CASE AUTH/2168/9/08

ROCHE v NOVARTIS

Zometa exhibition panel

Roche complained about the promotion of Zometa (zoledronic acid) by Novartis on an exhibition panel at the VII International Meeting on Cancer Induced Bone Disease 29 June – 2 July 2008.

The exhibition panel was headed 'Zometa reduces the risk of SREs [skeletal related events] more than any other bisphosphonate in advanced breast cancer'. The claim 'Intravenous zolendronate 4mg … reduces rate of skeletal events, delays the time to a skeletal event, and significantly reduces the risk of developing a skeletal event' appeared above a Forest plot which depicted the overall risk of skeletal events in advanced breast cancer by individual medicines at recommended dosing. The Forest plot was adapted from Pavlakis *et al* (2005), a Cochrane Review on Bisphosphonates for Breast Cancer (2005). This review was subsequently republished with edits on 16 July 2008.

Roche alleged that the exhibition panel headed 'Zometa reduces the risk of SREs more than any other bisphosphonate in advanced breast cancer' was inaccurate and unbalanced, misleading, incapable of substantiation and sought to disparage competitor products.

The original Cochrane diagram showed that the Zometa study was smaller than those with ibandronate and pamidronate. However, in the exhibition panel this diagram had been adapted so that all the studies appeared to contain a similar number of patients, in an attempt to misleadingly imply that they all carried the same weight.

The adapted diagram made no mention that it compared data from the reduction in risk of SREs for Zometa (an endpoint of events) with data derived from the reduction in skeletal morbidity period rate (SMPR) for ibandronate (an endpoint of time). Use of these different endpoints led to a perceived superiority in risk reduction for Zometa over ibandronate. However, elsewhere in the Cochrane report data were given for the same endpoint for these two medicines (skeletal event rate) and this showed a similar reduction in risk with both agents. Other publications also showed similar risk reductions for Zometa and ibandronate, when the same efficacy endpoint was used. Roche alleged that the exhibition panel did not give a fair and balanced view and it did not reflect all the evidence available. It made a misleading comparison between products, seeking to exaggerate the relative efficacy of Zometa in its class.

Roche alleged that the strapline 'Maintaining strength. Relieving pain' [which appeared beneath the product logo in the right-hand bottom corner of the exhibition panel] was ambiguous and all-embracing. In inter-company dialogue during April and May 2008, Novartis had agreed that when using this strapline it would add references to studies which substantiated these features of Zometa. However, no references were attached to the strapline on the exhibition panel in Edinburgh, in breach of undertaking and of the high standards expected in promotion.

The detailed response from Novartis is set out below.

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 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 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. Inter-company correspondence referred firstly to the absence of randomised controlled trials comparing the risk of SREs for Zometa versus clodronate or versus 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 at issue set out below [final two paragraphs of the full

Panel ruling]. 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. 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 very strong. 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 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 within each medicine's licence. 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 the Code was ruled.

The Panel noted that the Forest plot was adapted from one published in 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. 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 the Code 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 the Code was ruled on the narrow point alleged.

The Panel noted that the claim 'Maintaining strength. Relieving pain' appeared as a strapline beneath the product logo in the bottom right hand corner of the exhibition panel. The Zometa summary of product characteristics (SPC), pharmacodynamic properties explained that the selective action of bisphosphonates on bone was based on their high affinity for mineralised bone, but the precise molecular mechanism leading to the inhibition of osteoclastic activity was still unclear. In long-term animal studies zolendronic acid inhibited bone resorption without adversely affecting the formation, mineralisation or mechanical properties of bone. The Panel noted that any maintenance of bone strength was a consequence of Zometa's principal pharmacodynamic action, the inhibition of bone resorption. The Zometa SPC also discussed clinical trial results in the prevention of SREs in patients with advanced malignancies involving bone. In one trial patients receiving Zometa reported less increase in pain than those receiving placebo, and the difference reached significance at months 3, 9, 21 and 24. Another study reported showed that Zometa patients showed a statistically significant improvement in pain scores (using the Brief Pain Inventory) at 4 weeks and at every subsequent time point during the study when compared to placebo. The pain score for Zometa was consistently below baseline and pain reduction was accompanied by a trend in reduced analgesics score. The Panel did not consider the claim 'Maintaining strength. Relieving pain' ambiguous or all-embracing as alleged. The Panel considered that the exhibition panel was such that the claim at issue had been placed sufficiently within Zometa's licensed indication. No breach of the Code was ruled.

The Panel noted the parties' submissions about inter-company dialogue in relation to the allegation that the claim 'Maintaining Strength. Relieving Pain' should be referenced. The parties gave differing accounts of the agreement reached. The Panel considered that it was important that companies complied with agreements reached during inter-company dialogue. Such agreements should be clear. Nonetheless it was not a breach of the Code to fail to do so. Irrespective of any such agreement the Panel noted that there was no requirement under the Code to reference the claim in question. The claim had to be capable of substantiation, not misleading and otherwise comply with the Code. The Panel ruled no breach of the Code.

Roche Products Limited complained about the promotion of Zometa (zoledronic acid) by Novartis Pharmaceuticals UK Ltd on an exhibition panel at the VII International Meeting on Cancer Induced Bone Disease in Edinburgh, 29 June to 2 July 2008.

The exhibition panel was headed 'Zometa reduces the risk of SREs [skeletal related events] more than any other bisphosphonate in advanced breast cancer'. The claim 'Intravenous zolendronate 4mg … reduces rate of skeletal events, delays the time to a skeletal event, and significantly reduces the risk of developing a skeletal event' appeared above a Forest plot which depicted the overall risk of skeletal events in advanced breast cancer by individual medicines at recommended dosing. The Forest plot was adapted from Pavlakis *et al* (2005), a Cochrane Review on Bisphosphonates for Breast Cancer (2005). This review was subsequently republished with edits on 16 July 2008.

Roche supplied Bonviva (ibandronic acid). Both medicines were bisphosphonates. Inter-company dialogue had left several issues unresolved.

The clauses cited in this complaint were the same in the 2008 as in the 2006 Code.

COMPLAINT

Roche summarised its concerns, detailed in inter-company dialogue, as follows:

1 Roche alleged that the exhibition panel headed 'Zometa reduces the risk of SREs more than any other bisphosphonate in advanced breast cancer' was inaccurate and unbalanced, misleading, incapable of substantiation and sought to disparage competitor products, in breach of Clauses 7.2, 7.3, 7.4 and 8.1 of the Code.

2 The exhibition panel contained a diagram reproduced from the Cochrane Review of 2005, which purportedly substantiated the heading about SREs. The original Cochrane diagram showed that the Zometa study was smaller than those with ibandronate and pamidronate. However, in the exhibition panel this diagram had been adapted so that all 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.

3 The adapted diagram made no mention that it compared data from the reduction in risk of SREs for Zometa (an endpoint of events) with data derived from the reduction in skeletal morbidity period rate (SMPR) for ibandronate (an endpoint of time). Use of these different endpoints led to a perceived superiority in risk reduction for Zometa over ibandronate. However, elsewhere in the Cochrane report data were given for the same endpoint for these two medicines (skeletal event rate) and this showed a similar reduction in risk with both agents. Other publications also showed similar risk reductions for Zometa and ibandronate, when the same efficacy endpoint was used. Roche alleged that the exhibition panel did not give a fair and balanced view and it did not reflect all the evidence available. It made a misleading comparison between products, seeking to exaggerate the relative efficacy of Zometa in its class, in breach of Clauses 7.2, 7.3, 7.8, 7.10 and 8.1.

4 The diagram misleadingly reproduced from the Cochrane report was also shown, by the chairman, in the Novartis-sponsored satellite symposium at the Edinburgh meeting. He stated that the graph demonstrated superior efficacy of Zometa versus other bisphosphonates which Roche alleged was also a breach of Clauses 7.2, 7.3, 7.4 and 8.1.

5 Roche alleged that the strapline 'Maintaining strength. Relieving pain' [which appeared beneath the product logo in the right-hand bottom corner of the exhibition panel] was ambiguous, all-embracing and in breach of Clauses 7.2 and 7.10. In inter-company dialogue during April and May 2008, Novartis had agreed that when using this strapline it would add references to studies which substantiated these features of Zometa. However, no references were attached to the strapline on the exhibition panel in Edinburgh, in breach of undertaking and of the high standards expected in promotion. Roche alleged a breach of Clause 9.1.

RESPONSE

Novartis stated that Roche had failed to comply with the 'Guidance on inter-company dialogue' produced by the Authority. Details were given.

Novartis explained that the Cochrane review aimed to review the efficacy of bisphosphonates on skeletal events (defined as any of new bone metastases, pathological fractures, spinal cord compression, irradiation of or surgery on bone, development or progression of bone pain). The authors commented on the heterogeneity in the reporting of skeletal event endpoints and in particular the rate of events over time. They stated that recent methodological reviews of 'multiple event reporting such as events per person per year', assumed constant event rates per patient in a given time period resulted in criticism of that method and had quoted a paper in support.

Cook and Major (2001), based on a substantial study of 380 patients with metastatic breast cancer, tested the validity of the 'events per person years' methodology. This was a commonly used technique for the analysis of SREs related over constant time periods. The authors concluded that this method of estimating SREs underestimated the variability in the data. This led to an unduly narrow confidence interval for complication rates (skeletal events) and inflated false positive error rates in treatment

comparisons. Therefore in conducting the meta-analysis, the Cochrane collaborative, defined as its main objective the assessment of efficacy using the total number of SREs reported in papers. In the event of insufficient information being reported in a paper, the authors were contacted for additional information pertinent to the review methodology.

Other papers also cited the primary results (skeletal event rates) of the Cochrane meta-analysis, giving further credibility to the need for such a study and of its conclusions. For example Aapro *et al* (2007), 'Guidance on the use of bisphosphonates in solid tumours: recommendations of an international expert panel' in which the table at the centre of this complaint was also reproduced. Aapro *et al* emphasised the overall risk reduction of skeletal events, as expressed by hazard ratios for each compound at currently licensed doses as a clinically relevant outcome.

According to the paper, Roche was given the opportunity together with all manufacturers of bisphosphonates, to comment on the manuscript. As far as Novartis was aware Roche had no objection to the use of this table, as the paper was now in the public domain in its final form.

Roche alleged that the exhibition panel headed 'Zometa reduces the risk of SREs more than any other bisphosphonate in advanced breast cancer' was inaccurate and unbalanced, misleading, incapable of substantiation and sought to disparage competitor products, in breach of Clauses 7.2, 7.3, 7.4 and 8.1. In inter-company dialogue, the reason given was that there were no randomised controlled trials which compared the reduction in the risk of SREs for Zometa versus clodranate or versus ibandronate.

In the absence of comparative data derived from randomised controlled studies, the methodology employed by the Cochrane Collaborative in the form of meta-analysis, was a validated approach, with an a priori hypothesis which required strict criteria for studies to be eligible. These studies had to contain sufficient commonality (study design, patient population, similar intervention etc) for an indirect meta-analysis to be conducted. Meta-analysis was also used by the National Institute for Health and Clinical Excellence (NICE) and the Medicines and Healthcare products Regulatory Agency (MHRA) in conducting their reviews for the purpose of evaluation of medicines, licences, guidelines and guidances.

Novartis failed to see how the exhibition panel disparaged other competitors or their products. Studies that aimed to show relative differences in endpoints, where some of the products might show benefit did not disparage the remaining products. Roche had consistently alluded to breaches of Clause 8.1 in this and previous complaints. Novartis submitted this did not reflect the spirit of the Code nor did it become an organisation that should respect and adhere to the highest standards of practice.

Novartis therefore maintained that in the absence of direct head-to-head studies, a meta-analysis was a valid and substantiated method by which to derive and present relative efficacies in a clinically meaningful way.

Roche stated that the exhibition panel contained a diagram reproduced from the Cochrane review, which purportedly substantiated the headline about SREs. The original Cochrane diagram showed that the Zometa study was smaller than those with ibandronate and pamidronate. However, in the exhibition panel this diagram had been adapted so that all the studies appeared to contain a similar number of patients, in an attempt to mislead the viewer that they all carried the same weight and in breach of Clause 7.8.

Whilst Novartis acknowledged that the boxes were of different sizes in the original report, the clear provision of confidence intervals, p values and relative risk reduction figures in the diagram prevented the misinterpretation of the data. When considering a Forest plot, absolute sample size was of statistically lesser importance than the p value, confidence intervals and distance from the equivalence line. These data had been presented accurately.

Novartis denied the exhibition panel was misleading.

Roche stated that the adapted diagram made no mention that it compared data from the reduction in risk of SREs for Zometa (an endpoint of events) with data derived from the reduction in SMPR for ibandronate (an endpoint of time) in breach of Clauses 7.2, 7.3, 7.8, 7.10 and 8.1.

The Cochrane review's primary outcome measure (number of SREs) relied on the total number of skeletal events reported in each paper, in preference to adding together each type of skeletal event. Roche was concerned that for studies whose primary endpoints were not skeletal events, such as SMPR, that data would need to be derived or manipulated in order to calculate the total skeletal event rates. The Cochrane review in its section 'Data collection and analysis' and 'Statistical analysis' explained how this bias was avoided. Studies were included in the review if they contained sufficient data on total skeletal events. If insufficient data was reported, authors were contacted to provide this information directly. Novartis therefore failed to see why Roche had raised this concern.

The Cochrane review provided data in two ways; as meta-analysis of plots/tables, as used in the exhibition panel and as ratios of event rates/times to events as in table 2 of the published paper. Roche had referred to this table in inter-company dialogue as a basis for its concern. Roche stated that these data suggested similar reductions in skeletal events for both Zometa and ibandronate contradicting the

results depicted in the exhibition panel.

Novartis submitted that this table was inappropriate to use in promotional materials as data within it was for unlicensed doses of some medicines. The data presented in the exhibition panel were for the relevant licensed doses of each medicine. Further, given the concerns highlighted by the Cochrane collaborative with respect to the accuracy interpreting results from certain time-related endpoints, Novartis again submitted that this was not the most appropriate table to use. In choosing the data it had adhered to both the Code and the MHRA's regulations on the 'Promotion of Medicinal Products'.

Roche also made inappropriate reference to other individual studies, as evidence that substantial data existed outside of this meta-analyses in comparing overall risk reduction for skeletal events for bisphosphonates. The objective of the Cochrane analysis was to fill this present knowledge gap. This was acknowledged by Roche.

Novartis therefore submitted that there was no basis for this concern.

In relation to Roche's allegation that the Forest plot was misleadingly reproduced from the Cochrane report and shown by the chairman in the Novartis-sponsored satellite symposium, Novartis believed that it had addressed this in previous comments in that the provision of comprehensive statistics (point estimates, confidence intervals, p values and relative risk reductions) shown in this presentation prevented the misinterpretation of data. In addition Roche was incorrect in its belief that the slide shown by the chairman had incorrect sample size boxes. Novartis provided a copy of the slide.

Novartis therefore submitted that there was no basis for this concern.

Use of the strapline 'Maintaining strength. Relieving pain' could not be interpreted as giving additional strength to muscle or providing a substantial analgesic effect as originally stated by Roche in inter-company dialogue. In Novartis' response it had mentioned that additional references would be added. Nowhere did this state that references would be added to the strapline in all materials, as Novartis believed clinicians experienced in the use of bisphosphonates would understand the intended meaning. Novartis had provided an example of promotional material where additional references had been included.

There was a substantial body of evidence both clinical and observational that attributed pain and pathological fractures to the process of malignant spread of cancers to bone. The malignant process involved both bone invasion by cancer deposits and subsequent erosion. This resulted in pathological fractures (SREs) which could be extremely painful and debilitating, requiring both medical and social support. The use of bisphosphonates reduced the occurrence of pathological fractures by preventing the bone erosion (by reducing the activity of bone absorbing cells) therefore maintaining the bone matrix architecture and intrinsic strength.

Also important in the relief of pain by bisphosphonates was the action on osteoclasts (cells that absorbed bone) leading to their apoptosis (cell death). Pain associated with bone metastasis was considered to result from increased osteoclast activity. Osteoclasts degraded bone minerals by secreting protons through the vascular H+- ATPase, as such increased osteoclast activity was likely to lead to increased acidity in the local bone environment. This activated Acid-Sensing Ion Channel (ASIC) and Transient Receptor Potential Channel Vanilloid subfamily members leading to pain that was sometimes incapable of relief by analgesics. This gave a credible hypothesis as to why bisphosphonates might have an impact on pain in patients separate from the way more conventional analgesics worked.

Expert clinicians who specialised in cancer care, palliative care, orthopaedic surgery, radiotherapy, care of the elderly had considerable exposure to the use of this class of medicines. It was commonly accepted that bisphosphonates maintained bone strength and relieved the pain predominantly by preventing pathological fractures. The Cochrane review commented on the prevention of skeletal events and the reduction in pain. Draft NICE guidelines on 'Advanced Breast Cancer: Diagnosis and Treatment' also referred to the use of bisphosphonates in preventing fractures and their impact on pain. The Cochrane group conducted a further analysis of the use of bisphosphonates in prostate cancer in which the primary outcome under investigation was a reduction in pain.

Novartis therefore denied a breach of the Code.

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The Director noted each party's submission about inter-company dialogue. Taking all the circumstances into account the Director decided that the requirements of Paragraph 5.2 had been satisfied, save in relation one allegation and thus this matter was thus not referred to the Panel.

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PANEL RULING

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 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. The Panel noted that companies had previously been advised to submit a wholly separate and complete complaint to the Authority.

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 versus clodronate or versus 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 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 medicine's 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 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 noted that the claim 'Maintaining strength. Relieving pain' appeared as a strapline beneath the product logo in the bottom right hand corner of the exhibition panel. The Panel noted Novartis' submission that bisphosphonates reduced the occurrence of pathological fractures by preventing the bone erosion process thus

maintaining the bone matrix architecture and intrinsic strength. The Zometa summary of product characteristics (SPC), pharmacodynamic properties explained that the selective action of bisphosphonates on bone was based on their high affinity for mineralised bone, but the precise molecular mechanism leading to the inhibition of osteoclastic activity was still unclear. In long- term animal studies zolendronic acid inhibited bone resorption without adversely affecting the formation, mineralisation or mechanical properties of bone. The Panel noted that any maintenance of bone strength was a consequence of Zometa's principal pharmacodynamic action, the inhibition of bone resorption.

The Zometa SPC also discussed clinical trial results in the prevention of SREs in patients with advanced malignancies involving bone. In the first trial patients receiving Zometa reported less increase in pain than those receiving placebo, and the difference reached significance at months 3, 9, 21 and 24. The fourth study reported showed that Zometa patients showed a statistically significant improvement in pain scores (using the Brief Pain Inventory) at 4 weeks and at every subsequent time point during the study when compared to placebo. The pain score for Zometa was consistently below baseline and pain reduction was accompanied by a trend in reduced analgesics score. The Panel did not consider the claim 'Maintaining strength. Relieving pain' ambiguous or all-embracing as alleged. The Panel considered that the exhibition panel was such that the claim at issue had been placed sufficiently within Zometa's licensed indication. No breach of Clauses 7.2 or 7.10 was ruled.

The Panel noted the parties' submissions about inter-company dialogue in relation to the allegation that the claim 'Maintaining Strength. Relieving Pain' should be referenced. The parties gave differing accounts of the agreement reached. The Panel considered that it was important that companies complied with agreements reached during inter-company dialogue. Such agreements should be clear. Nonetheless it was not a breach of the Code to fail to do so. Irrespective of any such agreement the Panel noted that there was no requirement under the Code to reference the claim in question. The claim had to be capable of substantiation, not misleading and otherwise comply with the Code. The Panel ruled no breach of Clause 9.1.

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 bisphophonates. 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 on this point.

Complaint received **19 September 2008**

Case completed **12 January 2009**