prominence to the bullet point detailing the study conclusions including the claim at issue 'No evidence for any treatment-related deterioration in renal function was seen for any patient – as assessed by change from baseline in [serum creatinine], calculated [creatinine clearance] or in the urinary excretion of markers of glomerular and tubular function'. The Panel considered that the claim was misleading; the authors had cited Bondronat as a possible cause for increased serum creatinine in one patient. A breach of Clause 7.2 was ruled. The Panel did not consider that the claim failed to encourage rational prescribing. No breach of Clause 7.10 was ruled.

The claim 'Time not to exclude patients due to renal dysfunction' headed page 11 of the detail aid which was tagged 'IV Dosing'. The Panel noted that the page reproduced the iv Bondronat dosing regimen for patients with varying degrees of renal function and showed that even patients with severe renal impairment could be treated with Bondronat albeit at a reduced dose with an infusion time of 1 hour. Thus impaired renal function was not a contraindication to Bondronat. The Panel thus did not consider the claim was either misleading or that it did not encourage rational prescribing. No breach of Clauses 7.2 and 7.10 was ruled.

During its consideration of this point the Panel noted that von Moos *et al* only recruited patients with an adequate renal function – creatinine clearance of ≥50ml/min. Page 9 gave details of the study population and endpoints but did not state the entry criteria. The Panel noted that pages 9 and 10 of the detail aid referred to the 15 minute infusion time and cited von Moos *et al* in support. The Panel noted that a 15 minute infusion time was not licensed for use in patients with a creatinine clearance of <50ml/min. Pages 9 and 10 failed to include the entry criteria for von Moos *et al* or make it clear that the study conclusions regarding the renal safety profile of the 15 minute infusion only related to those with a creatinine clearance ≥50ml/min. The Panel requested that the parties be advised of its view in this regard.

4 Statement 'Time to review bisphosphonates in hospital' (page 13 – page 14)

Page 13 headed 'Time to review bisphosphonates in hospital' discussed a clinical audit (Barrett-Lee *et al* 2006) which captured data on the whole patient experience of receiving iv bisphosphonate therapy. A diagram depicted the total mean patient time spent on a hospital unit for iv pamidronate as 2 hours 36 minutes and iv zoledronic acid 1 hour 38 minutes. A pie chart overleaf on page 14 showed the reasons for attending hospital for breast cancer patients receiving iv bisphosphonates; 77% of them attended a hospital unit for that therapy alone whereas 23% at the same time also received chemotherapy and/or a clinic appointment.

COMPLAINT

Novartis stated that there was no explanation of how these findings related to either Bondronat formulation. In the absence of data for either formulation this lack of comparison alone was misleading and disparaging as it seemed to serve no purpose other than to question whether patients should be switched from pamidronate or zoledronic acid as highlighted by the use of the phrase 'Time to review bisphosphonates in hospitals'.

Furthermore, the conclusions made on page 14 did not reflect the aim of the study to 'provide insight into the intravenous administration of bisphosphonates and how this impacts on hospital resources and patient experiences'. Novartis alleged that the conclusions on page 14, 'IV bisphosphonate administration involved time, cost and inconvenience for patients' and 'IV bisphosphonate administration involved substantial resource use for clinics and staff' were all-embracing as there was no data for iv Bondronat.

The fact that according to the SPC for iv Bondronat, infusion times ranged from 15 – 60 minutes depending on patients' renal function also meant that had it been included in the study, results for this compound might well lie between 1 hour 38 minutes seen for zoledronic acid and 2 hours 36 minutes seen for pamidronate. This was opposed to the 15 minute infusion time in the SPC for zoledronic acid and 90-270 minute infusion time in the SPC for pamidronate. In fact, iv Bondronat would sit somewhere between iv zoledronic acid and iv pamidronate in terms of overall time, cost and inconvenience for patients, and that for hospitals these would therefore be

equally applicable arguments for substantial resource use for iv ibandronate for clinics and staff. Therefore by explicitly highlighting these requirements only for competitor products Roche had unfairly disparaged zoledronic acid and pamidronate.

Novartis therefore alleged that the use of Barrett-Lee *et al* breached Clauses 7.2, 7.3, 7.10 and 8.1 for iv zoledronic acid and Clauses 7.2, 7.3 and 8.1 for iv pamidronate.

RESPONSE

Roche reiterated that breast cancer patients survived on average 2.5 years after diagnosis of metastatic bone disease and might receive bisphosphonates for much of that time, but they might not always receive concurrent chemotherapy. The iv administration of bisphosphonates, as shown on page 13, required patients to spend between 1.5 and 2.5 hours on the chemotherapy units of 3 major oncology hospitals in the UK. The chart on page 14 showed that for more than three quarters of visits to these hospitals, patients attended solely to receive an iv bisphosphonate.

These data were collected in order to inform NHS resource planning in the 3 centres. As chemotherapy unit capacity was very limited in some UK centres, such data helped health professionals to assess whether that capacity was being used to best effect. They might also assist the provision of greater choice to patients in how their therapy was delivered.

In this audit, no data were reported for iv Bondronat due to the clinicians' preference to prescribe pamidronate or zoledronic acid as their iv bisphosphonate of choice. This reflected the very low level of iv Bondronat prescribed in UK hospitals (2% of total iv usage). Introduction of iv Bondronat into this audit would have given it undue prominence for its UK market share. Oral Bondronat was also not included in the audit as the aim was to measure iv bisphosphonate usage. The audit was designed to examine the experience of patients receiving iv bisphosphonates as a group of agents, rather than the choice of iv bisphosphonate. Therefore, the use of this study was not misleading or disparaging but rather reflected NHS interest in resource and cost saving as well as maximising patient experience.

Page 14 which represented the conclusions from the study referred to iv bisphosphonates as a group and did not mention any specific product. This and the fact that the outcomes of the audit, in terms of the iv bisphosphonates used, reflected the prescribing habits of the clinicians involved in the study, as well as the wider prescribing community nationally, meant that the use of this study was not in breach of Clauses 7.2, 7.3, 7.10 and 8.1 for iv zoledronic acid nor was it in breach of Clauses 7.2, 7.3, and 8.1 for pamidronic acid.

PANEL RULING

The Panel noted that the audit was designed to quantify the current time involved in the administration of iv bisphosphonates and how this might impact on patient experience and cancer unit capacity. The Panel considered that page 13 made the objective of the audit clear. The audit was not designed to detect differences between specific bisphosphonates however page 13 stated that the audit findings were, that on average iv pamidronate patients spent 2 hours 36 minutes on a hospital unit and iv zoledronic acid patients spent 1 hour 38 minutes. The Panel considered that in the detail aid in question, and in the absence of a statement to the contrary, these times would be taken as an implied comparison with Bondronat. Barrett-Lee *et al*, however, had noted these times only in order to show that the preparation of bisphosphonates infusion was not the main driver for the time that patients spent on a unit and once the infusion was started they were, on average, completed in a similar time to the manufacturers' recommendations of 90 minutes for pamidronate and 15 minutes for zoledronic acid. This was not made clear in the detail aid. The Panel considered that some readers might assume that the infusion time for zoledronic acid was 1 hour 38 minutes which was not so. Similarly the recommended infusion time for pamidronate was 90 minutes and not the 2 hours and 36 minutes referred to in the detail aid. The Panel noted Barrett-Lee *et al's* view that it appeared use of an iv bisphosphonate with a shorter infusion time might not release as much capacity for a day care unit as might be expected. The Panel noted the emphasis throughout the detail aid of a 15 minute infusion time for Bondronat. It considered that without any information as to how long patients might spend on a unit in addition to the time receiving Bondronat iv and/or to not give the recommended infusion times for zoledronic acid and pamidronate created a misleading impression and exaggerated the differences between the products which could not be substantiated and was disparaging. Breaches of Clauses 7.2, 7.3, 7.10 and 8.1 were ruled.

The Panel noted that page 14 only referred to the iv administration of bisphosphonates and the time, cost and inconvenience for patients and the staff and clinic resources needed. In that regard the Panel did not consider that the lack of data for Bondronat meant that the claims were all embracing as alleged. No breach of Clause 7.10 was ruled.

5 Time to consider resources (page 15) and Time to save resources (page 16)

'Time to consider resources' headed page 15 which detailed the UK interim analysis of a pharmacoeconomic study (Wardley *et al* 2004). A bar chart compared the average resource time burden per patient of several aspects involved in the administration of iv zoledronic acid and oral

Bondronat; preparation of the infusion, infusion duration, and time spent by the clinician, nurse, laboratory technician and pharmacist. Oral Bondronat was described as a cost-effective choice compared with zoledronic acid.

'Time to save resources' headed page 16 which compared the additional clinician and nurse time required with zoledronic acid iv administration vs oral Bondronat over 12 months.

COMPLAINT

Novartis alleged that there was no substantiation that this pharmacoeconomic study (n=9) reflected the average resource and time burden; no reasonable conclusions could realistically be drawn from the very small population. As it was such a small population use of this study in promotional material was an unfair, scientifically invalid comparison and misleading. This was additionally misleading due to the presence of a later publication on pharmacoeconomics (Botteman *et al* 2006) which considered all available bisphosphonates, and their cost per quality adjusted life year (QUALY).

Novartis alleged that these findings were misleading, all-embracing and would be equally applicable to iv Bondronat. This compound though was not represented.

Novartis therefore alleged that the use of Wardley *et al* was in breach of Clauses 7.2, 7.3 and 7.8.

RESPONSE

Roche submitted that the pharmacoeconomic study on page 15 showed a comparison of hospital resources required to administer the two leading bisphosphonates in the UK for the treatment of bone metastasis in breast cancer. The low use of iv Bondronat in the UK reflected the fact that it was not used in the hospitals conducting this study and it was irrelevant to this comparison of leading agents. To introduce iv Bondronat, for comparative purposes might well have led to confusing data, as the health professionals involved were not accustomed to this agent in their routine practice.

There were only a small number of repeated observations in the study, as was customary for such pharmacoeconomic analyses. The variation in timing of repetitive processes such as preparation and dispensing was carefully monitored and more observations were added if there was great variability. In this study, the variation between repeat timings did not require additional measurements.

The results of this study were further supported by De Cock *et al* 2005 which was also referenced on page 15. However, Botteman *et al* was not relevant to this page, as it provided no actual measurements of time and resource usage for either oral or iv Bondronat administration. For iv Bondronat these data were estimated as an average of values for pamidronate and zoledronic acid and the 15 minute Bondronat infusion time was omitted.

The graph on page 16 (time to save resources) extrapolated the data from the study on page 15, to demonstrate how the differences in resources required to administer the two medicines might add up for different numbers of patients in a unit.

Roche believed that this study shown on pages 15 and 16 was not an invalid comparison nor was it misleading and its use was not in breach of Clauses 7.2, 7.3, and 7.8.

PANEL RULING

The Panel noted that Wardley *et al* was an interim analysis of the UK data from an open label sub-study of a clinical trial which assessed medical care utilization of iv zoledronic acid (4mg infusion every four weeks (n=5)) and oral Bondronat (50mg daily (n=4)).

The Panel did not consider that data from such a small interim analysis, for which no statistical analysis was reported, was sufficiently robust to support the claims made from it on pages 15 and 16. In that regard the Panel was particularly concerned about the claim 'Bondronat – a cost effective choice'. The Panel queried the validity of extrapolating clinician and nursing minutes saved per patient per infusion from a data set of 5 to the saving of 16 hours/patient/year to 200 days per 100 patients per year. The Panel considered the material on pages 15 and 16 were misleading as alleged. Breaches of Clauses 7.2, 7.3 and 7.8 were ruled.

6 Summary page 17 – Time for flexibility and consistency of care

In a series of bullet points page 17 summarised the data presented in the detail aid.

COMPLAINT

Novartis stated that Roche had agreed to change the heading to page 17 together with other non-specified changes. Roche was unable to give specific assurances. The points requiring reassurance included unfair comparisons between the products as highlighted above.

RESPONSE

Roche had agreed, to change the statement 'Time for flexibility and consistency of care' on this page and in order not breach that agreement, it would ensure that the statement was changed not only in letter but in spirit. However, Roche did not believe

that the Code required it to inform Novartis of the exact wording of the new headline. The remaining statements on the page repeated points from previous pages which, as shown above, Roche did not believe were in breach of the Code. Comparisons of medicines for the same needs or intended purposes were permitted if relevant, substantiable and representative features were compared and Roche believed this applied to the comparisons in the detail aid.

PANEL RULING

The Panel noted Novartis alleged that unfair comparisons between the products were covered by the rulings above. No specific clauses of the Code had been cited in relation to this page but Novartis had referred to matters highlighted above. The Panel noted that one comparative claim was featured on page 17 for oral Bondronat and zoledronic acid, 'Time for a cost-effective approach to resources. 16 hours time saved per patient per year with oral Bondronat vs zoledronic acid'. The Panel considered that this claim was covered by its ruling at point 5 above. Breaches of Clauses 7.2, 7.3 and 7.8 were ruled.

7 Use of American Society of Clinical Oncology (ASCO) Guidelines on page 17

COMPLAINT

Finally, Novartis wanted to highlight its concerns about use of ASCO guidelines to support the claims 'Time to initiate …' and 'Time to maintain …'.

The reasons were that Bondronat was not licensed in the US for the prevention of skeletal related events in patients with breast cancer and bone metastases and therefore ibandronate had not been reviewed within the guidelines. Novartis submitted that UK health professionals would not immediately be aware of this and therefore alleged that use of the ASCO guidelines to support these claims was misleading to UK health professionals in breach of Clauses 7.2 and 7.3.

RESPONSE

Roche stated that page 17 clearly stated that the ASCO guidelines on bisphosphonates were from 2003. ASCO summarised the data then available and noted that data from ongoing phase III studies of oral and iv Bondronat were presented at ASCO 2003, but were not included in the guideline report because they had not been fully published. The publication also stated that the choice of bisphosphonates was broader outside the US and each country must make its own relative cost benefit assessment.

These points from the 2003 ASCO publication, plus the fact that pivotal data for Bondronat efficacy were published in 2004 to 2006 (Body 2004; Body *et al* 2004 and Diel) made it unreasonable to suggest that, because the ASCO guideline did not include Bondronat, the principles of administration of bisphosphonates for metastatic disease should not apply to Bondronat.

In the absence of detailed UK guidelines on bisphosphonate therapy in metastatic bone disease, Roche quoted the latest (2003) ASCO guidelines. However, on page 17 of the detail aid there was no attempt to claim that the ASCO guidelines recommended Bondronat as a therapy. The guidelines were very clearly cited to demonstrate what ASCO considered to be best practice in the administration of bisphosphonates, as a class, for metastatic bone disease – that they be given to women with certain X-ray findings and continued until decline in performance status. These statements were neither misleading, nor in breach of Clauses 7.2, 7.3 or 7.4.

PANEL RULING

The Panel noted that the heading 'Time to initiate with IV Bondronat 15 minute infusion (for the majority of patients)' introduced the bullet point 'ASCO Guidelines 2003 – Bisphosphonates should be given to women with lytic destruction on X-ray and receiving systemic treatment for [metastatic bone cancer]'. The heading 'Time to maintain treatment with oral Bondronat' introduced the bullet point 'ASCO Guidelines 2003 – Bisphosphonates should continue until decline in patients performance status'.

The Panel noted that the ASCO Guideline 2003 did not include data from ongoing phase III studies of oral and iv Bondronat as they had not been fully published. The Panel did not accept, as suggested by Roche, that page 17 of the detail aid made no attempt to claim the ASCO Guideline recommended Bondronat as a therapy. The two bullet points in question were included on a page which summarised the whole of the Bondronat detail aid and in that context readers would assume the ASCO Guidelines reviewed Bondronat data and that was not so. The bullet points were misleading and incapable of substantiation as alleged. Breaches of Clauses 7.2 and 7.3 were ruled.

Complaint received **12 December 2008**

Case completed **4 March 2009**