CASE AUTH/2199/1/09

NOVARTIS v ROCHE

Bondronat leavepiece

Novartis complained about a Bondronat (ibandronate) leavepiece issued by Roche. Novartis supplied Zometa (zoledronic acid). Bondronat and Zometa were both 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.

Page 3 headed 'Effects of long-term therapy with bisphosphonates on the risk of developing a skeletal complication' featured three graphs comparing zoledronic acid and pamidronate, zoledronic acid and placebo and ibandronate and placebo for patients with breast cancer metastatic to bone. The primary end points for each of the three trials were given.

Novartis alleged that the graph (adapted from Body 2006) was misleading and unbalanced as it represented an indirect comparison between different studies, as data that could be directly compared on a common axis.

Novartis considered that the footnote 'NB: Caution should be exercised when using indirect comparison across trials' showed that Roche knew that the graph was inappropriate for use in promotional material. Novartis further alleged that Roche had failed to maintain the high standard of promotion expected of the pharmaceutical industry.

The Panel noted that all three graphs were contained, one below the other, within a highlighted box and each was drawn to the same scale such that the hazard ratios (x axis) lined up with each other. This was how they appeared in Body (2006) which was a review article. The three graphs compared zoledronic acid vs pamidronate (adapted from Rosen *et al* 2003), zoledronic acid v placebo (from Kohno *et al* 2005) and ibandronate (iv and oral) vs placebo (from Body *et al* 2004 and Body *et al* 2004b). To the right hand side of the boxed graphs was a short description of the primary endpoints of each study. The endpoints were not the same for each trial. The references for the four different studies were not given with the endpoints nor anywhere else on the page. Below the description of the endpoints was the statement 'NB: Caution should be exercised when using indirect comparisons across trials'. In the Panel's view this statement did not negate the incorrect implication that a direct comparison of the data was valid. Supplementary information stated that in general claims should not be qualified by the use of footnotes and the like. The final claim on the page '… the choice of a particular bisphosphonate for patients with metastatic bone disease should be based not only on efficacy but also on the risk for renal deterioration' would, in the Panel's view, further encourage direct comparison of the data from the four separate efficacy studies with different endpoints. The Panel considered that the data as shown was misleading as alleged; high standards had not been maintained. Breaches of the Code were ruled.

The claim 'Bondronat gives you renal safety reassurance' appeared as the heading to page 4 of the leavepiece and was referenced to three separate studies.

Novartis alleged that 'reassurance' was all embracing and the claim could not be substantiated, was misleading and failed to accurately reflect the Bondronat summary of product characteristics (SPC). It implied that Bondronat had no or limited renal safety concerns and further did not promote the rational use of the medicine. This was not consistent with the Bondronat SPC which detailed dose adjustments according to renal function.

The Panel considered that 'Bondronat gives you renal safety reassurance' implied that there were no renal issues with Bondronat which was not so. The dose of both iv and oral Bondronat had to be reduced in patients with severe renal impairment. The SPC for both formulations stated that, although clinical studies had shown no evidence of deterioration in renal function with long-term therapy, according to clinical assessment of the individual patient, renal function *inter alia* should be monitored in patients treated with Bondronat. With regard to adverse events the Bondronat Tablets SPC listed uraemia as an uncommon event; the SPC for Bondronat iv noted increased creatinine in 2% of patients in the phase 3 trials (n=152) and urinary retention and renal cysts as uncommon adverse events.

The Panel considered that the claim 'Bondronat gives you renal safety reassurance' appeared to be at odds with Roche's preliminary comment that it had instructed its sales force to advise health professionals to calculate creatinine clearance for every patient at the start of therapy, in addition to the monitoring required by the SPC. The Panel considered that the claim was misleading, exaggerated and could not be substantiated; it did not promote the rational use of Bondronat. Breaches of the Code were ruled.

Novartis alleged that representation of Meden *et al* and the use of a preclinical study (Body *et al*) to

support the claim 'Bondronat gives you renal safety reassurance' was unbalanced and misleading. Bullet points listed below the table [of data adapted from Meden *et al*] on page 4 were either data gathered from baseline or from an independent pre-clinical study. Novartis believed the reader would consider the bullet points to be results, or conclusions of results from the observational study. Since there was insufficient clarification of this, Novartis considered the page and bullet points misleading and ambiguous and not sufficiently complete to allow the reader to form their own opinion of the therapeutic value of medicine.

The Panel noted that page 4 detailed Meden *et al*, a poster representation of the interim analysis (n=1,704) of a running observational study which would eventually enrol 3,000 breast cancer patients with metastatic bone disease. The study had thus only enrolled 57% of its intended patients. The poster did not include any statistical analysis and the differences might not be clinically significant. There was no information to show how well matched for age, surgery etc patients who had received Bondronat previously were with those who had previously been treated with zoledronic acid. The Panel considered the data given on page 4 of the leavepiece was misleading. The study was incomplete which was not stated and claims such as 'Incidence of serum creatinine > 1.2 in zoledronic acid-treated patients was more than double that with Bondronat (26% vs 11%)' might change when the full data set was analysed. The comparisons were misleading and a breach of the Code was ruled.

Page 5 of the leavepiece, headed 'Is routine renal function monitoring performed?', included details of the interim results of a review by Houston *et al* (2008) and stated that the conclusion of the review was that the lack of routine renal function monitoring resulted in frequent overdosing with zoledronic acid.

Novartis alleged that the use of Houston *et al* was balanced and misleading. It failed to clarify that this study was a comparison of iv zoledronic acid and oral Bondronat, or the reasons for choosing these agents as adequate comparators. The study did not include a comparison with iv Bondronat.

The Panel noted Houston *et al* was a poster presentation of an interim analysis from 154 patients from a retrospective review of medical records of 200 patients; thus the interim analysis had included only 77% of the intended full data set. The poster did not include any statistical analysis and so it was impossible to know if the results of the study were clinically significant. Some of the claims taken from Houston *et al* might change on analysis of the full data set. The Panel noted that there were differences between Bondronat and zoledronic acid with regard to use in patients with renal impairment.

The Panel noted that there was no mention that Houston *et al* had compared changes in renal function in routine clinical practice with iv zoledronic acid and oral ibandronate. The results did not relate to iv Bondronat. The claims on page 5 which referred to Bondronat, however, did not differentiate between the oral or iv formulation. The Panel considered that the claims were misleading as alleged; breaches of the Code were ruled.

Novartis alleged that the bullet points on page 7 'With minimal risk of renal function concerns' and 'Time to show a good safety profile', were unbalanced, misleading and unsubstantiated. The statements also failed to adequately reflect the licence for Bondronat which required renal monitoring to make dose adjustments according to renal function. Stating that Bondronat was in effect safe was in breach of the Code.

The Panel noted that page 7 was headed 'Which bisphosphonate will you choose?' below which were two boxes of text. The left hand box read ' A bisphosphonate that requires constant monitoring and dosing adjustments to avoid risk of overdosing?' and was linked with 'or' to the second box which read 'Brondronat – an effective bisphosphonate which can be used: Irrespective of renal function; Irrespective of previous bisphosphonate history; With minimal risk of renal function concerns'. Below the boxes of text were five bullet points one of which was 'Time to show a good safety profile'.

The Panel considered that the bullet point 'With minimal risk of renal function concerns' sought to dispel any concerns that a prescriber might have about the renal safety of Bondronat. The Panel further considered that given the context in which it appeared the claim could not be substantiated; some prescribers might assume that there was no need to consider a patient's renal function either before or during therapy which was misleading. A breach of the Code was ruled.

The Panel similarly considered that, given the context in which it appeared, the claim 'Time to show a good safety profile' was misleading; a breach of the Code was ruled.

The Panel did not consider that page 7 included a claim that Bondronat was, in effect, safe as alleged. The page referred to the safety *profile* of Bondronat not just its safety; no breach of the Code was ruled

Novartis alleged that the leavepiece as a whole disparaged other companies' medicines and zoledronic acid in particular. The leavepiece inferred that Bondronat had no renal toxicity issues and by only presenting comparisons with zoledronic acid it questioned the renal safety of zoledronic acid. This was compounded by the fact that much of the comparative data was based on oral Bondronat vs iv zoledronic acid and that this was not always clear.

Novartis alleged that the leavepiece presented such a serious issue as to be in breach of Clause 2. There

were multiple breaches of the Code and attempts to disparage zoledronic acid. There was a failure to maintain the high standards expected in the promotion of medicines because of this. This discredited the pharmaceutical industry and reduced confidence in the industry.

Although noting its rulings above, on balance the Panel did not consider that overall the leavepiece had disparaged zoledronic acid or the activities of other pharmaceutical companies as alleged; no breach of the Code was ruled.

The Panel further did not consider that the leavepiece brought discredit upon or reduced confidence in the pharmaceutical industry as alleged. No breach of Clause 2 was ruled. Clause 2 was a sign of particular censure and reserved for such.

Novartis Pharmaceuticals UK Ltd complained about a leavepiece (ref P116532) for Bondronat (ibandronate) issued by Roche Products Limited. Novartis supplied Zometa (zoledronic acid). Bondronat and Zometa were both bisphosphonates which could be used to prevent skeletal events in patients with breast cancer and bone metastases.

Preliminary comments by Roche

Roche stated that it withdrew the leavepiece in November 2008 to update the prescribing information, however the claims at issue had been used in subsequent materials and so Roche had defended them through dialogue with Novartis. The leavepiece was used by the Bondronat hospital sales force with clinical and medical oncologists (consultants and specialist registrars) who treated metastatic breast cancer and also with breast care nurses.

Roche explained that bone metastases occurred in up to 75% of patients with metastatic breast cancer and such patients survived an average of 2.5 years from diagnosis of bone metastases. These patients required treatment to palliate bone pain and to reduce skeletal related events such as fractures, spinal cord compression and the need for surgery or radiotherapy to affected bones. Bisphosphonates reduced both the skeletal related events and pain associated with bone metastases. Although most patients did not undergo cytotoxic anticancer therapy continuously, bisphosphonate therapy was usually continued from the diagnosis of bone metastases until decline in performance status or death. Some patients however, had intermittent bisphosphonate therapy, as needed to control bone pain. This prolonged duration of therapy meant that many bisphosphonate patients might have some level of renal impairment, as a result either of their underlying disease or of their prior treatments (Body *et al* 2005). A recent large observation study of bisphosphonates in routine clinical practice showed some degree of renal impairment in up to 29% of patients (Meden *et al* 2007).

In man, up to 60% of the bisphosphonate reaching the circulation was rapidly bound to bone, while the remainder was eliminated unchanged by the kidneys, such elimination might occur more slowly in patients with low creatinine clearance, allowing medicine to accumulate. High doses accompanied by high molar concentrations of some bisphosphonates had been shown to overload the renal elimination mechanism and the retained medicine could damage renal cells (Body *et al* 2005). This was more likely to occur in renally impaired patients, where medicines were cleared more slowly. Under phase III clinical trial conditions renal toxicity was an infrequent, but potentially very serious, side-effect associated with the administration of intravenous (iv) bisphosphonates. The acute renal failure associated with iv bisphosphonate administration might be clinically reversible, but varying degrees of irreversible impairment might persist and eventually lead to chronic renal failure (Tanvetyanon and Stiff 2006). The level of renal side-effects seen in clinical trials differed between the various bisphosphonates and might be related to different renal half-lives (Body *et al* 2005). Thus Section 4.4 of the iv Bondronat summary of product characteristics (SPC) stated 'Clinical studies have not shown evidence of deterioration in renal function with long term Brondronat therapy', but Section 4.4 of the iv zoledronic acid SPC stated 'renal deterioration, progression to renal failure and dialysis have been reported in patients after the initial dose or a single dose of Zometa'. There were also instructions in the SPC for many bisphosphonates used in metastatic bone disease to reduce the dose in patients with renal impairment because of the increased accumulation in such patients. However, the recommended dose reductions were different for the various bisphosphonates.

Market research amongst 90 UK consultants and specialist registrars showed that they ranked side-effects as second in importance only to efficacy when prescribing bisphosphonates (Healthcare Partners, 2006). However, Roche knew from individual consultant oncologists and from an audit of clinical practice across four large UK teaching hospitals, that in a number of UK centres creatinine clearance was not routinely calculated for patients undergoing bisphosphonate therapy (Houston *et al* 2008). As the recommended dose reductions for bisphosphonates were based on creatinine clearance, a lack of routine creatinine clearance calculation was of considerable concern. Accordingly Roche had instructed its Bondronat sales force to advise health professionals to calculate creatinine clearance for every patient at the start of Bondronat therapy, in addition to the monitoring required by the SPC.

Bisphosphonates were available in both iv and oral formulations and overall in UK hospitals in 2008, 3% of breast cancer patients with metastatic bone disease received oral clodronate, 17% iv pamidronate, 35% Bondronat oral/iv and 44% iv zoledronic acid (IMS, Oncology Analyser, Sep 08).

Amongst breast cancer patients treated with iv bisphosphonates, the level of Bondronat usage in UK hospitals rose from 2% in 2007 to 6% in 2008 (IMS, Oncology Analyser, Sep 08).

The leavepiece sought to remind health professionals of this important area of patient safety and to help them to consider whether their routine clinical practice was sufficient to ensure best practice in the safe prescribing of bisphosphonates.

1 Page 3, graph of three studies, adapted from Body (2006)

The page was headed 'Effects of long-term therapy with bisphosphonates on the risk of developing a skeletal complication'. It included three graphs comparing zoledronic acid and pamidronate, zoledronic acid and placebo and ibandronate and placebo for patients with breast cancer metastatic to bone. The primary end points for each of the three trials featured were given.

COMPLAINT

Novartis alleged that the graph (adapted from Body 2006) was misleading and unbalanced in breach of Clauses 7.2, 7.3 and 7.8. The graph represented an indirect comparison between different studies, as data that could be directly compared on a common axis.

Novartis was not satisfied that Roche's response that the footnote 'NB: Caution should be exercised when using indirect comparison across trials' was sufficient to negate its alleged breaches of the Code.

Novartis considered that the footnote showed that Roche knew that use of the graph in this way was inappropriate in promotional material. Novartis further alleged a breach of Clause 9.1 as Roche had failed to maintain the high standard of promotion expected of the pharmaceutical industry.

RESPONSE

Roche submitted that, as mandated by the supplementary information to Clause 7.8, the graph had been faithfully reproduced from the original publication, with the only change being to substitute the full names of the various medicines, rather than the abbreviations used in the original. The graph showed a relevant and substantiable feature of three medicines used for the same intended purpose and no trade names were used. The graph was not misleading as it showed pre-planned analyses of the risk of skeletal complications from all the studies, without any distortion, exaggeration or undue emphasis. In addition, the page clearly stated the primary efficacy endpoint for each study, in order not to mislead the reader. The statement 'NB: Caution should be exercised when using indirect comparisons across trials' was not a footnote; it was in the same size typeface as other explanatory notes about the studies and italicised in order to bring it more clearly to the reader's attention.

Roche submitted that the graph was not in breach of Clauses 7.2, 7.3 or 7.8, nor was it inappropriate to use it in promotional material and as it did not constitute a failure to maintain high standards in promotion. Roche denied a breach of Clause 9.1.

PANEL RULING

The Panel noted that three graphs on page 4 showed the effects of long-term therapy with bisphosphonates on the risk of developing a skeletal complication. All three graphs were contained, one below the other, within a highlighted box and each was drawn to the same scale such that the hazard ratios (x axis) lined up with each other. This was how they appeared in Body (2006) which was a review article.

The three graphs compared zoledronic acid vs pamidronate (adapted from Rosen *et al* 2003), zoledronic acid v placebo (from Kohno *et al* 2005) and ibandronate (iv and oral) vs placebo (from Body *et al* 2004 and Body *et al* 2004b). To the right hand side of the boxed graphs was a short description of the primary endpoints of each study. The endpoints were not the same for each trial. The references for the four different studies were not given with the endpoints nor anywhere else on the page. Below the description of the endpoints was the statement 'NB: Caution should be exercised when using indirect comparisons across trials'. In the Panel's view this statement did not negate the incorrect implication that a direct comparison of the data was valid. The supplementary information to Clause 7 stated that in general claims should not be qualified by the use of footnotes and the like. The final claim on the page was a quotation referenced to Body *et al* (2005) that '… the choice of a particular bisphosphonate for patients with metastatic bone disease should be based not only on efficacy but also on the risk for renal deterioration'. In the Panel's view this would further encourage direct comparison of the data from the four separate efficacy studies with different endpoints. The Panel considered that the data as shown was misleading as alleged. Breaches of Clauses 7.2, 7.3 and 7.8 were ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled.

2 Claim 'Bondronat gives you renal safety reassurance'

This claim appeared as the heading to page 4 of the leavepiece and was referenced to Body *et al* (2003), Body *et al* (2004b) and McLachlan *et al* (2006). Data from an observational study in 1,704 patients from Meden *et al* (2007) was given.

COMPLAINT

Novartis submitted that 'reassurance' was all embracing and the claim as a whole could not be substantiated in light of the totality of clinical evidence on Bondronat, despite the statement being referenced. The claim was misleading and failed to accurately reflect the Bondronat SPC. The claim implied that Bondronat had no or limited renal safety concerns and further did not promote the rational use of the medicine in breach of Clause 7.10. This was not consistent with Section 4.2 of the Bondronat SPC which gave clear dose adjustments according to measures of renal function. Novartis alleged breaches of Clauses 7.2 and 7.4.

RESPONSE

Roche stated that it chose the verb to 'reassure' because it meant to 'restore confidence to' or 'dispel the apprehensions of'. The title on page 4, referenced to the clinical trials for Bondronat in breast cancer patients with metastatic bone disease, which showed levels of renal impairment similar to those in placebo patients, undertook to dispel a clinician's apprehension about the renal safety of Bondronat. The SPC for both iv and oral Bondronat stated in Section 4.4 'Clinical studies have not shown evidence of deterioration in renal function with long term Bondronat therapy'. Section 4.2 of the SPC for iv Bondronat also stated 'There is no evidence of a reduction in tolerability associated with an increase in exposure to ibandronate in patients with various degrees of renal impairment'. These statements and the published clinical trials for Bondronat should reassure prescribers that there were very limited renal safety concerns associated with Bondronat therapy. The recommendation in the SPCs to reduce the dose of both oral and iv Brondronat in patients with several renal impairment (creatinine clearance <30ml/min) was a pharmacokinetic consideration rather than one of tolerability (as indicated above, bisphosphonates were excreted primarily via the kidney). It did not suggest that there was evidence of renal damage with Bondronat, but that these reduced doses were more appropriate for patients with limited renal function who might therefore maintain a higher level of the medicine. The claim was thus not inaccurate, it was balanced, objective and capable of substantiation and therefore not in breach of Clauses 7.2 and 7.4. This claim was also not in breach of Clause 7.10 as it did not exaggerate, as shown by the statements from the SPCs and it contained no superlatives.

PANEL RULING

The Panel considered that 'Bondronat gives you renal safety reassurance' implied that there were no renal issues with Bondronat which was not so. The dose of both iv and oral Bondronat had to be reduced in patients with severe renal impairment (creatinine clearance < 30ml/min). The SPC for both formulations contained the recommendation in Section 4.4 special warnings and precautions for use that, although clinical studies had shown no evidence of deterioration in renal function with long-term therapy, according to clinical assessment of the individual patient, renal function *inter alia* should be monitored in patients treated with Bondronat. With regard to adverse events the Bondronat Tablets SPC listed uraemia as an uncommon event; the SPC for Bondronat iv noted increased creatinine in 2% of patients in the phase 3 trials (n=152) and urinary retention and renal cysts as uncommon adverse events.

The Panel considered that the claim 'Bondronat gives you renal safety reassurance' appeared to be at odds with Roche's preliminary comment that it had instructed its sales force to advise health professionals to calculate creatinine clearance for every patient at the start of therapy, in addition to the monitoring required by the SPC. The Panel considered that the claim was misleading and exaggerated; it did not promote the rational use of Bondronat. Breaches of Clauses 7.2 and 7.10 were ruled. The claim was not capable of substantiation. A breach of Clause 7.4 was ruled.

During its consideration of the matter, the Panel noted that Clause 7.9 of the Code required that the word 'safe' must not be used without qualification. The supplementary information to Clause 7.9 stated that the restrictions on the word 'safe' applied equally to grammatical derivatives of the word such as 'safety' and noted that phrases such as 'demonstrated safety' and 'proven safety' would be prohibited under Clause 7.9. The Panel requested that, although the claim at issue had been ruled in breach of other clauses of the Code, both parties be reminded of the requirements of Clause 7.9.

3 Inappropriate representation of data (Meden *et al*) to support the claim 'Bondronat gives you renal safety reassurance' and subsequent bullet points on page 4

COMPLAINT

Novartis alleged that representation of Meden *et al* and the use of a preclinical study (Body *et al*) to support the claim 'Bondronat gives you renal safety reassurance' was unbalanced and misleading. The bullet points listed below the table [of data adapted from Meden *et al*] were either data gathered from baseline, or from an independent pre-clinical study. Novartis believed the reader would consider the bullet points to be results, or conclusions of results from the observational study. Since there was insufficient clarification of this, Novartis considered the page and bullet points were misleading and ambiguous and not sufficiently complete to allow the reader to form their own opinion of the therapeutic value of medicine. Without clarification of inter-patient group factors that might have influenced the baseline readings or a statistical analysis allowing interpretation of the data this information also prevented the reader from drawing their own opinion

of the validity of the claim. Novartis alleged that this data did not support the claim, and that the way it was presented breached Clauses 7.2 and 7.3.

RESPONSE

Roche submitted that Meden *et al* represented a large and powerful collection of data from routine clinical practice, which gave clinicians a more realistic view of the range of patients who might enter their everyday oncology clinic than could be see in a phase III trial. The sometimes intermittent nature of bisphosphonate therapy to control bone pain meant that some patients requiring bisphosphonates might have received them previously. The fact that fewer patients treated with Bondronat (iv or oral) prior to study entry showed some degree of renal impairment (glomerular filtration rate, as measured by creatinine clearance, ≤50ml/min) than in the groups of patients pre-treated with the other 3 bisphosphonates, substantiated the claim. The first three bullet points below referred to the same dataset. This was neither misleading nor ambiguous. The study on page 4, by showing baseline renal function of patients commencing a course of bisphosphonate therapy, provided important data for clinicians considering prescribing bisphosphonates. These data and their presentation were not misleading, ambiguous, distorted or exaggerated and did not breach Clauses 7.2 or 7.3.

PANEL RULING

The Panel noted that page 4 detailed Meden *et al*. The cited reference was a poster presented at an international breast cancer symposium held in the US. The poster presented the interim analysis (n=1,704) of a running observational study which would eventually enrol 3,000 breast cancer patients with metastatic bone disease. The study had thus only enrolled 57% of its intended patients. The poster did not include any statistical analysis and the differences might not be clinically significant. There was no information to show how well matched for age, surgery etc patients who had received Bondronat previously were with those who had previously been treated with zoledronic acid. The Panel considered the data given on page 4 of the leavepiece was misleading. The study was incomplete which was not stated and claims such as 'Incidence of serum creatinine > 1.2 in zoledronic acid-treated patients was more than double that with Brondronat (26% vs 11%)' might change when the full data set was analysed. The comparisons were misleading and breaches of Clauses 7.2 and 7.3 were ruled.

4 Question 'Could many bisphosphonate patients be receiving too high a dose?' and the following bullet points and conclusion

Page 5 of the leavepiece was headed 'Is routine renal function monitoring performed?' It included details of the interim results of a review by Houston *et al* (2008) and stated that the conclusion of the review was that the lack of routine renal function monitoring resulted in frequent overdosing with zoledronic acid.

COMPLAINT

Novartis alleged that the use of Houston *et al* was unbalanced and misleading in breach of Clauses 7.2 and 7.3. It failed to clarify that this study was a comparison of iv zoledronic acid and oral Bondronat, or the reasons for choosing these agents as adequate comparators. As this study did not include a comparison with iv Bondronat, Novartis believed this further added to its allegation that Roche attempted to use misleading data and a lack of balance in its description to validate points or statements within promotional material.

RESPONSE

Roche noted that page 5 outlined the interim results of an audit of bisphosphonate therapy undertaken in a number of NHS hospitals. The page reinforced the message that patients might have some degree of renal impairment prior to starting bisphosphonate therapy and to show that in some UK centres routine monitoring of renal function was not sufficient to prevent overdosing of some patients. When Roche knew the interim results of Houston *et al* prior to publication, it not only instructed its sales force to advise health professionals to calculate creatinine clearance for every patient at the start of Bondronat therapy, but it also shared these results with Novartis to make it aware of data which might have an impact on patient safety.

The two bisphosphonates included in the audit, iv zoledronic acid and oral Bondronat, were those most commonly used in UK hospitals and they reflected the prescribing habits of the clinicians involved in the audit. Intravenous Bondronat was not included as it was not used in the hospitals which undertook this study, reflecting its low share of the UK iv bisphosphonate market (2% in 2007). However, if iv Bondronat had been included the conclusion might have been very similar. The SPCs for both oral and iv Bondronat stated that 'according to clinical assessment of the individual patient, it is recommended that renal function, serum calcium, phosphate and magnesium should be monitored in patients treated with Bondronat'. Dose reduction of either oral or iv Bondronat was recommended only for patients with severe impairment (creatinine clearance <30 ml/min). In contrast, the zoledronic acid SPC recommended measurement of serum creatinine prior to each dose and dose reduction was recommended in both mild and moderate renal impairment (creatinine clearance ≥ 30 to ≤ 60 ml/min). Zoledronic acid was not recommended for use in patients with severe

renal impairment and the SPC also recommended that treatment be withheld if renal function had deteriorated (ie a serum creatinine increase of 0.5mg/dl in patients with normal (<1.4mg/dl) baseline values and 1.0mg/dl where baseline was abnormal). The difference in renal monitoring and dose reduction requirements for zoledronic acid and Bondronat led to the different conclusions about overdosing of the two medicines in this audit. The data presented on page 5 referred to substantiable features of two medicines used for the same intended purpose, did not show a lack of balance and was not misleading. Roche denied breaches of Clauses 7.2 or 7.3.

During the inter-company dialogue with Novartis, Roche agreed to quote the recommendation for renal function monitoring from the Bondronat SPC in this piece and this had now been added to Roche's materials.

PANEL RULING

The Panel noted that page 5 detailed Houston *et al*, an interim analysis from 154 patients presented as a poster at an international meeting. The study involved a retrospective review of medical records of 200 patients thus the interim analysis had included only 77% of the intended full data set. The poster did not include any statistical analysis and so it was impossible to know if the results of the study were clinically significant. Some of the claims taken from Houston *et al* might change on analysis of the full data set. The Panel noted that there were differences between Bondronat and zoledronic acid with regard to use in patients with renal impairment.

The Panel noted that there was no mention that Houston *et al* had compared changes in renal function in routine clinical practice with iv zoledronic acid and oral ibandronate. The results did not relate to iv Bondronat. The claims on page 5 which referred to Bondronat, however, did not differentiate between the oral or iv formulation.

The Panel considered that the claims were misleading as alleged. Breaches of Clauses 7.2 and 7.3 were ruled.

5 Question 'Which bisphosphonate will you choose' on page 7 and the subsequent information on that page.

COMPLAINT

Novartis stated that the bullet point in the highlighted box for Bondronat 'With minimal risk of renal function concerns' along with the second bullet point below the linked boxes, 'Time to show a good safety profile', was unbalanced, misleading and unsubstantiated by the evidence provided in breach of Clause 7.2. The statements also failed to adequately reflect the licence for Bondronat which required renal monitoring to make dose adjustments according to renal function (Sections 4.2 and 4.4 of the iv and oral Bondronat SPCs respectively). Stating that Bondronat was in effect safe was in breach of Clause 7.9.

RESPONSE

Roche submitted that the bullet point 'With minimal risk of renal function concerns' was referenced to the data from the large observational study (Meden *et al*) in which patients given prior Bondronat showed no greater incidence of renal impairment than those who were bisphosphonate naïve. This large study of patients in routine clinical practice verified the statements about renal safety in Sections 4.2 and 4.4 of the Bondronat SPC and substantiated the bullet point on page 7. The bullet point 'Time to show a good safety profile' referred to the long-term follow up data over 4 years of Bondronat therapy, which showed a very low level of adverse events and substantiated the 'good safety profile' (McLachlan *et al* 2006). These bullet points were not unbalanced or misleading as they represented the available data. As discussed above, the recommendation in the SPCs to reduce the dose of oral and iv Bondronat in patients with severe renal impairment was not a suggestion that there was any evidence of renal damage with Bondronat and so this did not conflict the bullet points on page 7. This same page also neither claimed nor implied that Bondronat was safe; it referred the reader to the long-term safety profile and suggested there was a 'minimal risk' of renal function concerns. This page was fully referenced, was balanced and capable of substantiation, was not misleading and did not claim that Bondronat was safe. It compared material and relevant features of Bondronat with a medicine for the same intended purpose. It was not in breach of Clauses 7.2 or 7.9.

PANEL RULING

The Panel noted that page 7 was headed 'Which bisphosphonate will you choose?' below which were two boxes of text. The left hand box read ' A bisphosphonate that requires constant monitoring and dosing adjustments to avoid risk of overdosing?' and was linked with 'or' to the second box which read 'Brondronat – an effective bisphosphonate which can be used: Irrespective of renal function; Irrespective of previous bisphosphonate history; With minimal risk of renal function concerns'. Below the boxes of text were five bullet points one of which was 'Time to show a good safety profile'.

The Panel considered that the bullet point 'With minimal risk of renal function concerns' sought to dispel any concerns that a prescriber might have about the renal safety of Bondronat. The Panel further considered that given the context in which it appeared the claim could not be substantiated; some prescribers might assume that there was no

need to consider a patient's renal function either before or during therapy which was misleading. A breach of Clause 7.2 was ruled.

The Panel similarly considered that, given the context in which it appeared, the claim 'Time to show a good safety profile' was misleading. A breach of Clause 7.2 was ruled.

The Panel did not consider that page 7 included a claim that Bondronat was, in effect, safe as alleged. The page referred to the safety profile of Bondronat not just its safety. No breach of Clause 7.9 was ruled

6 The leavepiece as a whole

COMPLAINT

Novartis alleged that the leavepiece when considered as a whole disparaged other companies' medicines and zoledronic acid in particular in breach of Clause 8.1. Throughout the piece there was the story that Bondronat had no renal toxicity issues but that other bisphosphonates had. However the only comparator used was zoledronic acid and the aim of the leavepiece was to question the renal safety of zoledronic acid particularly and to state or suggest Bondronat had no renal toxicity issues. Questions like 'Are you confident your choice of bisphosphonate is not putting patients at risk of renal damage?' and statements like 'the choice of a particular bisphosphonate for patients with metastatic bone disease should be based not only on efficacy but also the risk for renal deterioration' and 'Could many bisphosphonate patients be receiving too high a dose?' clearly attempted to disparage iv zoledronic acid. This was compounded by the fact that much of the comparator data was based on oral Bondronat vs iv zoledronic acid and that this was not always clear from the statements and data presented.

Finally, Novartis alleged that the leavepiece, as a whole, presented such a serious issue as to be in breach of Clause 2. Within its 8 pages there were multiple breaches of Clause 7 and attempts to disparage zoledronic acid. There was a clear failure to maintain the high standards expected in the promotion of medicines because of this and because of the inappropriate use of studies. Even more serious there were points which disparaged health professionals and questioned their judgement and opinions. The use of data inappropriately with the potential to mislead prescribers and promote the irrational use of Bondronat that might lead to its use outside the product's licence (see Section 4.2 of the SPC and the need for dose adjustments for patients with renal deterioration) leading to very serious patient safety concerns. Also recognising the responses received from Roche in inter-company dialogue there seemed to be little understanding or recognition of the requirements of the Code. This as a whole discredited the pharmaceutical industry and reduced confidence in the industry.

Novartis noted that Roche made much of the fact that many of the statements in the leavepiece were questions which allowed a representative to introduce the piece and initiate discussion. Novartis was concerned that Roche's position in presenting such unbalanced information in the style and format of this leavepiece raised concerns as to what representatives were briefed to say in their ongoing discussions. Novartis therefore considered that the briefing material to sales representatives on how to use this leavepiece should also be central to the Authority's consideration of the balance of this piece.

RESPONSE

Roche submitted that Novartis' allegation that the leavepiece disparaged other companies' medicines and sought to question the renal safety of zoledronic acid in particular, was unfounded. The leavepiece used accurate and balanced comparisons of Bondronat with other medicines which were prescribed for the same intended purpose. The piece raised the question of whether sufficient renal function monitoring was performed in order to administer both Bondronat and zoledronic acid at the doses recommended in their SPCs. It did not seek to exaggerate the difference between the medicines, by setting out aspects of those SPCs. For example, although Section 4.4 of the SPC for Bondronat stated 'Clinical studies have not show evidence of deterioration in renal function with long term Bondronat therapy' and Section 4.4 of the zoledronic acid SPC stated 'renal deterioration, progression to renal failure and dialysis have been reported in patients after the initial dose or a singe dose of Zometa', Roche did not believe it was appropriate to include such statements in the piece.

Novartis also suggested that the leavepiece sought to show that Bondronat alone had no renal toxicity issues, while other medicines did. However, the piece neither claimed, nor attempted to give the impression that there was no renal toxicity with Bondronat and Roche showed clearly, on page 6 of the piece, that the iv dose should be given more slowly in mild renal impairment and both iv and oral doses should be reduced in severe renal impairment.

Novartis also complained that there was a lack of clarity about where oral Bondronat was compared with iv zoledronic acid. In terms of the requirement for renal monitoring and dose reduction for renal impairment, the SPC for oral and iv Bondronat were identical and for both formulations the same statement about lack of 'evidence of deterioration in renal function' was included in the SPC. Therefore in this leavepiece, with its emphasis on renal safety, renal monitoring and dose reductions, it was immaterial whether the data were generated with oral or iv Bondronat although the former was, with iv zoledronic acid, the most frequently used

bisphosphonate in UK hospitals. Roche therefore rejected the allegation of a breach of Clause 8.1.

Novartis also suggested that the leavepiece represented such a serious issue that it was in breach of Clause 2. This was based on the numerous alleged breaches of Clause 7 in the piece, the inappropriate use of studies and disparagement of prescribers and attempts to promote the use of Bondronat outside its product licence, leading to serious patient safety concerns. Roche believed it had shown, in the points above, that none of the alleged breaches of Clause 7 could in fact be substantiated. Moreover, the leavepiece did not disparage prescribers; the only statement which questioned prescribing habits 'lack of routine renal function monitoring results in frequent overdosing with zoledronic acid' (page 5) was a direct quotation from Houston *et al*, and used at the very specific request of the author who was a UK opinion leader in the use of bisphosphonates in metastatic breast cancer. Roche had not attempted to promote the use of Bondronat outside its licence in breast cancer patients with bone metastates and it clearly showed, in the table on page 6, the dosing recommendations for patients with all grades of renal impairment.

Roche took its obligations to ensure the renal safety of patients treated with Bondronat extremely seriously, as witnessed by instructions to its field force to recommend that clinicians monitored renal function in all patients before therapy. This instruction was made when Roche knew that the interim results of Houston *et al* demonstrated a lack of renal monitoring in routine practice in some centres. Had Roche not acted promptly to try and ensure adequate monitoring of Bondronat patients and had it not also brought the lack of renal function monitoring to Novartis's attention, it might be possible to suggest that Roche's conduct was likely to endanger patient safety and bring the industry into disrepute. However, in the present case and with regards to the disputed leavepiece, Roche categorically rejected the allegation of a breach of Clause 2.

PANEL RULING

Although noting its rulings above, on balance the Panel did not consider that overall the leavepiece had disparaged zoledronic acid or the activities of other pharmaceutical companies as alleged. No breach of Clause 8.1 was ruled.

The Panel further did not consider that the leavepiece brought discredit upon or reduced confidence in the pharmaceutical industry as alleged. No breach of Clause 2 was ruled. Clause 2 was a sign of particular censure and reserved for such.

Complaint received **13 January 2009**

Case completed **4 March 2009**