CASE AUTH/2246/7/09

# ROCHE/DIRECTOR v NOVARTIS

## Zometa leavepiece

**Roche complained about a leavepiece for Zometa (intravenous (iv) zoledronic acid) issued by Novartis. Zometa was indicated, *inter alia*, for the prevention of skeletal related events (SREs) in patients with advanced malignancies involving bone. The leavepiece was about metastatic breast cancer.**

**As Roche had alleged a breach of undertaking this aspect of the complaint was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings.**

**The detailed response from Novartis to each allegation is given below.**

**Roche alleged that the strapline, 'Protects them to the bone', directly and indirectly implied that Zometa prevented bone metastases from occurring in the first place, rather than preventing SREs, such as fractures, in breast cancer patients already diagnosed with advanced malignancies involving bone. Roche alleged that the strapline was all-embracing, ambiguous and incapable of substantiation.**

**Further, Roche alleged that the strapline could be seen as a 'teaser' to elicit interest in the expected licence for Zometa as adjuvant therapy to prevent bone metastases, which the European Medicines Evaluation Agency (EMEA) was currently considering. Study data supporting this application had been presented to several major oncology congresses and were therefore familiar to many of the leavepiece's audience. This constituted promotion of a medicine in an area where it did not have a marketing authorization. Moreover, the strapline failed to maintain high standards and brought discredit upon and reduced confidence in the industry in breach of Clause 2.**

**The Panel noted that the front page of the leavepiece was headed 'Fight skeletal destruction with Zometa'. Attached to a stylised picture of a hip joint with a bone metastases and apparent radiating fractures was the claim 'Patients with metastatic breast cancer lead a fragile existence Handle with Zometa'. The product logo and strapline at issue, 'Protects them to the bone' appeared in the bottom right hand corner.**

**The Panel noted that Zometa was currently indicated, *inter alia*, to prevent SREs in patients with advanced malignancies involving bone. The Panel noted the target audience for the leavepiece but nonetheless considered that the strapline was ambiguous. Some readers might consider that it meant that Zometa could be used to protect bone from metastases and this was not so. Some readers might be familiar with reports of the antimetastatic activity of zoledronic acid (Gnant *et al* 2008). Overall the Panel considered that the meaning of the strapline was opaque such that it was inconsistent with the SPC and a breach of the Code was ruled. This ruling was upheld upon appeal by Novartis. The Panel did not consider that the strapline amounted to promotion prior to the grant of the marketing authorization and no breach of the Code was ruled. The promotion of an unlicensed indication was prohibited by the Code and thus covered by the Panel's ruling above. The strapline was misleading and not capable of substantiation and as a result did not encourage the rational use of the medicine. Breaches of the Code were ruled which were upheld on appeal by Novartis. The strapline was not a teaser as the medicine was available and information about it had been given. Although the Panel considered that overall high standards had not been maintained and a breach of the Code was ruled this was overturned on appeal by Novartis. The Panel considered that the strapline in itself had not failed to recognise the special nature of medicines and the professional standing of the audience. Nor was it likely to cause offence. No breach of the Code was ruled. Clause 2 was used as a sign of particular censure and reserved for such use. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2; no breach of the Code was thus ruled.**

**The claim 'Zometa reduces the risk of SREs' appeared as the heading to page two of the leavepiece which depicted a Forest plot headed 'Overall risk of skeletal events in advanced cancer by individual drug at recommended dosing'. The claim was referenced to Pavlakis *et al* (2005) a Cochrane Review on Bisphosphonates for Breast Cancer. The Forest plot included risk reduction figures and p values from a number of studies for Zometa, iv pamidronate, iv ibandronate, oral ibandronate and oral clodronate vs placebo or no treatment. A footnote below the Forest plot stated that it was adapted from Pavlakis *et al* and that 'Original trials may have had different endpoints'.**

**Roche was concerned about the context in which the claim 'Zometa reduces the risk of SREs' was used. The Zometa trial shown in the Forest plot included only 228 Japanese women for whom no other bisphosphonates were available at that time. As this population was not comparable with that in the UK why should it alone be used to promote a UK medicine when other Level 1 evidence in a European population was available? This**

**constituted cherry picking of data.**

**Roche alleged that if, as submitted by Novartis, the heading was clearly supported by line 1 in the Forest plot, then only the top row of the Forest plot, which related to Zometa (Kohno *et al* 2005) needed to be included. Pavlakis *et al* was a meta-analysis of bisphosphonates as a class and was not designed to draw comparisons between the various bisphosphonates. Roche alleged the overall impression created by the page implied a comparison between Zometa and other bisphosphonates and a claim for superior efficacy which the authors had not intended. Therefore, 'Zometa reduces the risk of SREs' in the context in which it was used was an unbalanced reflection of the data presented, misled the reader and was incapable of substantiation by Pavlakis *et al* to which it was referenced. The page did not include data solely on Zometa and the title did not make it clear that the graph related to bisphosphonates as a whole.**

**The Panel considered that the heading 'Zometa reduces the risk of SREs' in itself was not unreasonable. The allegations related to the page as a whole ie the combination of the heading and the Forest plot. The Panel did not consider that it was necessarily cherry picking of the data to include data from Kohno *et al* as cited in Pavlakis *et al* in the leavepiece rather than the other data cited by Roche. The Panel noted that patients in Kohno *et al* were within the Zometa licence and relevant to the leavepiece at issue ie they were women with stage IV breast cancer with at least one osteolytic bone metastasis. No breach of the Code was ruled.**

**Nor did the Panel consider that the heading 'Zometa reduces the risk of SREs' necessarily meant that only Zometa data could be shown. The Panel considered however that the Forest plot invited a direct comparison between Zometa and the other bisphosphonates shown; Zometa appeared to reduce the risk of SREs more than the other products mentioned. This was not the intention of the cited reference. The Panel considered this aspect was covered in another matter below. On the narrow basis that readers would understand that the Forest plot related to data for a number of bisphosphonates bearing in mind that there was a separate heading to the Forest plot and the medicines were identified the Panel ruled no breaches of the Code.**

**Roche alleged that only the first line of the Forest plot (Kohno *et al*) was relevant to the leavepiece about the use of Zometa in patients with metastatic bone disease from breast cancer. The rest of the Forest plot did not need to be used as it did not pertain to, or substantiate, the efficacy of Zometa, and was a breach of the Code.**

**The modifications and omissions made to the Forest plot were not necessary to comply with the Code; they exaggerated the relative efficacy of zoledronic acid and implied that statistically and clinically Zometa was better than the other bisphosphonates listed. The modifications distorted as to the significance of the study and gave a visually misleading impression. Modifications that Roche alleged to be in breach were the use of footnotes, inclusion of the red arrows not found in the original publication, the emphasis made to Zometa by highlighting it red, and omission of the patient numbers and weightings for every study. Roche explained that the original Forest plot depicted the relative efficacy of each bisphosphonate at its recommended dose(s) compared with placebo or no bisphosphonate and this was stated as part of the heading in the same font size as the text within the plot. In the adapted Forest plot, this part of the heading had been made into a footnote in a font size smaller than the main text. Therefore, it did not make it adequately clear that the depicted relative risk reduction of each bisphosphonate was vs placebo or no bisphosphonate. Further, the confidence intervals for Zometa and pamidronate almost completely overlapped as was the case for the other bisphosphonates depicted. As such, there was no statistical basis for inviting a comparison as was denoted by the red arrows added to the diagram to show risk reduction. In Case AUTH/2168/9/08 the Panel advised both parties of confidence interval overlap and lack of comparator statement and stated that no ruling could be made at that time as it had no complaint on these points. The fact that Novartis had ignored the Panel's concerns breached the spirit of the Code.**

**Further, the published Forest plot showed the patient numbers for every study. This was reflected in the size of the boxes depicting the relative risk and so the size of the studies relative to one another was clear and transparent. In Case AUTH/2168/9/08, the Panel ruled that Novartis had breached the Code because it had not reproduced the 'relative risk' boxes in this plot as in the original diagram in the Cochrane review or included the sample size of every study. The Forest plot in the leavepiece now at issue did not include the sample size of the treatment or control groups from any of the studies. Furthermore, the varying sizes of the boxes did not accurately reflect the size of the boxes in the original publication, as the box for Zometa was still larger, relative to the other boxes, than in the original paper. In addition, the red box for Zometa gave it undue prominence, relative to the black boxes for all the other medicines. Roche thus believed the immediate impression created by the Forest plot in the leavepiece was misleading. The Forest plot also disparaged other companies' products. In addition, Novartis' failure to modify the Forest plot according to the ruling in Case AUTH/2168/9/08 was a breach of undertaking in breach of Clause 2.**

**Roche believed that Novartis had used the Forest plot to claim superior efficacy by inviting a comparison of Zometa with the other bisphosphonates. Nowhere had Novartis stated that there were no randomized, controlled,**

**comparative trials as suggested by the Panel in Case AUTH/2168/9/08. The Panel had also acknowledged that the objective of Pavlakis *et al* was to examine bisphosphonates as a class; it was not designed to draw distinctions between any of the medicines studied. This was contrary to the visual impression created and failed to reflect all the available evidence. By using the Forest plot in this manner, Novartis had ignored the Panel and the spirit of the Code.**

**Roche alleged that, given all of the points raised by the Panel in Case AUTH/2168/9/08, the continued use of the adapted Forest plot from Pavlakis *et al* demonstrated Novartis' disregard for the spirit and letter of the Code in breach of its undertaking and as such in breach of the Code including Clause 2.**

**The Panel noted that Roche alleged that including data for bisphosphonates other than Zometa beneath the heading 'Zometa reduces the risk or SREs' was a breach of the Code. The Panel noted its ruling above. The Panel considered that the inclusion of data for other products beneath the claim was not unacceptable per se and on the narrow grounds alleged no breach of the Code was ruled.**

**With regard to the modification of the Forest plot, the Panel noted that the version in the leavepiece had a 'Risk Reduction' column added and for each product a percentage figure for the risk reduction was cited in a downward red arrow. The published Forest plot included only the risk ratio (plus 95% confidence intervals). The risk ratios were cited in an untitled column before the column headed 'Risk Reduction'. The Panel considered that the leavepiece did not faithfully reproduce the published Forest plot and had not been modified for the purpose of complying with the Code. A breach of the Code was ruled. This ruling was not appealed.**

**The Panel examined its rulings in the previous case, Case AUTH/2168/9/08, and reproduced relevant extracts which appeared in the full Panel ruling below.**

**The Panel considered the Forest plot in the leavepiece at issue in this case was different to the one at issue in Case AUTH/2168/9/08. The heading in the leavepiece 'Zometa reduces the risk of SREs' was different to the exhibition panel previously at issue which stated 'Zometa reduces the risk of SREs more than any other bisphosphonate in advanced breast cancer.'**

**The leavepiece included some indication of size of the patient population by means of reproducing the size of various boxes used in the original publication. No actual patient numbers were included in the leavepiece although these were given in the published Forest plot.**

**The Panel noted that in Case AUTH/2168/9/08 the Forest plot was only ruled in breach in relation to the narrow allegation that it had been adapted so that all of the studies appeared to contain a similar number of patients in an attempt to mislead the reader that they all carried the same weight in breach of the Code. Novartis submitted that this had been addressed by the inclusion of the various sized boxes to reflect the sample sizes. The Panel considered, however, that this was insufficient as the prominent downward red 'risk reduction' arrows for each bisphosphonate were all of an equal size. In that regard the Forest plot misled as to the comparative size of the studies as before and a breach of the Code was ruled. In the Panel's view this represented a breach of the undertaking given in Case AUTH/2168/9/08; high standards had not been maintained. Breaches of the Code were ruled. Upon appeal by Novartis the Appeal Board noted the differences between the Forest plot now at issue, the Forest plot at issue in Case AUTH/2168/9/08 and the Forest plot as published by Pavlakis *et al*. The Appeal Board also noted the Panel's rulings in Case AUTH/2168/9/08. Turning to the current case, Case AUTH/2246/7/09, the Appeal Board noted that the promotional item at issue was a leavepiece which contained limited information. In the Appeal Board's view, Forest plots were a sophisticated way of presenting data and some readers would require a degree of explanation before they fully understood the data presented. The Appeal Board noted that Novartis had not appealed the Panel's ruling that the leavepiece did not faithfully reproduce the published Forest plot and had not been modified so as to comply with the Code. The Appeal Board considered that the Forest plot was misleading with regard to the comparative size of the studies as before; the downward red arrows added to this misleading representation. The Panel's rulings were upheld. The Panel considered that the failure to comply with the undertaking was such that Novartis had brought discredit upon and reduced confidence in the pharmaceutical industry; a breach of Clause 2 was ruled. Upon appeal by Novartis, however, the Appeal Board considered that some effort had been made to comply with the undertaking and the Panel's ruling was overturned. No breach of Clause 2 was ruled.**

**The Panel noted Novartis' submission as to how it had changed its material to take account of the previous ruling. The Panel noted, however, that its rulings had to reflect the complainant's allegations and the Panel's lack of comment about an aspect did not imply approval. In making its rulings the Panel could also not state precisely how a piece should be changed; it could not, in effect, pre-approve material.**

**The Panel noted that it had expressed concern about the impression of the exhibition panel in Case AUTH/2168/9/08. In the Panel's view it was clear that although it had only been able to make a ruling on the narrow grounds of the complaint it considered that any claim for superiority for Zometa vs other bisphosphonates, however depicted, could not be substantiated using the**

**Forest plot from Pavlakis *et al*. There had been no allegation in this regard and thus no rulings had been made. Thus in the case now before it, Case AUTH/2246/7/09, there could be no breach of undertaking in this regard and therefore no breaches of the Code including Clause 2 was ruled.**

**The Panel was extremely disappointed that it appeared that Novartis had not taken notice of the Panel's wider comments in Case AUTH/2168/9/08 about the Forest plot. This was disingenuous and unacceptable. The fact that the heading had been changed did not in the Panel's view mean that the Forest plot in itself did not imply superiority for Zometa vs the other bisphosphonates listed. In the Panel's view any graph/diagram etc which incorporated data for a number of medicines inevitably invited a direct comparison of those medicines. The leavepiece at issue thus visually misled the reader; it invited a direct comparison between the products and implied superiority of Zometa vs other bisphosphonates. It was not known if the differences between the products were statistically or clinically significant. Pavlakis *et al* was not designed to draw distinction between any of the medicines contrary to the impression given. The Panel ruled breaches of the Code. The Panel considered that the Forest plot in the leavepiece disparaged other companies' products. A breach of the Code was ruled.**

**Roche stated that on 13 March 2009, one of its employees, a pharmacist, had asked Novartis to email a copy of a poster, Hoer *et al* (2005), cited as a supporting reference in the leavepiece, but nothing was received. After the third request a 2005 conference abstract, but not the poster, was provided twelve working days from the date of the original request. The first time the pharmacist received the actual poster was as an attachment to Novartis' inter-company correspondence dated 11 May. Roche alleged that Novartis' failure to supply the references to support the claims made in its leavepiece within ten working days was in breach of the Code.**

**In addition, on 2 April 2009 the pharmacist requested another poster (Heatley *et al*, 2006) also referenced in the leavepiece. Novartis supplied an abstract but a second request for the poster was not acknowledged. The first time the poster was provided was as an attachment to the letter from Novartis dated 11 May, over a month after the original request, again in breach of the Code.**

**The abstracts did not substantiate the claims in the leavepiece. Roche alleged that as the pharmacist was a health professional and entitled to be provided, within ten working days, with information to substantiate materials, as outlined in the Code, Novartis had failed to maintain high standards in breach of the Code including Clause 2.**

**As Novartis was unable to provide the first poster in a timely manner, Roche conducted a literature search and found a 2006 analysis of the study with data which differed from that published in the 2005 abstract. As the most recent Hoer *et al* data had not been used, Roche alleged that the data had been cherry-picked.**

**The Panel noted that there was no exemption for proof of substantiation to be provided within ten working days for health professionals employed by pharmaceutical companies. The Panel was sympathetic to Novartis' view that its medical information department would prioritise requests from clinicians. With regard to the provision of Hoer *et al*, there appeared to be a difference between the parties; Roche stated that it had only received the poster as part of the inter-company dialogue and Novartis stated that the abstract had been sent on 20 and 30 March. According to Novartis, Hoer *et al* (2005) had been incorrectly cited in the leavepiece by omitting to state the material was a poster.**

**The Panel noted that Novartis had provided the Hoer *et al* abstract to Roche on 30 March. It was not entirely clear from Novartis' records exactly what had been sent. An allegation that the abstract failed to substantiate the claims would be considered below. Substantiation had been sent by post within ten working days and followed up by email when Roche contacted Novartis again. It appeared that the copy sent in the post had not been received. In the circumstances the Panel ruled no breach of the Code.**

**Novartis accepted that the second poster had not been sent. As Roche had, in effect, requested substantiation, the Panel ruled a breach of the Code as substantiation had not been provided in response to a request from a health professional. The Panel did not consider that the failure to supply the poster meant that high standards had not been maintained nor that Novartis had brought discredit upon or reduced confidence in the pharmaceutical industry. No breach of the Code including Clause 2 was ruled.**

**The Panel noted the difference between Hoer *et al* (2005) and the 2006 data, this being 1% more patients still on therapy at 6 months ie 36% in 2006 instead of 35% in the 2005 publication. The Panel did not accept that Novartis had cherry-picked the data as alleged. No breach of the Code was ruled.**

**Roche noted that page 3, headed 'There are compliance issues with oral bisphosphonates', featured a graph headed 'Compliance with oral bisphosphonates' which depicted discontinuation rates at 3 months (44%) and 6 months (65%). The graph was adapted from the poster Hoer *et al* and was a retrospective observation study of health insurance claims. Roche considered the presentation of the data from Hoer *et al* was misleading. The leavepiece was for use with health professionals involved in the treatment and management of patients with metastatic bone disease from breast cancer. Hoer *et al* could not substantiate claims about such patients as it**

**comprised a mixed population of men and women with differing diagnoses only 58/497 (11.7%) of which had breast cancer with bone metastases. Evidence suggested that adherence and persistence to oral therapy was better in cancer patients vs patients who had non-oncological chronic disease. Furthermore, it was not possible from the data reported in the poster to know which treatments the patients with breast cancer received; and because the persistency rates were not reported by diagnosis it was not clear from the poster or leavepiece what the persistency rate was in the 58 breast cancer patients with metastatic bone disease. The claims made from this reference were misleading and not substantiated by the data supplied.**

**The Panel noted that Hoer *et al* was a retrospective observational study using data from health insurance claims. Not all the patients had advanced malignancies involving bone. 109 of the 497 patients had bone metastasis. There were a number of limitations listed including that the analysis was limited to the outpatient prescriptions of oral bisphosphonates. The study stated that the risk of being not persistent with therapy was higher for patients with bone metastasis than without such a diagnosis.**

**The Panel noted that only one of the four oral bisphosphonates used, clodronate, was licensed in the UK for use in cancer patients with bone metastases. The only other oral bisphosphonate so licensed in the UK was Roche's product Bondronat, but this had not been included in the study.**

**The Panel considered that the heading 'There are compliance issues with oral bisphosphonates' was not unreasonable per se. The Panel considered, however, that given the leavepiece was specifically about patients with metastatic breast cancer the graph would be assumed to apply to the use of bisphosphonates available in the UK for the prevention of SREs in that patient group. The data was not so limited and thus the graph and specific discontinuation claims at 3 and 6 months were misleading and had not been substantiated. Breaches the Code were ruled. The Panel did not consider that the comparison between iv Zometa and oral bisphosphonates was misleading per se and no breach of the Code was ruled. The graph did not give a fair and balanced view of the data and thus a breach of the Code was ruled.**

**Roche considered that the heading 'There are compliance issues with oral bisphosphonates', use of Hoer *et al* and the overall impression created when page 3 was viewed with the Forest plot on the facing page, was that all oral bisphosphonates were the same which was all-embracing, incapable of substantiation, created confusion and misled the reader both by the visual impression given and as to the significance of Hoer *et al*. The title disparaged oral Bondronat, as the market leading oral bisphosphonate, by the overall impression created and the all-embracing claims. Roche alleged that use of these data in this manner was inappropriate, failed to maintain high standards and brought discredit to the pharmaceutical industry.**

**The Panel noted its comments about Hoer *et al* and its rulings above which covered many of the allegations here. The Panel considered that the heading in the context of the graph was disparaging and all-embracing. Breaches of the Code were ruled.**

**The Panel noted that the leavepiece was clearly promotional material and not sponsored material and it ruled no breach of the Code.**

**The Panel considered that high standards had not been maintained and ruled a breach of the Code. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 and ruled accordingly.**

**Roche noted that directly beneath the graph on page 3 were the following three quotations; 'Because IV bisphosphonates are administered in a hospital or infusion centre, compliance with therapy is not a concern' (Heatley *et al*); 'Oral administration requires precautionary measures to ensure absorption and – for some [bisphosphonates] – to avoid gastrointestinal adverse events' (Aapro *et al*) and 'If not taken properly, oral bisphosphonates can cause a high incidence of [gastrointestinal] adverse events, including esophagitis, mucositis, nausea, vomiting and diarrhoea, and may exacerbate this side effects of anticancer therapy' (Conte and Guarneri).**

**Roche believed readers would consider the quotations immediately below the graph from Hoer *et al* to directly refer to that study. Roche alleged that the quotation, 'Oral administration requires precautionary measures to ensure absorption and – for some [bisphosphonates] – to avoid gastrointestinal adverse events', was taken out of context. Particularly as the sentence following it was referenced to a study about compliance of bisphosphonate therapy in patients with osteoporosis rather than metastatic bone disease from breast cancer. Roche alleged that the quotations and the context in which they were used were misleading as they did not accurately and clearly reflect the studies in question nor the overall meaning of the authors. The quotations were taken out of context, unbalanced, misled as to their overall significance and disparaged oral Bondronat. This did not allow the reader to form their own opinion of the therapeutic value of oral bisphosphonates for the treatment of patients with metastatic bone disease and thereby failed to maintain high standards. The quotations were misleading, disparaging and cherry picked the data.**

**The Panel considered that it was clear from the leavepiece that the quotations were from different studies. The Panel did not consider that the readers would assume that the quotations applied to the**

**discontinuation data from Hoer *et al*. In the Panel's view the quotations referred to general compliance issues with oral bisphosphonates.**

**The Panel did not agree that the quotation from Aapro *et al* was out of context given the next sentence referred to its use in oestoporosis. Precautions to ensure absorption of oral bisphosphonates and to avoid gastrointestinal events would apply whatever the diagnosis. Oral Bondronat was to be taken after an overnight fast of at least six hours and before the first food or drink of the day. Fasting had to continue for at least 30 minutes after taking the tablet and patients should not lie down for 60 minutes after taking the tablet. The Panel did not consider that the quotations disparaged Bondronat. Nor were they misleading or cherry picking the data as alleged. The Panel ruled no breach of the Code. The quotation was faithfully reproduced and accurately reflected the meaning of the authors. No breach of the Code was ruled.**

**The Panel did not consider that the quotation from Heatley *et al* 'Because IV bisphosphonates are administered in a hospital or infusion centre, compliance with therapy is not a concern' had been taken out of context or was misleading. No breach of the Code was ruled. The quotation was clearly about iv bisphosphonates and not linked to the Hoer *et al* data in the graph above it. The Panel did not consider that the quotation was clearly cherry picking of the data as alleged or that it disparaged Bondronat as alleged. No breach of the Code was ruled. In the Panel's view the quotation was faithfully reproduced and accurately reflected the meaning of the authors. No breach of the Code was ruled. The alleged breach of the Code in relation to the Heatley study was considered above.**

**The Panel similarly considered that the quotation from Conte and Guarneri had not been taken out of context, was not misleading and did not disparage Bondronat. In the Panel's view the quotation accurately reflected the meaning of the authors. No breaches of the Code were ruled.**

Roche complained about a leavepiece for Zometa (intravenous (iv) zoledronic acid) issued by Novartis. Zometa was indicated, *inter alia*, for the prevention of skeletal related events (SREs) (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcaemia) in patients with advanced malignancies involving bone. The leavepiece was about metastatic breast cancer.

Roche marketed iv and oral Bondronat (ibandronic acid). Both formulations were indicated for the prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases.

Inter-company dialogue had not been successful.

As Roche had alleged a breach of undertaking this aspect of the complaint was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings.

**1 Strapline 'Protects them to the bone'**

The strapline appeared as part of the Zometa brand logo on pages 1 and 3 of the leavepiece.

**COMPLAINT**

Roche alleged that the strapline 'Protects them to the bone' directly and indirectly implied that Zometa prevented bone metastases.

As stated in the prescribing information Zometa was licensed for the treatment of tumour-induced hypercalcaemia and prevention of SREs in patients with advanced malignancies involving bone. The word 'to' expressed motion or direction toward a point, person, place, or thing approached and reached. Therefore, 'Protects them to the bone' could be interpreted to mean that Zometa prevented bone metastases from occurring in the first place, rather than preventing SREs, such as fractures, in breast cancer patients already diagnosed with advanced malignancies involving bone. This misled the reader both by distortion and exaggeration, potentially leading to inappropriate and unfounded expectations on the part of the health professional and patient in terms of the clinical value and impact of Zometa. Roche alleged that the strapline was all-embracing, ambiguous and incapable of substantiation in breach of Clauses 7.2, 7.4 and 7.10.

In addition, Roche did not believe that this potential meaning of the strapline was substantiated by the Zometa summary of product characteristics (SPC). It could be interpreted as a 'teaser' to elicit interest in the expected licence for Zometa adjuvant therapy to prevent bone metastases, which was currently being considered by the European Medicines Evaluation Agency (EMEA). This application was based on study data which had been presented to several major oncology congresses (Gnant *et al* 2008, Gnant *et al* 2009, Ougari *et al* 2009) and were therefore familiar to many of the leavepiece's audience.

This constituted promotion of a medicine in an area where it did not have a marketing authorization in breach of Clauses 3.1, 3.2, 9.1 and 9.2. Moreover, the strapline failed to maintain high standards and brought discredit upon and reduced confidence in the industry in breach of Clause 2.

**RESPONSE**

Novartis believed that Roche had misinterpreted the strapline 'Protects them to the bone'. 'To' reflected the rapid take up and binding of Zometa to mineralised bone as substantiated by pharmacokinetic data cited in Section 5.2 of the Zometa SPC ie 'Over the first 24 hours, 39 ± 16% of

the administered dose is recovered in the urine, while the remainder is principally bound to bone tissue'.

During inter-company dialogue Roche referred to the phrase as 'could be misinterpreted', demonstrating that this was its interpretation. Novartis considered that clinicians experienced in the use of bisphosphonates would consider the strapline only in relation to the prevention of SREs and treatment of tumour-induced hypercalcaemia. Both indications were within Zometa's current licence.

Novartis submitted that Roche's interpretation that the strapline meant that Zometa prevented bone metastases from occurring was a further misinterpretation and misrepresentation of its meaning. Even if Roche's interpretation of the strapline was to cover an anti-tumour effect, which was not Novartis' use or view of the strapline, Novartis noted that Section 5.1 of the Zometa SPC stated; 'In addition to being a potent inhibitor of bone resorption, zoledronic acid also possesses several anti-tumour properties that could contribute to its overall efficacy in the treatment of metastatic bone disease'. Therefore, the data would substantiate the concern raised by Roche.

Novartis noted that there should be a reasonable expectation that competitors only complained if, having fully researched and considered all associated evidence, they continued to have a reasonable belief that claims could not be substantiated or that health professionals were being misled. This thorough evaluation of all the information did not appear to have been the case here.

In preventing SREs, Zometa clearly offered bone protection. This was supported by Section 5.1 of the SPC and the results of several randomised controlled trials. The Panel had noted in Case AUTH/2168/9/08 that the selective action of bisphosphonates on bone was based on their high affinity for mineralised bone. The use of the word 'protects' was clearly in the context of protecting patients from the effects of both tumour-induced hypercalcaemia and SREs in patients with advanced malignancy.

Novartis firmly rejected Roche's allegation that the strapline was a 'teaser' to elicit interest in the expected licence for Zometa as adjuvant therapy to prevent bone metastases.

Novartis did not believe that the strapline was in breach of Clause 9.1 or 9.2 as there was no reasonable expectation that a health professional would draw the same conclusions as Roche. As such it did not tease the recipient by eliciting an interest in something which would follow, or would be available at a later date, without providing any actual information about it (supplementary information to Clauses 9.1 and 9.2). Furthermore the strapline did not promote any future licence, real or perceived. As the strapline could be substantiated by the Zometa licence and the SPC, Novartis denied breaches of Clauses 2, 3.1, 3.2, 7.2, 7.4, 7.10, 9.1 and 9.2.

**PANEL RULING**

The Panel noted that the front page of the leavepiece was headed 'Fight skeletal destruction with Zometa'. Attached to a stylised picture of a hip joint with a bone metastases and apparent radiating fractures was the claim 'Patients with metastatic breast cancer lead a fragile existence Handle with Zometa'. The product logo and strapline at issue, 'Protects them to the bone' appeared in the bottom right hand corner.

The Panel noted that Zometa was currently indicated, *inter alia*, to prevent SREs in patients with advanced malignancies involving bone. The Panel noted the target audience for the leavepiece but nonetheless considered that the strapline was ambiguous. Some readers might consider that it meant that Zometa could be used to protect bone from metastases and this was not so. Some readers might be familiar with reports of the antimetastatic activity of zoledronic acid (Gnant *et al* 2008). Roche had submitted that Zometa as adjuvant therapy to prevent bone metastases was being considered by the EMEA although Novartis had not commented on this point. Overall the Panel considered that the meaning of the strapline was opaque such that it was inconsistent with the SPC and a breach of Clause 3.2 was ruled. The Panel did not consider that the strapline amounted to promotion prior to the grant of the marketing authorization and no breach of Clause 3.1 was ruled. The promotion of an unlicensed indication was prohibited by Clause 3.2 and thus covered by the Panel's ruling above. The strapline was misleading and not capable of substantiation and as a result did not encourage the rational use of the medicine. Breaches of Clauses 7.2, 7.4 and 7.10 were ruled. The strapline was not a teaser as the medicine was available and information about it had been given. The Panel considered that, nonetheless, overall high standards had not been maintained and a breach of Clause 9.1 was ruled. The strapline in itself had not failed to recognise the special nature of medicines and the professional standing of the audience. Nor was it likely to cause offence. No breach of Clause 9.2 was ruled. The Panel noted that Clause 2 was used as a sign of particular censure and reserved for such use. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2; no breach of Clause 2 was thus ruled.

**APPEAL FROM NOVARTIS**

Novartis submitted that the strapline in its current context accurately reflected the marketing authorization for Zometa and was consistent with the SPC. It was not ambiguous or opaque. The strapline appeared initially on the front page of the leavepiece and subsequently on page 3. The front page was entitled 'Fight skeletal destruction with

Zometa'. Attached to a stylised picture of a hip joint with fractures radiating from a bone metastasis was the claim 'Patients with metastatic breast cancer lead a fragile existence. Handle with Zometa'. The product logo and strapline at issue, 'Protects them to the bone', appeared in the bottom right hand corner. The strapline should be interpreted in the context of the page on which it appeared and the leavepiece as whole ie in the setting of metastatic breast cancer where pre-existing metastases lead to bone fracture. This context was clearly stated on the cover and was the main theme of the leavepiece. The leavepiece was designed to tell clinicians what they could do for a patient with metastatic cancer in their bones. Novartis submitted that it could not be read to be about what clinicians could do to prevent the formation of bone metastases. Novartis submitted that the latter interpretation, on which the Panel based its ruling, could not be sustained on the evidence of the leavepiece taken as whole. The stylised picture itself implied that Zometa protected against pathological fractures (SREs) caused by metastases to bone. The picture did not suggest to the target audience of sophisticated hospital specialists that Zometa protected against the formation of metastases. All of this was consistent with the therapeutic indications section of the Zometa SPC (Section 4.1). Such consistency was noted by the Panel but Novartis considered this had not been given sufficient consideration. The strapline should not have been considered in isolation. Consideration should be given to the primary target audience in the first instance rather than a minor ill defined secondary audience who could be misled by the material.

Novartis noted that information on the status of any extension to the licensed indications for Zometa was commercially confidential. Such information could be provided separately in confidence. It was public knowledge that Zometa was under investigation in randomised controlled clinical trials for any potential anti-tumour activity. Gnant *et al* 2008 did not show any statistical improvement in the number of metastases in breast cancer following treatment with Zometa but showed statistical improvements in disease free and progression free survival. Thus, the specialist audience would be sufficiently well informed and not misled into the conclusion that Zometa prevented the spread of tumour cells to the bone. This would be an incorrect inference given the findings of Gnant *et al* (2008) but it was, nevertheless, the conclusion drawn by both Roche and the Panel. Novartis submitted that the Panel's conclusion in this regard could not stand. Novartis did not consider that the target audience was likely to have been misled. Novartis submitted that the leavepiece was not in breach of Clauses 7.2, 7.4 or 7.10 and so would not have breached Clause 9.1.

Novartis submitted that the strapline was consistent with the Zometa SPC. Zometa was indicated to prevent and, therefore, to protect patients against pathological fractures caused by pre-existing bone metastases. This was clearly conveyed in the strapline 'Protects them to the bone'. The close proximity of the prescribing information on page 4 of the leavepiece was also relevant to Novartis' submission that neither the strapline, the picture nor the leavepiece as a whole was misleading or inconsistent with the SPC. The prescribing information clearly stated the indications for which Zometa held a marketing authorization.

Novartis submitted that the strapline 'Protects them to the bone' was wholly consistent and capable of substantiation against the Zometa SPC. The notion of protection conveyed in the strapline was directly and clearly derived from and substantiated by the therapeutic indications section of the Zometa SPC (Section 4.1) which stated: 'Prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcaemia) in patients with advanced malignancies involving bone', and was supported by clinical studies in the SPC. Novartis submitted that 'prevention' implied a pre-emptive effect on the pathological actions of metastases on bone. The statement 'Protects them to the bone' was a natural, reasonable and justifiable interpretation of this pre-emptive action. The SPC was as clear as it could be that Zometa was indicated in the 'prevention' of skeletal related events.

Novartis submitted that the effect on bone was also clearly reflected in and substantiated by the Zometa SPC. Novartis noted that Section 5.1 of the SPC stated 'Zoledronic acid belongs to the class of bisphosphonates and acts primarily on bone. It is an inhibitor of osteoclastic bone resorption. The selective action of bisphosphonates on bone is based on their high affinity for mineralised bone, but the precise molecular mechanism leading to the inhibition of osteoclastic activity is still unclear'.

Novartis submitted that the SPC thus described the high affinity of Zometa both for bone and its strong osteoclastic inhibitory properties which justified use of the word 'bone' in the strapline. 'To' in the strapline also reflected the rapid uptake and binding of Zometa 'to' mineralised bone as substantiated by pharmacokinetic data for Zometa. Section 5.2 of the Zometa SPC stated that following intravenous (iv) infusion with Zometa 'Over the first 24 hours, 39 ± 16% of the administered dose is recovered in the urine, while the remainder is principally bound to bone tissue'. This reflected the rapid take up from the iv compartment 'to' bone and the binding of Zometa 'to' mineralised bone.

Novartis submitted that the strapline 'Protects them to the bone' was, thus, wholly consistent with the Zometa SPC and marketing authorization and properly reflected the scientific studies which underlined those documents as approved by the relevant regulatory authority. Novartis submitted that no breach of Clause 3.2 could be established on these facts.

Novartis submitted that as the claim was fair,

balanced and unambiguous there had been no breach of Clause 7.2. The strapline could be substantiated by the Zometa SPC and, thus, there had been no breach of Clause 7.4. The strapline did not encourage irrational use of the medicine and thus no breach of Clause 7.10. High standards had been maintained and there had been no breach of Clause 9.1.

**RESPONSE FROM ROCHE**

Roche alleged that the licensed patient population of patients with bone metastases was not stated clearly. The most obvious interpretation of 'Protects them to the bone' was prevention of bone metastases which was not consistent with the licensed indication. The claim did not encourage rational use of the medicine. All the points together indicated high standards had not been maintained. Roche alleged that the strapline breached Clauses 3.2, 7.2, 7.4, 7.10 and 9.1.

Novartis argued that the claim 'Protects them to the bone' accurately reflected the Zometa marketing authorization. However, nowhere on the leavepiece (other than in the prescribing information) was it clearly stated that the licensed indication for Zometa was the treatment of patients with advanced malignancies already involving bone. The front page referred to 'Patients with metastatic breast cancer' not 'Patients with metastatic bone disease' or 'Patients with advanced malignancies involving bone' in line with the indication. The Medicines and Healthcare products Regulatory Agency (MHRA) emphasised strongly this key point in its' 'Tips for prevetting of promotional material' ie 'The importance of clearly stating the authorized indication of the product. This helps to ensure that the claims made are set in a clear context.' This point had been emphasised in each of the MHRA's annual reports on advertising. This suggested deficiencies in training and knowledge as well as the thoroughness of the review of materials, and the standards expected by the MHRA had not been maintained. As the indication, and/or population for which Zometa was indicated, was not clearly stated the claims made in the leavepiece were not set in a clear context, which could encourage misinterpretation and inappropriate use of the medicine. High standards did not appear to have been maintained.

A key element of marketing could be wordplay and double meanings; however these should never mislead. Regrettably, as was the convention with straplines, 'Protects them to the bone' was not referenced. Referencing might have provided some clear direction as to Novartis' intention for the interpretation of the claim. Roche submitted that there were at least four possible interpretations of 'Protects them to the bone' some of which were actively misleading:

1 Zoledronic acid targeted bone.
2 An effect in line with the licensed indication to protect against skeletal related events in those with bone metastases.
3 An effect in preventing the development, or prophylaxis, of bone metastases.
4 A more general effect on the tumour and/or metastases generally.

Roche alleged that had the claim been 'Protects bone' then the meaning could have been straightforward and clear. However the inclusion of 'them to' made the claim far less transparent. The key to the interpretation of the claim appeared to lie in the meaning of the word 'to.' Also, in deciding which was the most likely interpretation by health professionals it was important to consider not only the context in the material itself but also the wider context of the scientific literature, congresses and the like. 'To' in the context of the claim could mean 'in the direction of' bone or be the boundary of an effect as in 'soaked to the skin' or 'rotten to the core.' Neither of these was consistent with interpretation 2 above and the licensed indication. The former was consistent with interpretation 3 and the latter with interpretation 4. Contrary to Novartis' appeal Roche did not believe that Zometa's uptake and binding by bone was an obvious interpretation of the claim, because of the construction of the phrase.

Roche alleged that as already discussed this leavepiece did not clearly set out the population for which Zometa was indicated. The patient population stated on the leavepiece in question was 'Patients with metastatic breast cancer.' Patients with metastatic breast cancer might not already have bone metastases and so the interpretation of prophylaxis of bone metastases was certainly likely, if not encouraged. The inclusion of the indication in the prescribing information was insufficient to define the eligible patient population for Zometa given the broader descriptor, 'Patients with metastatic breast cancer', on the front cover. Promotional material itself must comply with Clause 7.2 and be accurate and unambiguous.

Roche alleged that in the wider context beyond the leavepiece, there had been much discussion in the literature, at satellite symposia and conferences of clinical trials to prevent bone metastases, and even data suggesting effects of Zometa on soft tissue metastases and the tumour itself by inducing apoptosis or inhibiting angiogenesis (Aapro *et al* 2008, Bedard *et al* 2009, Winter *et al* 2008, Doggrell 2009, Coleman 2009, Novartis CIBD satellite 2008). Bedard *et al* even suggested that patients receiving adjuvant ovarian suppression should have the possible reductions in the risk of breast cancer relapse discussed with them. Bedard *et al* concluded 'There is reason to believe that newer generation bisphosphonates may deliver greater efficacy [than clodronate] and effects outside bone.' Zoledronic acid was described as providing a hostile soil for the tumour seed. Roche therefore disagreed with Novartis' assertion that the primary target audience would not be misled by the material. A less well informed audience might interpret the claim 'Protects them to the bone'

literally ie Zometa prevented spread of breast cancer to bone. However, a more informed audience would be aware of the data and debate relating to prevention of spread to bone and potential extra-skeletal effects on tumours and interpret the claim in a much broader way.

Roche alleged that Novartis had not adequately addressed the fundamental issues with this claim. It was not obvious what it meant. The literal meaning would constitute promotion outside of the licensed indication in breach of Clause 3.2. It was misleading, not substantiable and did not encourage rationale use in line with the SPC in breach of Clauses 7.2, 7.4 and 7.10. Given the context of the development of Zometa for adjuvant use and the literature in the area, utmost care was required to avoid misinterpretation of claims. This care did not seem to have been taken; high standards were not maintained and a ruling of a breach of Clauses 3.2, 7.2, 7.4, 7.10 and 9.1 was justified.

**APPEAL BOARD RULING**

The Appeal Board noted that the front page of the leavepiece was headed 'Fight skeletal destruction with Zometa'. Attached to a stylised picture of a hip joint with a bone metastases and emerging rays was the claim 'Patients with metastatic breast cancer lead a fragile existence Handle with Zometa'. Some members of the Appeal Board thought the emerging rays signified metatastic activity rather than fractures as described by the Panel. The product logo and strapline at issue, 'Protects them to the bone' appeared in the bottom right hand corner. It also appeared on page 3 of the leavepiece.

The Appeal Board noted that Zometa was currently indicated, *inter alia*, to prevent SREs in patients with advanced malignancies involving bone. The Appeal Board noted that approximately 65% of patients with metastatic breast cancer had bone metastases. It followed, therefore, that approximately 35% of patients with metastatic breast cancer would not have bone involvement; these patients would not be suitable for Zometa therapy. The Appeal Board considered that the front page of the leavepiece did not make it clear that Zometa was indicated to prevent skeletal fracture when bone metastases were already present. Some readers might consider that Zometa could be used to protect bone from metastases and this was not so. Overall the Appeal Board considered that the meaning of the strapline was ambiguous such that it was inconsistent with the particulars listed in the SPC. The Appeal Board upheld the Panel's ruling of a breach of Clause 3.2. The strapline was misleading and not capable of substantiation and as a result did not encourage the rational use of the medicine. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2, 7.4 and 7.10. The appeal on these points was unsuccessful.

The Appeal Board noted its rulings above but nonetheless did not consider that high standards had not been maintained and no breach of Clause 9.1 was ruled. The appeal on this point was successful.

**2 Claim 'Zometa reduces the risk of SREs'**

The claim appeared as the heading to page two of the leavepiece which depicted a Forest plot headed 'Overall risk of skeletal events in advanced cancer by individual drug at recommended dosing'. The claim was referenced to Pavlakis *et al* (2005) a Cochrane Review on Bisphosphonates for Breast Cancer. The Forest plot included risk reduction figures and p values from a number of studies for Zometa, iv pamidronate, iv ibandronate, oral ibandronate and oral clodronate vs placebo or no treatment. A footnote below the Forest plot stated that it was adapted from Pavlakis *et al* and that 'Original trials may have had different endpoints'.

**COMPLAINT**

Roche was concerned about the context in which the claim 'Zometa reduces the risk of SREs' was used.

In inter-company dialogue, Novartis had stated that the heading was supported by Pavlakis *et al* and the Zometa SPC, Section 5.1. This detailed the two clinical trials that supported the licence for the use of Zometa in the prevention of SREs in patients with breast cancer; the placebo-controlled trial by Kohno et al (2005) and a randomized, double-blind trial demonstrating comparable efficacy of zoledronic acid vs pamidronate in the prevention of SREs. Roche questioned why Novartis had not included the Kohno data and the Level 1 evidence from the trial vs pamidronate but instead had presented a meta-analysis which only contained a single study of Zometa and several studies of other agents. The Zometa trial shown in the Forest plot included only 228 Japanese women for whom no other bisphosphonates were available at that time. This population was not comparable with the UK population for which Zometa was being promoted and Roche questioned why this population alone should be used to promote a UK marketed medicine, when other Level 1 evidence in a European population was available. This constituted cherry picking of data in breach of Clause 7.2.

If, as submitted by Novartis, the heading was clearly supported by line 1 in the Forest plot, then only the top row of the Forest plot, which related to Zometa (Kohno *et al*) needed to be included. There was no reason to include the rest of the Forest plot, which did not substantiate the efficacy of Zometa nor was it supported by the heading, unless Novartis intended to make a claim for efficacy of Zometa compared with other bisphosphonates. This was contrary to the Panel's comments in Case AUTH/2168/9/08 and contravened the spirit of the Code. Roche maintained that overall the heading, in conjunction with the Forest plot, suggested superior efficacy of Zometa vs other bisphosphonates. This

was misleading and incapable of substantiation. The Cochrane review was a meta-analysis of bisphosphonates as a class and was not designed to draw comparisons between the various bisphosphonates as highlighted by the Panel in Case AUTH/2168/9/08.

In Case AUTH/2177/10/08 (Allergan vs Merz) the Panel had stated, 'Nonetheless the Panel considered that even when a claim was true the context in which it was used was very important'. Roche believed the overall impression created by the page implied a comparison between Zometa and other bisphosphonates and a claim for superior efficacy which was not the intention of Pavlakis *et al*. Therefore, the heading, 'Zometa reduces the risk of SREs' in the context in which it was used was an unbalanced reflection of the data presented, misled the reader and was incapable of substantiation by Pavlakis *et al* to which it was referenced. The page neither included data solely on Zometa nor made it clear and transparent from the title that the graph related to bisphosphonates as a whole and was in breach of Clauses 7.2 and 7.4.

**RESPONSE**

Novartis considered Roche's statements to be inaccurate and failed to interpret the Code correctly.

Novartis stated that substantiation need not be provided in relation to the licensed indications. Section 5.1 of the Zometa SPC supported the licensed indications. Pavlakis *et al* further supported the heading 'Zometa reduces the risk of SREs' which was an acceptable heading for this page. Use of an independent meta-analysis in promotional material was a well accepted method to demonstrate efficacy of a medicine in a therapeutic field, especially in the absence of head-to-head studies and was accepted by the Panel in Case AUTH/2168/9/08. The data would be considered by the reader under the heading 'Zometa reduces the risk of SREs' and was not, as alleged by Roche, an invitation to compare Zometa with other bisphosphonates. Furthermore, Novartis believed additional comments made by the Panel in Case AUTH/2168/9/08 regarding the meta-analysis graphic related specifically to its use under the heading 'Zometa reduces the risk of SREs more than any other bisphosphonate in advanced breast cancer'.

The leavepiece now at issue was wholly concerned with metastatic breast cancer, and the benefit Zometa might, in that context, have in preventing SREs.

Case AUTH/2177/10/08 was not relevant to this case. There was no attempt to have the reader consider other bisphosphonates in the table presented on Page 2 or claim superior efficacy for Zometa. The data was neither misleading nor an unbalanced reflection of the Cochrane meta-analysis which stated that Zometa was as effective as pamidronate in the prevention of SREs.

Also as recognised by the Panel in Case AUTH/2168/9/08, the Code did not require the claim in question to be referenced. The claim had to be capable of substantiation, not misleading and otherwise comply with the Code. Novartis believed the claim met this requirement and denied breaches of Clauses 7.2 and 7.4.

Novartis believed that in citing Case AUTH/2177/10/08 Roche knew the implications of that case. Novartis was specifically ruled in breach of Clause 7.8 for not using the appropriately sized boxes to reflect the study sample sizes. Therefore Novartis was surprised that in being familiar with this case Roche continued to contend that Novartis had not complied with the undertaking given in Case AUTH/2168/9/08. Roche would be aware that the Appeal Board had noted that no specific ruling had been made with regard to the image and consequently the Appeal Board did not consider that Merz Pharma had breached its undertaking and no breach of the Code was ruled.

**PANEL RULING**

The Panel considered that the heading 'Zometa reduces the risk of SREs' in itself was not unreasonable. The allegations related to the page as a whole ie the combination of the heading and the Forest plot. The Panel did not consider that it was necessarily cherry picking of the data to include data from Kohno *et al* as cited in Pavlakis *et al* in the leavepiece rather than the other data cited by Roche. The Panel noted that patients in Kohno *et al* were within the Zometa licence and relevant to the leavepiece at issue ie they were women with stage IV breast cancer with at least one osteolytic bone metastasis. The results of the study were cited in the Zometa SPC. No breach of Clause 7.2 was ruled.

Nor did the Panel consider that the heading 'Zometa reduces the risk of SREs' necessarily meant that only data for Zometa could be shown. The Panel considered however that the inclusion of the Forest plot invited a direct comparison between Zometa and the other bisphosphonates shown; Zometa appeared to reduce the risk of SREs more than the other products mentioned. This was not the intention of the cited reference. The Panel considered this aspect was the subject of Point 3 below. On the narrow basis that readers would understand that the Forest plot related to data for a number of bisphosphonates bearing in mind that there was a separate heading to the Forest plot and the medicines were identified the Panel ruled no breach of Clauses 7.2 and 7.4.

**3 The use of the Forest plot from Pavlakis *et al***

**COMPLAINT**

Roche alleged that the overall impression created by the Forest plot from Pavlakis *et al*, the manner in which it had been adapted from the original publication, and its proximity to the claim 'Zometa

reduces the risk of SREs', placed undue emphasis on the efficacy of Zometa compared with other bisphosphonates. It also invited the reader to directly compare the studies shown, many of which were of a bisphosphonate vs placebo or no bisphosphonate.

The way in which the Forest plot was modified misled as to the nature of the study and exaggerated the results; it suggested to the reader that the meta-analysis was designed to compare the efficacy of bisphosphonates in their class which was not so. The objective of the analysis was to assess the effect of bisphosphonates in women with metastatic bone disease as stated by the Panel in Case AUTH/2168/9/08.

Moreover, Clause 7.8 clearly stated that graphs and tables should only be included if they were relevant to the claims and comparisons being made. Only the first line of the Forest plot (Kohno *et al*) was relevant to the leavepiece about the use of Zometa in patients with metastatic bone disease from breast cancer. Therefore, Roche did not consider there was any reason for the remainder of this Forest plot to be used in such promotional materials as it did not pertain to, or substantiate, the efficacy of Zometa, and was a breach of Clause 7.8.

Furthermore, the modifications and omissions made to the Forest plot were not necessary to comply with the Code and simply exaggerated the relative efficacy of zoledronic acid in its class, implying that statistically and clinically Zometa was better than the other bisphosphonates listed. The supplementary information to Clause 7.8 stated, 'If a graph, table or suchlike is taken from a published study it must be faithfully reproduced except where modification is needed in order to comply with the Code'. It was clear that the modifications were not made for this purpose, they distorted as to the significance of the study and gave a visually misleading impression in breach of Clause 7.8.

Novartis had rejected further modifications requested by Roche as they added little. Roche highlighted that the supplementary information to Clause 7.8 also stated that published data should be faithfully reproduced, care should be taken with graphs to ensure that they did not mislead by their incompleteness and graphs must be adequately labelled so that the information could be readily understood.

The Code was clear that graphs etc should be accurately reproduced thereby enabling the reader to form their own opinion of the data. Novartis had omitted vital details necessary to enable the reader to form their own opinion of the data. Novartis' apparent lack of understanding around the use of published data enhanced Roche's concerns regarding the company's comprehension and implementation of the Code, standard operating procedures and approval processes.

Modifications that Roche alleged to be in breach were the use of footnotes, inclusion of the red arrows not found in the original publication, the emphasis made to Zometa by highlighting it red, and omission of the patient numbers and weightings for every study. Roche detailed its concerns below.

The original Forest plot depicted the relative efficacy of each of the available bisphosphonates at their recommended doses compared with placebo or no bisphosphonate and this was stated as part of the heading in the same font size as the text within the plot. In the adapted Forest plot, this part of the heading had been moved from this prominent position and made into a footnote in a font size smaller than the main text. Therefore, it did not make it adequately clear that the depicted relative risk reduction of each bisphosphonate was compared to placebo or no bisphosphonate. Further, the confidence intervals for Zometa and pamidronate almost completely overlapped as was the case for the other bisphosphonates depicted. As such, there was no statistical basis for inviting a comparison as was denoted by the red arrows added to the diagram to show risk reduction, therefore a comparison should not be made in this manner. These modifications gave a visually misleading impression to the reader, distorted as to the significance of the Forest plot, and were in breach of Clause 7.8. In Case AUTH/2168/9/08 the Panel advised both parties of confidence interval overlap and lack of comparator statement and stated that no ruling could be made at that time as it had no complaint on these points. The fact that Novartis had ignored the concerns raised by the Panel contravened the spirit of the Code.

In addition, the published Forest plot showed the patient numbers for every study. This was also reflected in the size of the boxes depicting the relative risk. Thus the size of the studies relative to one another was clear and transparent. In Case AUTH/2168/9/08, the Panel ruled that Novartis had breached Clause 7.8 because it had not reproduced the 'relative risk' boxes in this plot as in the original diagram in the Cochrane review or included the sample size of every study. The adapted Forest plot used in the leavepiece now at issue did not include the sample size of the treatment or control groups from any of the studies. Furthermore, the varying sizes of the boxes on the adapted Forest plot did not accurately reflect the size of the boxes in the original publication, as the box for Zometa was still larger, relative to the other boxes, than in the original paper. In addition, the red colour of the Zometa box gave it undue prominence, relative to the black boxes for all the other medicines. Therefore, Roche believed the immediate impression created by the Forest plot in the leavepiece was misleading in breach of Clause 7.8. The Forest plot also disparaged other companies' products in breach of Clause 8.1. In addition, Novartis' failure to modify the Forest plot according to the ruling in Case AUTH/2168/9/08 was a breach of undertaking in breach of Clause 2.

Roche believed that Novartis had used the Forest plot solely to claim superior efficacy by inviting a comparison of Zometa with the other bisphosphonates. Nowhere had Novartis stated that there were no randomized, controlled, comparative trials as suggested by the Panel in Case AUTH/2168/9/08. The Panel had also acknowledged that the objective of the Cochrane study (Pavlakis *et al*) was to examine bisphosphonates as a class; it was not designed to draw distinctions between any of the medicines studied. This was contrary to the visual impression created and failed to reflect all the available evidence. By using the Forest plot in this manner, Novartis had ignored the Panel and the spirit of the Code.

Roche included the previous Panel judgments below in inter-company dialogue to help Novartis understand its concerns about the leavepiece. It was Roche's intention that it would help to expedite a resolution to this case and thereby avoid protracted dialogue. Novartis considered the judgments irrelevant but did not explain its reasoning.

Case AUTH/869/4/99: the Panel ruled that placement of information from different studies on top of each other invited readers to directly compare the information which was unfair and misleading in breach of Clause 7.2.

Cases AUTH/2061/10/07 and AUTH/2062/10/07 the Panel ruled that the use of secondary endpoints to make a claim in promotional material was misleading and unacceptable.

Roche firmly believed the immediate impression created by the Forest plot, the way in which it had been adapted and the comparisons which it invited were not fair, balanced or based on an up-to-date evaluation of all the evidence. This misled by implication, exaggeration and undue emphasis in breach of Clauses 7.2 and 7.8. Roche also believed the use of these data created confusion between Zometa and other bisphosphonates in the class and disparaged other agents in the class in breach of Clauses 7.2, 7.3, 7.4, and 8.1.

The Panel raised a number of concerns about the use of the adapted Forest plot in Case AUTH/2168/9/08. However, the Panel was unable to make a ruling as a complaint on these specific issues was not made. Roche was concerned as Novartis appeared to have cherry-picked specific excerpts from the Panel ruling and placed undue emphasis on statements which had been taken out of context. Novartis highlighted that, in Case AUTH/2168/9/08, the Panel noted that meta-analysis was an established and valid methodology particularly in the absence of head-to-head trials. However, it was important not to take the Panel's comments out of context, as it went on to state in the following sentence: 'However, the claim was a very strong claim. Readers might expect the supporting data to include randomized, controlled, comparative studies rather than a meta-analysis. There was in the Panel's view a claim for superior efficacy but there had been no complaint in this regard about the exhibition panel'. Although, a breach was not ruled by the Panel on this occasion, Roche believed Novartis had ignored the spirit of the Code by continuing to use the Forest plot from Pavlakis *et al* underneath a slightly modified headline from that ruled on in Case AUTH/2168/9/08.

Roche alleged that, given all of the points raised by the Panel in Case AUTH/2168/9/08, the continued use of the adapted meta-analysis figure from Pavlakis *et al* showed that Novartis had disregarded both the spirit and letter of the Code in a breach of undertaking (as per the Panel's ruling of a breach of Clause 7.8) and as such in breach of Clauses 2 and 9.1.

**RESPONSE**

Novartis rejected Roche's claim that the heading placed undue emphasis on Zometa's efficacy or led readers to compare the compound's efficacy to that of other bisphosphonates. All studies included in the plot were, as stated in the footnote, either against placebo or no treatment (not 'many' as suggested by Roche.)

The meta-analysis and graph clearly supported the heading that 'Zometa reduces the risk of SREs'. Cochrane collaborations were an independent group, whose publications were highly valued by clinicians and regulatory authorities. The table was not misleading or exaggerated, and was relevant to clinicians treating patients with bone metastases secondary to advanced breast cancer. As such, use of the Forest plot was not a breach of Clause 7.2.

The Panel ruling in Case AUTH/2168/9/08 regarding use of Pavlakis *et al* stated that, 'The Panel noted that meta-analysis was an established and valid methodology particularly in the absence of head-to-head trials'. Novartis chose on this basis to continue to use the Cochrane publications and other independent analyses in its promotional material.

The Panel had, in addition, ruled in Case AUTH/2168/9/08 that an inaccurate 'immediate' impression was created by Novartis using an adaptation of the analysis using the same sized sample size boxes and that this breached Clause 7.8. Novartis subsequently amended the sample size boxes to reflect the sizes referred to in each publication and as originally published. As the Panel had not stated that the sample size needed to be added, Novartis submitted that it had not breached its undertaking. By using proportionately sized sample boxes and including p-values, Novartis believed the adapted Forest plot was no longer misleading and the page contained sufficient information to allow the reader to consider the statistical validity of an individual study. As the reader was only invited to consider the efficacy of Zometa with the heading 'Zometa reduces the risk of SREs', Novartis believed sufficient information was available for the reader to substantiate the heading.

Novartis submitted that every effort had been taken to depict the boxes accurately and the visual inaccuracy in the previous case had not been repeated. The heading for this page in the leavepiece differed from that in the previous case and no claim was made of Zometa's superiority.

Novartis gave due consideration to the previous Panel ruling and the required amendments were made to both the graph and heading. The use of a footnote was at the suggestion of the Panel and demonstrated Novartis's commitment to maintaining the standards of the Code. The graph was accurately labelled and the reader had adequate information to make a judgement on the statistical validity of the results.

Novartis did not believe highlighting Zometa in red breached the Code and furthermore that Roche's references to Panel comments such as 'the confidence intervals for Zometa and pamidronate almost completely overlap' were taken out of context as they specifically addressed the fact that the heading for a claim for superiority in the previous case could not be substantiated when this data was scrutinised.

Novartis therefore denied breaches of Clauses 2, 7.2, 7.3, 7.4, 7.8, 8.1 and 9.1.

With regard to Roche's view that graphs and tables should be faithfully represented, Novartis believed that stylised adaptation was permitted as long as this was not misleading and did not change the meaning. If graphs and tables were to be faithfully reproduced, then any data from black and white journals must be placed in promotional material in black and white. Novartis was concerned of the precedent that this would set for the industry if this were so.

With regard to the previous cases cited by Roche, no clarification of the relevance of these cases to the current case was given. With regard was Case AUTH/869/4/99 the meta-analysis was previously accepted by the Panel as an acceptable use of data in the absence of head-to-head studies, Novartis could not understand the relevance of this case.

Similarly with regard to Cases AUTH/2061/10/07 and AUTH/2062/10/07 as the Pavlakis *et al* meta-analysis did not consider secondary endpoints, Novartis could not understand the relevance to the current case.

Novartis stated that it was incumbent on Roche to explain how and why these previous cases had relevance.

**PANEL RULING**

The Panel noted that Roche alleged that including data for bisphosphonates other than Zometa beneath the heading 'Zometa reduces the risk or SREs' was a breach of Clause 7.8 of the Code. The Panel noted its ruling in Point 2 above. The Panel considered that the inclusion of data for other products beneath the claim was not unacceptable per se and on the narrow grounds alleged no breach of Clause 7.8 was ruled.

With regard to the modification of the Forest plot, the Panel noted that the version in the leavepiece had a 'Risk Reduction' column added and for each product a percentage figure for the risk reduction was cited in a downward red arrow. The published Forest plot included only the risk ratio (plus 95% confidence intervals). The risk ratios were cited in an untitled column before the column headed 'Risk Reduction'. The Panel considered that the leavepiece did not faithfully reproduce the published Forest plot and the modifications were not made for the purpose of complying with the Code. A breach of Clause 7.8 was ruled. This ruling was not appealed.

The Panel examined its rulings in the previous case.

**RELEVANT EXTRACTS FROM THE PANEL RULING IN CASE AUTH/2168/9/08**

The Panel noted that the Cochrane review was a meta-analysis of 21 randomised studies which assessed the effect of bisphosphonates, as a class, on skeletal events, bone pain, quality of life and survival in women with early and advanced breast cancer. The primary outcome measure was the number of skeletal events. In nine studies compared with placebo or no bisphosphonates, bisphosphonates reduced SRE risk by 17%. This benefit was most certain with intravenous (iv) pamidronate 90mg, iv zolendronate 4mg and oral clodronate 1600mg. Bisphosphonates in women with advanced breast cancer without clinically evident bone metastases did not reduce skeletal event incidence. The authors' overall conclusion was that in women with advanced breast cancer and clinically evident bone metastases, bisphosphonates reduced the risk of developing skeletal events and skeletal event rate as well as delaying the time to skeletal event.

When discussing implications for clinical practice the authors concluded, *inter alia*, that iv zolendronate (4mg every 3 to 4 weeks) was as effective as iv pamidronate (90mg), with regard to the risk of developing a skeletal event, skeletal morbidity rate, time to a skeletal event, pain and quality of life.

The Panel noted that Roche had alleged breaches of Clauses 7.2, 7.3, 7.4 and 8.1 of the Code in relation to the claim 'Zometa reduces the risk of SREs more than any other bisphosphonate in advanced breast cancer'. The company did not cite any reasons but referred to inter-company correspondence for details of its allegations.

In a letter to Novartis, dated 7 August, Roche gave brief details about why it considered the claim at issue 'Zometa reduces the risk of SREs more than any other bisphosphonate in advanced breast

cancer' was in breach of the Code and referred firstly to the absence of randomised controlled trials comparing the risk of SREs for Zometa vs clodronate or vs Bondronat; and secondly to the fact that the data presented in the Forest plot did not show the risk reduction for SREs for all the medicines and thus did not support the claim.

The Panel noted its concerns about the claim set out below. The Panel also queried whether the exhibition panel made it sufficiently clear that the study was a meta-analysis and there were no randomised controlled trials. The Panel noted that it had no allegation before it on these points. The Panel considered that Roche had made a narrow allegation about the principle of meta-analysis. Novartis had responded accordingly. The Panel noted that meta-analysis was an established and valid methodology particularly in the absence of head-to-head trials. However the claim was a very strong claim. Readers might expect the supporting data to include randomised controlled comparative studies rather than a meta-analysis. There was in the Panel's view a claim for superior efficacy but there had been no complaint in this regard about the exhibition panel. The Panel did not consider that the absence of randomized controlled trials comparing Zometa with clodronate or Bondronat was alone sufficient to render the claim 'Zometa reduces the risk of SREs more than any other bisphosphonate' in breach of Clauses 7.2, 7.3, 7.4 and 8.1 of the Code on the very narrow grounds alleged. No breach was ruled accordingly on this narrow point.

The Panel noted Novartis' submission that the data presented in the Forest plot were for licensed doses lying within each medicines licensed indication. The Panel had concerns about the exhibition panel nonetheless it did not consider that the failure to depict all presentations of medicines examined in the meta-analysis on the Forest plot rendered the claim 'Zometa reduces the risk of SREs more than any other bisphosphonate in advanced breast cancer' misleading, incapable of substantiation or disparaging on the very narrow ground alleged. Only licensed doses were depicted. No breach of Clauses 7.2, 7.3, 7.4 and 8.1 of the Code was ruled accordingly.

The Panel noted that the Forest plot was adapted from one published in the Cochrane Review 2005. The original Forest plot stated the sample size which was also reflected in the varying sizes of the accompanying boxes. Zometa 4mg had the smallest sample treatment size at 114 (control = 113) whilst iv pamidronate had the largest at 367 (treatment) and 384 (control). The exhibition panel did not reflect the sample size. The box for the smallest sample size, Zometa 4mg appeared in red at the top of the Forest plot and was a similar size to the black box for the largest sample size, pamidronate immediately beneath. Whilst p values and confidence intervals were given the Panel, nonetheless, considered the immediate impression created by the Forest plot on the exhibition panel was misleading on this point as alleged; a breach of Clause 7.8 was ruled.

The Panel noted Roche's allegation that the Forest plot compared data from the reduction in risk of SREs for Zometa (an endpoint of events) and the skeletal morbidity rate for ibandronate (an endpoint of time). The Panel noted that the study section 'Data collection and analysis' stated that it relied for the primary outcome measure (number of skeletal events) on the total number of skeletal events reported in each paper. Authors were contacted for additional information that was not in the published trial to permit meta-analysis. The authors noted that the reporting of skeletal events and in particular the rate of events over time varied across the studies. Due to differences in the way outcomes were reported the study reported survival and skeletal event data in two ways: as numbers of events and risk ratios and as ratios of event rates or time to an event. The Cochrane review stated that description and meta-analysis was restricted to those trials from which suitable data could be extracted. The Panel did not consider that the Forest plot was misleading, exaggerated or disparaging as the data was derived from different endpoints as alleged. The Cochrane paper addressed this issue. No breach of Clauses 7.2, 7.3, 7.8, 7.10 and 8.1 was ruled on the narrow point alleged.

The Panel was very concerned about the exhibition panel. The prominent heading in a highlighted red band 'Zometa reduces the risk of SRE's more than any other bisphosphonate in advanced breast cancer' was a strong, unequivocal, comparative claim. It implied that statistically and clinically Zometa was better than the other bisphosphonates listed. The data beneath would be read in light of it. The Forest plot, depicting the overall risk of skeletal events in advanced breast cancer by individual medicine at recommended dosing showed zoledronic acid had the greatest risk reduction at 41%, p=0.001. The data was referenced to the Cochrane review, Pavlakis *et al* (2005) which examined bisphosphonates as a class. It was not designed to draw distinctions between any of the medicines studied contrary to the impression given by the exhibition panel. The Panel noted that whilst the Cochrane study authors commented favourably on individual Zometa studies they did not make a strong unequivocal statement in favour of the comparative efficacy of Zometa as inferred by the heading 'Zometa reduces the risk of SRE's more than any other bisphosphonate in advanced breast cancer' and the data beneath.

The Panel noted that the original Forest plot in the Cochrane review depicted the relative efficacy of each of the available bisphosphonates at their recommended doses compared with placebo or no bisphosphonate. It showed that Zometa achieved the greatest relative risk reduction compared to placebo or no bisphosphonates. Nonetheless the Panel did not consider that the heading was a fair reflection of the study authors' overall conclusions which were more equivocal. In this regard the Panel

noted that the confidence intervals for Zometa and pamidronate almost completely overlapped. Nor did the Forest plot on the exhibition panel make it clear that it depicted the relative risk reduction of each bisphosphonate compared to placebo or no bisphosphonate. It was also unclear where the relative risk reduction of pamidronate at 23% (p=0.00002) depicted on the exhibition panel had come from. The Cochrane review referred to a relative risk reduction of 33%. The position was unclear. The Panel noted however that it had no complaint on these points and thus could make no ruling about them. The Panel considered that the parties should be advised of its views.

**Case AUTH/2246/7/09**

The Panel considered the Forest plot in the leavepiece at issue in this case was different to the one at issue in Case AUTH/2168/9/08. The heading in the leavepiece 'Zometa reduces the risk of SREs' was different to the exhibition panel previously at issue which stated 'Zometa reduces the risk of SREs more than any other bisphosphonate in advanced breast cancer.'

The leavepiece included some indication of size of the patient population by means of reproducing the size of various boxes used in the original publication. No actual patient numbers were included in the leavepiece although these were given in the published Forest plot.

The Panel noted that in Case AUTH/2168/9/08 the only ruling of a breach regarding the Forest plot was in relation to the narrow allegation that it had been adapted so that all of the studies appeared to contain a similar number of patients in an attempt to mislead the viewer that they all carried the same weight in breach of Clause 7.8. Novartis submitted that this had been addressed by the inclusion of the various sized boxes to reflect the sample sizes. The Panel considered, however, that this change was insufficient as the prominent downward red arrows which depicted risk reduction for each bisphosphonate were all of an equal size. In that regard the Forest plot was misleading with regard to the comparative size of the studies as before and a breach of Clause 7.8 of the Code was ruled. In the Panel's view this represented a breach of the undertaking given in Case AUTH/2168/9/08 and thus a breach of Clause 25 was ruled. Novartis had not maintained a high standard and a breach of Clause 9.1 was ruled. The failure to comply with the undertaking was such that Novartis had brought discredit upon and reduced confidence in the pharmaceutical industry; a breach of Clause 2 was ruled. These rulings were appealed.

The Panel noted Novartis' submission as to how it had changed its promotional material to take account of the previous ruling. The Panel noted, however, that its rulings had to reflect the complainant's allegations and the Panel's lack of comment about an aspect of promotional material did not imply approval. In making its rulings the Panel could also not state precisely how a piece should be changed; it could not, in effect, pre-approve material.

The Panel noted that it had expressed concern about the impression of the exhibition panel in Case AUTH/2168/9/08. In the Panel's view it was clear that although it had only been able to make a ruling on the narrow grounds of the complaint it considered that any claim for superiority for Zometa vs other bisphosphonates, however depicted, could not be substantiated using the Forest plot from Pavlakis *et al*. There had been no allegation in this regard and thus no rulings had been made. Thus in the case now before it, Case AUTH/2246/7/09, there could be no breach of undertaking in this regard and therefore no breach of Clauses 25, 9.1 and 2 was ruled.

The Panel was extremely disappointed that it appeared that Novartis had not taken notice of the Panel's wider comments in Case AUTH/2168/9/08 about the Forest plot. This was disingenuous and unacceptable. The fact that the heading which was a comparative claim had been changed did not in the Panel's view mean that the Forest plot in itself did not imply superiority for Zometa compared to the other bisphosphonates listed. In the Panel's view any graph/diagram etc which incorporated data for a number of medicines would inevitably invite a direct comparison of those medicines. The leavepiece at issue thus visually misled the reader; it invited a direct comparison between the products and implied superiority of Zometa compared with other bisphosphonates. There was no way of knowing if the differences between the products were statistically or clinically significant. Pavlakis *et al* was not designed to draw distinction between any of the medicines contrary to the impression given. The Panel ruled a breach of Clauses 7.2, 7.3, 7.4 and 7.8 of the Code. The Panel considered that the Forest plot as presented in the leavepiece disparaged other companies' products. A breach of Clause 8.1 was ruled. These rulings were not appealed.

**APPEAL FROM NOVARTIS**

Novartis submitted that it unequivocally respected the Panel's rulings and regarded undertakings and assurances given to the Authority with the utmost seriousness. Novartis had recently improved its processes and increased its resource in order to improve compliance.

Novartis submitted that the Panel's rulings above were heavily dependent on its consideration of its ruling in Case AUTH/2168/9/08. The crucial part of that ruling found that 'The exhibition panel did not reflect the sample size. The box for the smallest sample size, Zometa 4mg appeared in red at the top of the Forest plot and was a similar size to the black box for the largest sample size, pamidronate immediately beneath. Whilst p values and confidence intervals were given the Panel, nonetheless, considered the immediate impression

created by the Forest plot on the exhibition panel was misleading on this point as alleged; a breach of Clause 7.8 was ruled'. The Panel also raised several concerns in Case AUTH/2168/9/08, upon which it could make no rulings as no complaint was made on these points. It did, however, ask that 'the parties should be advised of its views'. In outline, these were that

- The exhibition panel made it insufficiently clear that the study was a meta analysis and there were no randomised controlled trails.

- The heading to the piece did not fairly reflect of the study authors' overall conclusions which were more equivocal.

- The Forest plot did not make it clear that the relative risk reduction of each bisphosphonate was compared to placebo or no bisphosphonate (no treatment).

Novartis submitted that in the light of previous ruling and the undertakings and assurances given by Novartis to the Authority, key changes were made to both the Forest plot and the context in which it was used. Novartis amended the boxes to represent the sample sizes, confidence intervals and risk ratio used in Pavlakis *et al*. The use of different sized boxes to reflect the different sample size and consequent weighting of each study in the meta-analysis reflected conventional statistical methodology.

Novartis submitted that in the current ruling, the Panel had extrapolated from its earlier ruling to conclude that the Forest plot was misleading with regard to the comparative size of the studies because the downward red arrows that depicted risk reduction for each bisphosphonate were equal in size. It was clearly appropriate to represent the boxes according to sample size but it was not appropriate to extrapolate this methodology to the arrows representing risk reduction. The Panel ruled that Novartis had breached its earlier undertaking not to use promotional material similar to the exhibition panel that had been the subject of the ruling in Case AUTH/2168/9/08. However the Panel had stated that the leavepiece was different from the exhibition panel.

Novartis submitted that the Forest plot was a conventional way to represent the results of several studies contributing to a meta-analysis. The size of the box representing the point value for each study was usually made proportional to the contribution of that study to the overall meta-analysis. Thus, the boxes would be smaller for those studies which contained fewer patients and larger for those that contained greater numbers of patients. The size of the box had no significance whatsoever with the regard to the statistical significance of or the conclusions that could be drawn from any particular study. The red arrows used by Novartis in the leavepiece merely represented the point value for the risk ratio derived by Pavlakis *et al* in relation to each study. They were not intended to, and Novartis submitted that it was clear that they did not, represent the pooled data in the meta-analysis. They did not relate to any sample size or weight contribution to the meta-analysis. There was, therefore, no reason why the size of the arrow should be related to the size of the study. The p value was given for each study and it was this that indicated the likely reliability of the value for risk reduction, not the size of the study. It was possible that a more reliable study might contain fewer patients: it might simply be better designed and, thus, more likely to reflect the true difference.

As a consequence of the Panel's advice in Case AUTH/2168/9/08, Novartis also changed its further use of the information contained in the Forest plot (a graphical overview of these changes was provided).

- the heading was changed to 'Zometa reduces the risk of SREs', which was substantiated by the Forest plot underneath it. This was a fair, reasonable and balanced reflection of the authors' conclusions. No comparative claims were made or implied.

- the footnote was changed to 'Adapted from Pavlakis N *et al*, 2005. A review and *meta-analysis* of seven studies involving SREs for breast cancer *versus placebo or no treatment.* Prepared and maintained by the Cochrane Collaboration. Original trials may have had different endpoint' (emphasis added by Novartis). These changes made it clear the study was a meta-analysis and comparisons were made against placebo or no treatment. Novartis noted that, in any event, any of the target audience sufficiently well versed in statistics to derive any useful information from it would immediately recognise the data as representing a meta-analysis since this was by definition the type of study for which a Forest plot was an appropriate way to display the results.

Novartis noted that the red risk reduction arrows on which the ruling of breach of an undertaking was founded were also included on the Forest plot in Case AUTH/2168/9/08. In its ruling in that case the Panel made no comment or recommendation about these arrows. The size of the red arrows was neither the subject of the complaint nor the cause of the previous ruling and therefore should not be the basis of a breach of undertaking. In hindsight Novartis recognised that the inclusion of patient numbers in this graph would have provided greater clarity.

Novartis noted that in Case AUTH/2177/10/08 (Allergan vs Merz) Merz implied that Xeomin was free from complexing proteins and this conferred a clinical advantage which was depicted on a leavepiece with a claim and visual. This was ruled in breach by the Panel.

Merz subsequently produced another leavepiece

with a revised claim used with the (unchanged) visual. The Panel ruled both the claim and the visual separately misleading, as they both individually implied, again, that the fact that Xeomin was free from complexing proteins was a clinical advantage. The Panel also ruled this in breach of undertaking. The Appeal Board on appeal upheld the Panel's ruling that both the claim and the visual were misleading, but did not uphold the ruling of breach of undertaking on the basis that:

- The company had taken steps to comply with the undertaking by modifying the claim
- There had been no previous ruling specifically in relation to the visual

Novartis submitted that the Appeal Board's ruling should act as a precedent in this case which raised similar issues of principle.

Given the changes made to the Forest plot in light of Case AUTH/2168/9/08, Novartis submitted that it had not breached the undertaking and assurance which it gave to the Authority. Thus, as there had been no breach of Clause 25, it could not be said that high standards had not been maintained. Thus, there had been no breach of Clause 9.1 and no breach of Clause 2.

**RESPONSE FROM ROCHE**

Roche alleged that the Forest plot at issue implied superior efficacy of Zometa by inviting the reader to draw comparisons between the Zometa study and those for the other bisphosphonates. The Zometa data had been highlighted in red. Risk reductions had also been highlighted in red arrows to draw attention to them. The Forest plot had not been faithfully reproduced from the original. It distorted, misled, and did not reflect the intention of the authors of the meta-analysis. Patient numbers had not been included as recommended in the supplementary information for Clause 7.8 and by the Panel. The reworked Forest plot had not taken into account the Panel's opinion in Case AUTH/2168/9/08 and therefore should be considered as a breach of undertaking. The presentation of the Forest plot breached Clauses 2, 7.8, 9.1, and 25.

Roche alleged that Novartis had used the Forest plot by Pavlakis *et al* to claim superior efficacy of Zometa by inviting the reader to draw comparison between Zometa and other bisphosphonates. Novartis had not submitted any representative briefing materials regarding intended detailing of this Forest plot which would help refute this suggestion and have supported its case. A Forest plot was a legitimate way to present data from a meta-analysis, or subgroup analysis in an individual trial. However, this Forest plot had been modified inappropriately from the original to highlight and emphasize Zometa data. It had not been faithfully reproduced with the box and whiskers being different sizes from those in the original. Also the data points and confidence intervals from the Zometa study were highlighted in red in contrast to the other bisphosphonates which appeared in black. The risk reduction column had been added to the Forest plot by Novartis as highlighted red arrows, and the numbers were in a larger font, in contrast to the hazard ratios and p-values. These two creative elements gave particular prominence to certain data favouring Zometa and led the reader to inappropriate comparisons and conclusions regarding the meta-analysis.

The supplementary information to Clause 7.8 recommended inclusion of patient numbers wherever possible. Pavlakis *et al* had included them in its Forest plot but the numbers had been omitted from the leavepiece although their inclusion was suggested by the Panel in Case AUTH/2168/9/08. Novartis had also not stated in the leavepiece that there were no randomized controlled comparative trials as suggested by the Panel in Case AUTH/2168/9/08. The supplementary information for Clause 7 stated that claims in promotional material must be capable of standing alone and should not be qualified by the use of footnotes.

Roche alleged that it was clear from the authors' conclusions that the Cochrane meta-analysis was an attempt to more precisely determine the effect of bisphosphonates as a class on SREs not to draw distinctions between any of the medicines studied. The Panel also acknowledged in Case AUTH/2168/9/08 that the objective of Pavlakis *et al* was to examine bisphosphonate as a class; it was not designed to draw distinctions between any of the medicines studied. This was contrary to the visual impression created by use of the Forest plot in this leavepiece. By continuing to use the Forest plot in this manner, Novartis had not taken into account the Panel's ruling in Case AUTH/2168/9/08 and the spirit of the Code. Roche alleged the presentation of the Forest plot breached Clauses 2, 7.8, 9.1 and 25.

**APPEAL BOARD RULING**

The Appeal Board noted in Case AUTH/2168/9/08 the Panel had noted that the Forest plot was adapted from one published in the Cochrane Review 2005. The original Forest plot had stated the sample size which was also reflected in the varying sizes of the accompanying boxes. The exhibition panel did not reflect the sample size. The box for the smallest sample size, Zometa 4mg, appeared in red at the top of the Forest plot and was a similar size to the black box for the largest sample size, pamidronate, immediately beneath. Whilst p values and confidence intervals were given, the Panel nonetheless considered the immediate impression created by the Forest plot on the exhibition panel was misleading on this point as alleged; a breach of Clause 7.8 was ruled.

Turning to the current case, Case AUTH/2246/7/09 the Appeal Board noted that the promotional item now at issue was a leavepiece which contained limited information. In the Appeal Board's view, Forest plots were a sophisticated way of presenting

data and some readers would require a degree of explanation before they fully understood the data presented. The Appeal Board noted that in the present case, Case AUTH/2246/7/09, the Forest plot in the leavepiece at issue was different to the one at issue in Case AUTH/2168/9/08. The Appeal Board noted that no actual patient numbers were included in the Forest plot at issue although they were included in the original Forest plot published in the Cochrane Review. Novartis had not appealed the Panel's ruling that the leavepiece did not faithfully reproduce the published Forest plot and the modifications were not made for the purpose of complying with the Code. The Forest plot at issue gave some indication of the size of the patient populations by reproducing the size of various boxes used in the original publication. Some boxes were square and some were diamond shaped. There was nothing in the leavepiece to explain what the different box shapes meant or indeed that the box sizes were proportional to the size of the patient population in the various studies. The Forest plot was misleading with regard to the comparative size of the studies as before. In the Appeal Board's view the use of the downward red arrows depicting the risk reduction added to the misleading representation of the patient populations. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.8. In the Appeal Board's view this represented a breach of the undertaking given in Case AUTH/2168/9/08 and thus it upheld the Panel's ruling of a breach of Clause 25. Novartis had not maintained a high standard and the Appeal Board upheld the Panel's ruling of a breach of Clause 9.1. The appeal on these points was not successful.

The Appeal Board considered that Novartis had made some effort to comply with its undertaking by making the changes noted above. Thus, in that regard, Novartis had not brought discredit upon and reduced confidence in the pharmaceutical industry as alleged; no breach of Clause 2 was ruled. The appeal on this point was successful.

**4 Request for cited references**

**COMPLAINT**

Roche stated that on 13 March 2009, a company pharmacist asked Novartis to email her a copy of the poster, Hoer *et al* (2005), but nothing was received by email or post. After the third request a conference abstract (but not the poster) by Hoer *et al* 2005 was provided on 30 March, twelve working days from the date of the original request. Although Novartis claimed to have posted a response on 19 March this was never received and a copy of that letter had still not been provided. The first time the pharmacist received the actual poster to which the data were referenced was as an attachment to Novartis' inter-company correspondence dated 11 May. Roche alleged that Novartis' failure to supply the references to support the claims made in its leavepiece within ten working days was in clear breach of Clause 7.5.

In addition, on 2 April 2009 the pharmacist emailed a separate request for the Heatley *et al* (2006) poster also referenced in the leavepiece. Novartis supplied an abstract but a second email request, sent on 3 April, which emphasized that the poster was required, was not acknowledged. The first time the referenced poster was provided was as an attachment to the letter from Novartis dated 11 May, over a month after the original request, again in breach of Clause 7.5.

The abstracts did not contain sufficient information to substantiate the claims in the leavepiece. Roche was alarmed at Novartis' inability to provide references to substantiate the data, claims and comparisons. This further affirmed Roche's belief that Novartis did not take its concerns, or the Code, seriously. It was not within the spirit of the Code for Novartis to discriminate in the level of service offered depending on who had requested the information, as suggested in its letters of 11 May and 5 June. Roche noted that the pharmacist as a health professional, was entitled to be provided, within ten working days, with information to substantiate materials, as outlined in Clause 7.5. The signature on all her emails indicated that she was a qualified health professional. This suggested to Roche that the level of service provided by Novartis to health professionals disregarded the requirements of the Code for providing substantiation of information, claims and comparisons and failed to maintain high standards in breach of Clauses 2, 7.5 and 9.1.

As Novartis was unable to provide the Hoer *et al* poster in a timely manner, Roche conducted a literature search for this reference. Although it found the poster it identified a more recent analysis of the Hoer *et al* study published in 2006 with data which differed from that published in the 2005 abstract. The Code stated that, 'Information, claims and comparisons must be based on an up-to-date evaluation of all the evidence'. As the most recent analysis of the Hoer *et al* had not been used in the leavepiece, Roche alleged that the data had been cherry-picked in breach of Clause 7.2.

**RESPONSE**

Novartis noted that pharmaceutical companies were required to have a scientific services department. It was already common for companies to contact competitors only when they were unable to source cited references eg abstracts, posters, hard to source journals and data-on-file. In this case medical information departments were prepared to respond within the inter-company liaison expectations of ten days rather than response times in Clause 7.5. Therefore Novartis believed that despite citation of this clause by Roche, companies already in principle accepted a slightly differing response expectation than that cited by this clause. This was also clear from the Roche request to the medical information department.

Furthermore Clause 7.5 specifically stated that it

related to requests from 'members of the health professions or appropriate administrative staff'. If this principle was not accepted and Clause 7.5 also applied to competitor companies, then competitors could require all cited references to be supplied regardless of whether they could be easily sourced or not. Thus a pharmaceutical company could easily overwhelm the resources of companies with small medical information departments.

Novartis re-iterated that outside this clause there was still an expectation to provide competitor companies a reasonable response time within the inter-company dialogue rules.

However Novartis re-iterated that customers or health professionals who were treating patients and needed information to make a prescribing decision or consider appropriate use of the medicine must be a priority. These other customers of a medical information department did not have such readily available access to additional resources and would have patients under consideration.

Roche stated Clause 7.5 referred to health professionals who worked for pharmaceutical companies also. Novartis emphasised that this was a very important distinction and that such contact by a health professional was made solely as an employee of the company and not in a professional capacity, in this case as a pharmacist. Again this was a very important distinction as to accept any other interpretation would leave companies who employed individuals who were not health professionals at an unfair disadvantage.

The Hoer *et al* reference was incompletely cited in the leavepiece. Novartis accepted that this was in breach of Clause 7.6. A breach of this clause had not been alleged by Roche. [Novartis had ensured that this referencing error in the leavepiece had been amended.] Roche therefore could not have requested the poster and its communication to Novartis supported this. Consequently, due to a citation error a copy of the abstract was sent on 20 March. This showed that the enquiry was responded to well within ten days. A follow-up to this enquiry flagging non-receipt (30 March) was actioned the same day by email. Evidence to support this sequence of events was provided in confidence only to the Panel - an audit trail of the medical information enquiry from the database.

The Heatley *et al* poster was requested on 3 April, actioned the same day although an abstract was sent in error. Roche contacted Novartis on 7 April to re-iterate that the poster was requested, not the abstract. Novartis accepted that due to confusion at this point this follow-up enquiry was not responded to in a timely manner. In this regard Novartis accepted that it fell short of the standards under which its medical information department operated. Novartis had spoken to the individuals concerned and had reviewed processes to ensure no recurrence. However, whilst this was an unfortunate set of circumstances, Novartis reassured Roche that there was no intention to withhold the information requested.

Novartis rejected Roche's allegation that it had cherry-picked the data. Having found, through a literature search, a 2006 publication of the same study, Roche alleged Novartis was in breach of Clause 7.2, noting that the data differed from that published in 2005. Novartis rejected this as the difference Roche noted was 1% in the percentage of patients on treatment after 6 months of therapy (35% in 2005 vs 36% in 2006). Importantly the 2006 publication also stated a statistically significant risk of patients with a diagnosis of bone metastases not being persistent compared to patients without a diagnosis of bone metastases (p=0.005), which strengthened Novartis' use of Hoer *et al* as a whole to emphasise the issue of oral compliance in metastatic bone disease. The 1% difference did not represent a significant change in the overall conclusions between the 2005 poster and 2006 abstract.

Novartis rejected claims that this represented breaches of Clauses 2, 7.5, and 9.1.

**PANEL RULING**

The Panel noted that Clause 7.5 required substantiation to be provided as soon as possible and within ten working days at the request of members of the health professions or appropriate administrative staff. There was no exemption for health professionals employed by pharmaceutical companies. The Panel was sympathetic to Novartis' view that its medical information department would prioritise requests from clinicians. Nonetheless, in this instance the request had been for references cited in the leavepiece. In the Panel's view these should have been easily to hand. The Code required substantiation for any information claims or comparisons to be provided within ten working days to any health professional. The Code required substantiation of claims on request and the provision of data on file (Clause 7.7). Clause 7.5 did not require cited references to be provided per se, however the Panel considered that it was helpful to include relevant cited references when asked for substantiation. Additional material could of course be provided. With regard to the provision of Hoer *et al*, there appeared to be a difference between the parties; Roche stated that it had only received the Hoer poster as part of the inter-company dialogue and Novartis stated that the abstract had been sent on 20 and 30 March. According to Novartis, Hoer *et al* (2005) had been incorrectly cited in the leavepiece by omitting to state the material was a poster.

The Panel noted that Novartis had provided the Hoer *et al* abstract to Roche on 30 March. It was not entirely clear from Novartis' records exactly what had been sent. There was no allegation at Point 4 that the abstract failed to substantiate the claims. This would be considered at Point 5 below. Substantiation had been sent by post within ten working days and followed up by email when Roche

contacted Novartis again. It appeared that the copy sent in the post had not been received. In the circumstances the Panel ruled no breach of Clause 7.5.

With regard to the Heatley poster Novartis accepted that this had not been sent. The Panel considered that Roche had, in effect, requested substantiation and thus ruled a breach of Clause 7.5 as substantiation had not been provided in response to a request from a health professional. The Panel did not consider that the failure to supply the Heatley poster meant that high standards had not been maintained. Nor that Novartis had brought discredit upon or reduced confidence in the pharmaceutical industry. No breach of Clauses 9.1 and 2 was ruled.

The Panel noted the difference between Hoer *et al* (2005) and the 2006 data, this being 1% more patients still on therapy at 6 months ie 36% in 2006 instead of 35% in the 2005 publication. The Panel did not accept that Novartis had cherry-picked the data as alleged. No breach of Clause 7.2 of the Code was ruled.

**5 Hoer *et al* reference, claims not substantiated**

Page 3 was headed 'There are compliance issues with oral bisphosphonates' followed by a graph headed 'Compliance with oral bisphosphonates' which depicted discontinuation rates at 3 months (44%) and 6 months (65%). The graph was adapted from the poster Hoer *et al* and was a retrospective observation study of health insurance claims.

**COMPLAINT**

Roche considered the way in which the data from Hoer *et al* were presented misled the reader.

Roche complained to Novartis that the claims referenced to Hoer *et al* were misleading and not substantiated by the abstract supplied by Novartis on 30 March. Novartis provided the poster to Roche during inter-company dialogue. Once Roche had reviewed the full poster it notified Novartis that it strongly believed it was inappropriate to use the data in this manner. The leavepiece was intended for use with health professionals involved in the treatment and management of patients with metastatic bone disease from breast cancer. Hoer *et al* could not substantiate claims about such patients as it comprised a mixed population of men and women with differing diagnoses only 58/497 (11.7%) of which had breast cancer with bone metastases. Evidence suggested that adherence and persistence to oral therapy was better in cancer patients vs patients who had non-oncological chronic disease who, on average, only took half of their prescribed oral medicines. This was thought to be because cancer patients understood the risks, specifically survival, associated with not taking medicines as prescribed (Ruddy *et al* 2009). The use of this reference, without caveats, in the leavepiece was therefore misleading and created confusion.

Furthermore, it was not possible from the data reported in the poster to know which treatments the patients with breast cancer received; and because the persistency rates were not reported by diagnosis it was not clear from the poster or leavepiece what the persistency rate was in the 58 breast cancer patients with metastatic bone disease.

The claims made from this reference were misleading, confusing and not substantiated by the data supplied. Therefore, it was inappropriate to use these data in this manner in breach of Clauses 7.2, 7.3, 7.4, 7.5, and 7.8.

**RESPONSE**

Novartis responded to points 5 and 6 together and its response is set out below.

Novartis noted that during inter-company dialogue Roche stated in a letter (24 April) that 'As Novartis provided support for the study by Hoer *et al* and one of the authors was a Novartis employee, Novartis should be fully conversant with these data. Therefore, Roche strongly considers use of these data in this manner in promotional materials is inappropriate, fails to maintain high standards and brings discredit to the pharmaceutical industry and as such Roche believes is in breach of Clauses 2, 9.1 and 9.10'. Although dropped from the complaint to the Authority, Novartis strongly believed this kind of misrepresentation of the Code when raising concerns about competitor promotional materials was unreasonable. Novartis strongly believed that in all correspondence there should be a reasonable expectation that the complaint had been fully researched and was appropriate because important resources were used to respond to such complaints.

Novartis considered Roche had misunderstood the relevance of Ruddy *et al* which looked directly at the important issue of oral compliance highlighted in the heading at issue 'There are compliance issues with oral bisphosphonates'. Ruddy *et al* made no mention of bisphosphonates and focused on antineoplastic therapies, but importantly did mention the importance of understanding the issue of compliance in oral therapies, and how this might impact on patient outcomes, and the difficulty in collecting this data, specifically data relating to oncology.

Hoer *et al* presented as a poster and given as a handout at an international conference in 2005 represented a large retrospective observational study from health insurance claims as clearly stated in the footnote under the graph. Novartis did not consider that readers would draw any conclusions other than those presented in the graph, regardless of the actual numbers in the 2005 handout or the 2006 publication. Nor in the company's view would the reader have felt misled having looked at both and drawn conclusions regarding compliance issues with oral bisphosphonates.

The heading set up the representative to discuss the

fact there were compliance issues with oral bisphosphonates as with any oral agent.

Hoer *et al* represented a very large patient number, making its conclusions robust, and specifically presented data for oncology patients rather than the larger patient numbers seen in other publications on persistence with oral bisphosphonates as seen in the post-menopausal osteoporosis setting. Furthermore, this represented a 'real world' compliance data compared with that gathered in prospective randomised controlled trials.

Hoer *et al* looked at all bisphosphonate use based on patients with advanced disease of which the majority of those with metastatic bone disease had breast cancer (53.2%). Despite this study including medicines outside of licensed indication it was most representative of the 'real world' issue of compliance with oral bisphosphonates. Trial data which suggested there were issues related to compliance tended to under report the rate of non-compliance. As there were no randomised controlled trials examining the issue of non-compliance, Novartis maintained this study provided the best representation of potential issues involving the use of oral bisphosphonates. It was well known that bisphosphonates were often inappropriately prescribed out of their licensed indications eg pamidronate or Bondronat in prostate cancer and compliance data in these unlicensed areas was limited.

Greater amounts of compliance data were available for patients taking oral bisphosphonates for post-menopausal osteoporosis, but Novartis considered that only data from the oncology setting should be presented. Novartis maintained that under the heading of oral compliance issues it had used truly representative data to reflect a well recognised issue with oral bisphosphonates in the real world. As such Novartis had acted within the spirit and the letter of the Code and was not in breach of Clauses 7 2, 7.3, and 7.8.

Novartis made no attempt to differentiate around the medicines within Hoer *et al* as all the data suggested it was not just the adverse events, tolerability and benefit outcomes which were important to compliance but also the patient's age, socio-economic factors and the perceived risk-benefit of the medicine especially in chronic disease such as cancer.

Novartis disagreed with Roche's view that because oral Bondronat was not included, the results of the study did not reflect the real world setting in the UK or that it disparaged oral Bondronat. The results were taken from a German population but as Bondronat had approval throughout the European Union in breast cancer it was a therapeutic option in Germany.

As the headings on pages 2 and 3 (facing) of the leavepiece clearly set up what the subsequent graph was representing, Novartis rejected Roche's claims that readers would suppose the bisphosphonates in Pavlakis *et al* were the same as those in Hoer *et al*. There was no attempt in the way this leavepiece was set up to review the information provided on one page and use it to discern something on the other. Roche appeared unnecessarily concerned about this issue in any case as the meta-analysis was not designed for comparison of individual medicines but to show benefit for a class. In the same way page three was not designed to show poor compliance for individual agents but a lowering of compliance rates over time for the class.

No specific compounds were mentioned and this was intentional because compliance issues were recognised as an issue for all oral bisphosphonates. This was supported by the referenced quotations from Heatley *et al*, Conte and Guarneri *et al* (2004) and more recently Aapro *et al* (2008) which were recommended by an international expert panel on bisphosphonate use in solid tumours. Aapro *et al* was sponsored by Novartis but also reviewed and the factual statements and references signed off by all the major manufacturers of bisphosphonates including Roche.

Novartis trusted that the Panel would be satisfied that Novartis was not in breach of the Code as alleged.

**PANEL RULING**

The Panel examined Hoer *et al* and noted that it was a retrospective observational study using data from health insurance claims. Not all the patients had advanced malignancies involving bone. 109 of the 497 patients had bone metastases. There were a number of limitations listed including that the analysis was limited to the outpatient prescriptions of oral bisphosphonates. The study stated that the risk of being not persistent with therapy was higher for patients with bone metastasis than without such a diagnosis.

The Panel noted that the oral bisphosphonates used were clodronate, alendronate, risedronate, etidronate and/or eidronate and calcium. Of those treatments, only oral clodronate was licensed in the UK for use in cancer patients with bone metastases. The only other oral bisphosphonate so licensed in the UK was Bondronat, marketed by Roche, but this had not been included in the study.

The Panel considered that the heading 'There are compliance issues with oral bisphosphonates' was not unreasonable per se. The Panel considered, however, that given the leavepiece was specifically about patients with metastatic breast cancer the graph would be assumed to apply to the use of bisphosphonates available in the UK for the prevention of SREs in that patient group. The data was not so limited and thus the graph and specific discontinuation claims at 3 and 6 months were misleading and had not been substantiated in that regard. The Panel ruled a breach of Clauses 7.2 and

7.4. The Panel did not consider that the comparison between Zometa (which was administered iv) and oral bisphosphonates was misleading per se and no breach of Clause 7.3 was ruled. The alleged breach of Clause 7.5 regarding the failure to supply Hoer *et al* was dealt with in Point 4 above. The graph did not give a fair and balanced view of the data and thus a breach of Clause 7.8 was ruled.

**6 Use of data from Hoer *et al***

**COMPLAINT**

Roche strongly believed the information from Hoer *et al* presented in the leavepiece was incomplete, ambiguous, misleading, disparaged Bondronat, and included data on medicines not licensed for use in the UK.

The impression created by the page heading above the graph, 'There are compliance issues with oral bisphosphonates' in a leavepiece about Zometa in patients with metastatic bone disease from breast cancer implied the results of Hoer *et al* applied to all oral bisphosphonates prescribed to patients with metastatic bone disease due to breast cancer in the UK. This was compounded by the fact that there were no statements on the page to show which bisphosphonates were studied by Hoer. The study did not include oral Bondronat which accounted for 23% of bisphosphonate usage in UK hospitals, in contrast to oral clodronate which had 3% market share (IMS, Oncology Analyser, September '08) and was included in the study. Clodronate had a different treatment schedule, tablet size, and safety profile from oral Bondronat and so extrapolation of data from one medicine to the other was not justified. Importantly, 39% of the data reported by Hoer *et al* included alendronate which was not licensed for use in metastatic bone disease in the UK.

No information was provided as to the patient characteristics, such as pre-existing comorbidities or which bisphosphonate they received, which might have influenced the outcomes of the study. In addition, no reasons were given for treatment discontinuations, which might have been due to death or to change of therapy. Roche considered the omission of this information and details of which bisphosphonates were used misrepresented the study, was unbalanced, misled and confused readers and prevented them from drawing their own opinion of the validity of the claims made in breach of Clauses 7.2, 7.3, and 7.8.

The impression that the heading 'There are compliance issues with oral bisphosphonates' applied to Bondronat was further emphasized by the Forest plot on the facing page in which the only oral agents shown were Bondronat and clodronate. The overall impression given by these two facing pages was that Hoer *et al* included the same oral bisphosphonates as Pavlakis *et al* and this also encouraged the reader to compare oral bisphosphonates with Zometa.

Roche considered that the heading 'There are compliance issues with oral bisphosphonates', use of Hoer *et al* and the overall impression created when viewed with the Forest plot on the facing page sought to label all oral bisphosphonates as being the same and so were all-embracing, incapable of substantiation, created confusion and misled the reader both by the visual impression given and as to the significance of Hoer *et al*. The title disparaged oral Bondronat, as the market leading oral bisphosphonate, by the overall impression created and the all-embracing claims and was in breach of Clauses 7.2, 7.3, 7.4, 7.8, 7.10, 8.1. Roche strongly considered use of these data in this manner in promotional material was inappropriate, failed to maintain high standards and brought discredit to the pharmaceutical industry in breach of Clauses 2, 9.1 and 9.10.

**RESPONSE**

Novartis referred to its response at Point 5 above.

**PANEL RULING**

The Panel noted its comments about Hoer *et al* and its rulings in Point 5 above which covered many of the allegations in Point 6. The Panel considered that the heading in the context of the graph was disparaging and all-embracing. Breaches of Clauses 7.10 and 8.1 were ruled.

The Panel ruled no breach of Clause 9.10. The leavepiece was clearly promotional material and not sponsored material as referred to in Clause 9.10.

The Panel considered that high standards had not been maintained and ruled a breach of Clause 9.1. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 and ruled accordingly.

**7 Quotations on page 3**

Directly beneath the graph on page 3 were the following three quotations; 'Because IV bisphosphonates are administered in a hospital or infusion centre, compliance with therapy is not a concern' (Heatley *et al*); 'Oral administration requires precautionary measures to ensure absorption and – for some [bisphosphonates] – to avoid gastrointestinal adverse events' (Aapro *et al*) and 'If not taken properly, oral bisphosphonates can cause a high incidence of [gastrointestinal] adverse events, including esophagitis, mucositis, nausea, vomiting and diarrhoea, and may exacerbate this side effects of anticancer therapy' (Conte and Guarneri).

**COMPLAINT**

Roche believed readers would consider the quotations immediately below the graph from Hoer

*et al* to be in direct reference to that study. Furthermore, the quotations had been taken out of context and thus were not a true reflection of the individual study outcomes and conclusions thereby constituting cherry picking of data.

The quotation from Heatley *et al* was referenced to a poster which Novartis was unable to provide in response to a request by Roche – only the abstract was sent by Novartis prior to Roche initiating inter-company dialogue, and Roche believed this was in breach of Clause 7.5.

The Heatley abstract appeared to be the result of a literature search to source data on gastrointestinal side effects during oral bisphosphonate therapy. The search only identified one study of breast cancer patients receiving oral bisphosphonate therapy for metastatic bone disease. This was a trial of 55 patients receiving oral clodronate therapy in which the overall compliance was reported to be approximately 90%. A compliance rate of 90% did not reflect or support the claim of 50% non-compliance from Hoer *et al*, as would be expected by the reader, and significantly misled the reader.

Furthermore, Conte and Guarneri listed non-compliance levels with oral Bondronat of 8% and 11-22% for oral clodronate both of which were substantially lower than the 50% non-compliance suggested by the graph.

Finally, Aapro *et al* was produced by an expert panel of clinical oncologists who reviewed the available evidence on the use of bisphosphonates in solid tumours and provided clinical recommendations. Roche alleged that the quotation, 'Oral administration requires precautionary measures to ensure absorption and – for some [bisphosphonates] – to avoid gastrointestinal adverse events', was taken out of context. Particularly as the sentence following it was referenced to a study about compliance of bisphosphonate therapy in patients with osteoporosis rather than metastatic bone disease from breast cancer.

Roche alleged that the quotations and the context in which they were used were misleading as they did not accurately and clearly reflect the slides in question nor the overall meaning of the authors. None of these studies supported the claim that over 44% of patients receiving oral bisphosphonate therapy did not comply with treatment. In fact, they demonstrated 92% complied with oral Bondronat, the most frequently used oral bisphosphonate for the treatment of metastatic bone disease in UK hospitals (IMS, Oncology Analyser, September '08). The quotations were taken out of context, unbalanced, misled as to their overall significance and disparaged oral Bondronat. This was unjustified knocking copy and did not allow the reader to form their own opinion of the therapeutic value of oral bisphosphonates for the treatment of patients with metastatic bone disease and thereby failed to maintain high standards. The use of these quotations was misleading, disparaging and constituted cherry picking of data. Roche alleged breaches of Clauses 7.2, 8.1, and 10.2

**RESPONSE**

Novartis believed that all the quotations were substantiated by the references cited. As each was appropriately referenced it did not believe that readers would be misled into believing they all referred to Hoer *et al* as suggested. All three explained issues around compliance with oral bisphosphonates and were not taken out of context.

Novartis did not believe the use of the quotations or the context in which they were used misrepresented the authors' publications or that Novartis had cherry-picked the data. Compliance was clearly an important issue for clinicians to consider. Novartis had presented the largest known study of oral agents in the real world metastatic setting. The figures quoted by Roche from Conte and Guarneri simply represented the patient population which withdrew from treatment because of adverse events commonly associated with oral compliance issues. The figures were not specifically a measure of compliance, and so Roche's allegation represented a greater level of cherry picking.

Conte and Guarneri described over 50% non-compliance in osteoporosis suggesting Hoer *et al* was accurate. The authors noted compliance issues might be different from those in a 'real world situation' and this was the data Novartis had used to represent this important clinical issue. Conte and Guarneri also noted that when adverse events could be directly attributable to the medicine, compliance could be even less. The only prospective data in this setting designed to look at compliance came from clodronate studies and there was no trial data to specifically evaluate compliance alone. This, in Novartis' opinion, did not fully represent this issue and was why Hoer *et al* was used.

If Conte and Guarneri was read in full it could be used to support the statement that there were compliance issues with oral bisphosphonates. Hoer *et al* was not unrepresentative of the data in this setting which related to one study with one oral agent. Equally, Novartis denied there was any attempt to link the graph and the referenced quotations as being from the same paper. They were all clearly attributed to different authors, the commonality being concern about oral compliance. As no mention of specific compounds was made, Novartis failed to see how this disparaged Bondronat.

Aapro *et al* was written by the leading oncologists in the field of metastatic bone disease with the lead authors taking part in the registration studies in this setting together with many other international key opinion leaders. Novartis failed to see how the quotation 'Oral administration requires precautionary measures to ensure absorption and - for some [bisphosphonates] – to avoid

gastriointestinal events' had been taken out of context. The paper from which it had been taken was entitled 'Guidance on the use of bisphosphonates in solid tumours: recommendations of an international expert panel' and the quotation appeared under the sub-heading 'choice of administration route'. Although Roche might not be happy with the quotation, it was accurate and taken from an international panel of experts. The reference used to support this statement might not be from the oncology setting which further substantiated the appropriateness of Novartis' earlier use of Hoer *et al*.

Novartis denied breaches of Clauses 7.2, 8.1, and 10.2.

**PANEL RULING**

The Panel considered that it was clear from the leavepiece that the quotations were from different studies. The Panel did not consider that the readers would assume that the quotations applied to the discontinuation data from Hoer *et al*. In the Panel's view the quotations referred to general issues related to compliance with oral bisphosphonates.

The Panel did not agree that the quotation from Aapro *et al* was out of context given the next sentence referred to its use in oestoporosis. Precautions to ensure absorption of oral bisphosphonates and to avoid gastrointestinal events would apply whatever the diagnosis. Oral Bondronat was to be taken after an overnight fast of at least six hours and before the first food or drink of the day. Fasting had to continue for at least 30 minutes after taking the tablet and patients should not lie down for 60 minutes after taking the tablet.

The Panel did not consider that the quotations disparaged Bondronat. Nor were they misleading or cherry picking the data as alleged. The Panel ruled no breach of Clauses 7.2 and 8.1 of the Code. The quotation was faithfully reproduced and accurately reflected the meaning of the authors. No breach of Clause 10.2 was ruled.

The Panel did not consider that the quotation from Heatley *et al* 'Because IV bisphosphonates are administered in a hospital or infusion centre, compliance with therapy is not a concern' had been taken out of context or was misleading. No breach of Clause 7.2 was ruled. The quotation was clearly about iv bisphosphonates and not linked to the Hoer *et al* data in the graph above it. The Panel did not consider that the quotation was clearly cherry picking of the data as alleged or that it disparaged Bondronat as alleged. No breach of Clause 8.1 was ruled. In the Panel's view the quotation was faithfully reproduced and accurately reflected the meaning of the authors. No breach of Clause 10.2 was ruled. The alleged breach of Clause 7.5 in relation to the Heatley study was considered in Point 4 above.

The Panel similarly considered that the quotation from Conte and Guarneri had not been taken out of context, was not misleading and did not disparage Bondronat. No breach of Clauses 7.2 and 8.1 were ruled. In the Panel's view the quotation accurately reflected the meaning of the authors. No breach of Clause 10.2 was ruled.

**Complaint received** **6 July 2009**

**Case completed** **29 October 2009**