CASE AUTH/1870/7/06

AMGEN v ROCHE

Promotion of NeoRecormon

Amgen complained about an exhibition panel, a brochure and slides which Roche had used to promote NeoRecormon (epoetin beta) at the European Dialysis and Transplant Association Congress in July 2006. The materials at issue referred to a poster presentation, Goldsmith *et al* (2005). Amgen supplied Aranesp (darbepoetin alfa).

The claim 'In a retrospective study, a 24% dose reduction has been demonstrated with NeoRecormon SC compared with darbepoetin alpha SC' appeared on the exhibition panel. Dose reduction claims were also referred to in a slide which featured a bar chart headed 'Route of Administration Dose Saving with Epoetin ß SC vs IV' and depicted the percentage dose saving of subcutaneous (SC) vs intravenous (IV) administration as 33% at 7-12 months and 19% at 1-6 months.

Amgen alleged that the claim that 'a 24% dose reduction has been demonstrated with NeoRecormon SC compared with darbepoetin alfa SC' did not represent the available data and was neither fair nor balanced. Goldsmith *et al* was not a prospective head-to-head-study, it was a retrospective analysis that had not been peer reviewed nor had it subsequently been published in a peer-review journal. Imbalances between patient groups could not be excluded as this was not a randomised study, distribution of brands between countries differed and the study design did not ensure similar evaluation periods.

In contrast Amgen submitted that Tolman *et al* (2005) was a well designed, prospective, randomised study which evaluated the doses of NeoRecormon and Aranesp needed to maintain stable haemoglobin. 162 unselected haemodialysis patients were converted from thrice-weekly SC NeoRecormon to a weekly administration of Aranesp (n=81) or NeoRecormon (n=81). After 9 months, the difference in haemoglobin level and dose between the two treatment arms was measured. The study showed that to maintain haemoglobin levels, a significantly higher dose of NeoRecormon than Aranesp was required ($p<0.001$). The mean dose of NeoRecormon was 44% higher than the dose of Aranesp at the end of the study. These results clearly contradicted Goldsmith *et al*.

The Panel noted that the exhibition panel was headed 'NeoRecormon', followed by 'Energy to make a difference. NeoRecormon SC is a cost efficient option for treatment of anaemia'. The claim at issue 'In a retrospective study, a 24% dose reduction has been demonstrated with NeoRecormon SC compared with darbepoetin alfa SC', was referenced to the Revised European Best Practice Guidelines 2004 (EBPG) and appeared as a bullet point immediately above a table, referenced to Goldsmith *et al*, which compared the mean weekly IV and SC doses of NeoRecormon and darbepoetin alfa.

The Panel noted that Goldsmith *et al* was a retrospective analysis which assessed anaemia management and current treatment practices with erythropoietins in patients on haemodialysis with particular emphasis on the impact that different erythropoietins and their routes of administration had on haemoglobin (Hb) control. Mean Hb levels were similar between the three cohorts: NeoRecormon, darbepoetin alfa and epoetin alfa. Hb control was defined as the proportion of Hb values within the target range of 10-12g/dl. Mean weekly SC doses for darbepoetin alfa and for epoetin beta were 10,210 IU and 7,890 IU respectively. A 24% dose reduction was possible with SC epoetin beta vs SC darbepoetin alfa.

Tolman *et al* was an open label, prospective, randomized, 9 month study which compared the clinical effectiveness of SC weekly NeoRecormon and darbepoetin alfa on conversion from thrice weekly SC NeoRecormon. There was no control group. Patients were managed according to their Hb levels. Over the course of the study maintenance of Hb levels was associated with a need to increase NeoRecormon doses whilst darbepoetin alfa doses fell. The Hb target range was 11-12g/dl. The mean weekly epoetin beta dose at 9 months was 44% higher than the mean darbepoetin alfa dose (133 IU/kg vs 92 IU/kg). The authors noted that they had failed to observe complete dose and Hb stabilization in both arms until at least week 28 after conversion.

The Panel noted that Roche had referred to a number of other studies which it considered supported its claim eg Locatelli *et al* (2003), Locatelli *et al* (2001) and Vanrenterghem *et al*. Although these studies showed that lower doses of SC epoetin beta were required than SC darbepoetin the differences between the two were less than the 24% reported by Goldsmith *et al* and ranged from 12.3% to 16.4%. Locatelli *et al* (2003) reported that the dose increase seen in patients on darbepoetin appeared to be due to the fact that they had been sub-optimally controlled whilst on SC epoetin. The studies all differed in the Hb targets which they set.

Overall the Panel considered that the data was such that the claim at issue was an oversimplification of the situation and thus did not represent the balance of the evidence. The claim was misleading as alleged. A breach of the Code was ruled.

The Panel noted that the slide depicting the bar chart entitled 'Route of Administration Dose Saving with Epoetin ß SC vs IV' was referenced to data on file and made no comparison with darbepoetin alfa. The subsequent bar chart compared the achievement of Hb target range of all erythropoietin stimulating agents (ESAs). The Panel did not know how the slide was presented at the symposium. On the evidence before it the Panel did not consider the slide constituted a misleading comparison with darbepoetin alfa and thus on this narrow point considered that it was not misleading as alleged.

The slide was also reproduced in the brochure alongside the abstract entitled 'Hb Control: Current Clinical Practice'. The Panel did not consider that it invited a comparison with darbepoetin alfa as alleged and on this narrow point no breach of the Code was ruled.

With regard to target haemoglobin levels Amgen noted that a Roche exhibition panel headed 'NeoRecormon achieves Hb stability in practice' featured the claims 'In a retrospective study (n=1098) NeoRecormon SC controls Hb levels within a 10-12g/dl range in 75% of haemodialysis patients' and 'Significantly more haemodialysis patients treated with NeoRecormon achieve constant Hb control within a 10-12g/dl range compared with darbepoetin alfa'. The claims were referenced to Goldsmith *et al*.

Furthermore, in connection with a Roche sponsored satellite symposium entitled 'Anaemia Management : from Targets to Reality', Roche distributed a brochure which included a bar chart based on Goldsmith *et al*. The bar chart was headed 'Staying Within Hb Target Range. Are all ESAs Equal' which Amgen stated purportedly showed that Aranesp enabled fewer patients to reach the Hb target range of 10-12g/dl than NeoRecormon.

Amgen alleged that Roche's claims were misleading in their treatment of target haemoglobin levels. Specifically, the target haemoglobin level (10-12g/dl) used in Goldsmith *et al* did not have real clinical relevance and was inconsistent with the EBPG recommendation that, in general, patients with chronic kidney disease should maintain a target haemoglobin concentration of > 11g/dl. ESAs should be given to all chronic kidney disease patients with haemoglobin levels consistently < 11g/dl where all other causes of anaemia had been excluded.

Also in the brochure, a haemoglobin level of ≥ 11g/dl was said to be 'recommended'. Applying the EBPG, it could be seen, even with Goldsmith at al, that more patients achieved the target level with Aranesp than with NeoRecormon: 58% of Aranesp patients reached Hb > 11g/dl, whereas only 46% of NeoRecormon patients achieved such levels.

The failure to draw readers' attention either in the exhibition panel or the brochure to the fact that Goldsmith *et al* was not consistent with the EBPG was alleged to be a distortion and directly misled the audience by undue emphasis. The material was not sufficiently complete to enable the reader to form their own opinion of the therapeutic value of the medicine.

The Panel noted that the EBPG discussed haemoglobin targets for anaemia treatment: this was dependent upon patient population and was recommended in general to be >11g/dl. Goldsmith *et al* stated that Hb control was defined as the proportion of the Hb values within the target range of 10-12g/dl during the 12 month study period. This range reflected current licences and was based on reports relating to clinical outcomes to provide acceptable variability (±1g/dl) around the EBPG Hb target of 11g/dl. The Panel noted Amgen's submission that if the EBPG were applied to Goldsmith *et al* more patients achieved the target level with darbepoetin alfa than with NeoRecormon; 58% of darbepoetin alpha patients reached Hb > 11g/dl compared to 46% of NeoRecormon.

The Panel considered that the exhibition panel was not sufficiently complete to enable the reader to form their own opinion of the therapeutic value of the medicine as alleged. The EBPG recommended target was not mentioned. A breach of the Code was ruled.

In relation to the brochure the Panel noted that the bar chart at issue depicting data from Goldsmith *et al* accompanied an abstract headed 'Hb Control: Current Clinical Practice'. The abstract began by stating 'International studies and registry data have shown consistent improvement in the management of CKD [chronic kidney disease] related anaemia, with an increasing proportion of patients achieving recommended Hb levels ≥ 11g/dl with erythropoiesis stimulating agents (ESAs)'.

The accompanying bar chart depicting the results of Goldsmith *et al*, however, referred to an Hb target range of 10-12g/dl and showed that more patients hit this range with NeoRecormon than darbepoetin alpha. The Panel considered that to refer to one target level in the text but to depict results relating to another was inconsistent and thus misleading. A breach of the Code was ruled.

Amgen alleged that the statement 'Guidelines favour SC administration for both clinical and economic reasons' referenced to EBPG was misleading. The EBPG only made such a statement regarding epoetin alfa [sic] (NeoRecormon) and only in CKD patients not undergoing dialysis and in transplant patients.

Moreover by placing this statement directly under the comparison with darbepoetin alfa regarding dose requirements via the SC route of administration, this amounted to a claim relying on an implicit comparison with Aranesp which was misleading and incapable of substantiation. The relevant parts of the EBPG were referred to. The statement that SC was recommended for economic and practical reasons was only true and capable of substantiation for epoetin alfa and epoetin beta. It was not true or capable of substantiation for darbepoetin alfa; IV darbepoetin alfa was as cost efficient as SC administration. Accordingly, the EBPG specifically pointed out that darbepoetin alfa, in contrast to NeoRecormon, could be administered either IV or SC without dose adjustments. Again this directly relevant fact was absent on the exhibition panel.

The Panel noted that the claim at issue appeared on the same exhibition panel as the comparative bullet point in the first point above and immediately beneath a table comparing the mean weekly SC and IV dose of NeoRecormon and darbepoetin alfa. The exhibition panel also featured some claims which were clearly only about NeoRecormon. Given the context in which it appeared it was unclear as to whether the claim 'Guidelines favour SC administration for both clinical and economic reasons' related only to NeoRecormon or was a comparison of NeoRecormon with darbepoetin alfa.

The Panel noted that the the EBPG read 'The recommended route of administration is dependent on the patient group being treated and the type of ESA used'. The Panel noted the economic, clinical

and practical points listed in relation to the route of administration and choice of epoetin for each patient group. Economic reasons were mentioned in relation to NeoRecormon SC for patients on dialysis, CKD patients not undergoing dialysis and in transplant patients. A table summarizing the recommendations gave SC administration as the recommended route for all patient types.

The guidelines stated that darbepoetin alfa could be given either IV or SC without dose adjustment in all CKD patients. In haemodialysis patients, darbepoetin alfa might be easier to administer IV but the SC rate was preferable in all other CKD patients. Given that there was no dose difference between IV and SC darbepoetin there was no economic reason to use the SC route. The Panel considered that given the context in which it appeared, the claim 'Guidelines favour SC administration for both clinical and economic reasons' was misleading about the guidelines' recommendations for darbepoetin alfa and not capable of substantiation in this regard. Breaches of the Code were ruled.

Amgen Limited complained about the promotion of NeoRecormon (epoetin beta) by Roche Products Limited. The materials at issue referred to a poster presentation, Goldsmith *et al* (2005), and comprised an exhibition panel, a brochure and slides which had been used by Roche at the European Dialysis and Transplant Association Congress in Glasgow, 15-17 July. Amgen supplied Aranesp (darbepoetin alfa).

1 Claim 'In a retrospective study, a 24% dose reduction has been demonstrated with NeoRecormon SC compared with darbepoetin alpha SC'

This claim appeared on Roche's exhibition panel. Dose reduction claims were also referred to in a slide presentation the relevant part of which was subsequently circulated by Roche as part of a brochure at the Congress. The slide at issue featured a bar chart headed 'Route of Administration Dose Saving with Epoetin ß SC vs IV' and depicted the percentage dose saving of subcutaneous (SC) vs intravenous (IV) administration as 33% at 7-12 months and 19% at 1-6 months.

COMPLAINT

Amgen alleged that the claim that 'a 24% dose reduction has been demonstrated with NeoRecormon SC compared with darbepoetin alfa SC' did not represent the current state of scientific research and available data. The supporting reference Goldsmith *et al* did not describe a prospective head-to-head-study, which would be the only valid evidence for the claimed advantages of NeoRecormon towards Aranesp. Goldsmith *et al*, a poster displayed at the American Society of Nephrology in November 2005, was a retrospective analysis which had not been peer reviewed, nor had it subsequently been published in a peer-review journal. Imbalances between patient groups could not be excluded as this was not a randomised study, distribution of brands between countries differed and the study design did not ensure similar evaluation periods between brands.

To comply with the Code promotional material must be accurate, balanced, fair and unambiguous and based on an up-to-date evaluation of all the evidence and reflect that evidence clearly (Clause 7.2). Amgen alleged that promotional material which relied on Goldsmith *et al* and ignored the conclusions of the well designed, prospective, randomised study of Tolman *et al* (2005) did not comply with the Code. Tolman *et al* demonstrated that dose increases were required with NeoRecormon. The conference displays were neither fair nor balanced and were not an up to date evaluation of all the evidence.

Tolman *et al* evaluated the doses of NeoRecormon and Aranesp needed to maintain stable haemoglobin. 162 unselected haemodialysis patients were converted from thrice-weekly SC NeoRecormon to weekly administration of Aranesp (n=81) or NeoRecormon (n=81). After 9 months, the difference in haemoglobin level and dose between the two treatment arms was measured. The study showed that to maintain haemoglobin levels, a significantly higher dose of NeoRecormon than Aranesp was required ($p<0.001$). The mean dose of NeoRecormon was 44% higher than the dose of Aranesp at the end of the study.

These results clearly contradicted Goldsmith *et al*. As a retrospective analysis, Goldsmith *et al* had a lower evidential value than Tolman *et al* and could not be used to disprove the results of Tolman *et al*. As it was, Tolman *et al* was not even mentioned in the conference materials. Furthermore, Roche failed to provide the relevant details of Goldsmith *et al* to enable readers to evaluate it for themselves. Amgen considered that Roche's misleading claims in relation to dose reduction were compounded by their use in a slide presentation of graphs which referred only to Roche data on file and Goldsmith *et al* and not to Tolman *et al*. Copies of selected slides, including the slide containing the graphs, were subsequently circulated by Roche at the congress. Amgen alleged that the exhibition panel, the brochure and the graphs were all in breach of Clause 7.2 of the Code.

RESPONSE

Roche stated that the claim was referenced solely to Goldsmith *et al*. However, Roche disputed that this was not a true representation of the current state of scientific research and of the available data. Data supplied to Amgen confirmed that the majority of multicentre, randomised, peer-reviewed published clinical studies that demonstrated dose difference between patients on darbepoetin and epoetin confirmed that, assuming that dose ratio was 200:1 as per Aranesp summary of product characteristics (SPC), a relatively smaller dose of SC epoetin was required than SC darbepoetin (Locatelli *et al* 2003; Locatelli *et al* 2001; Macdougall *et al* 2003; Vanrenterghem *et al* 2002 and Locatelli *et al* 2002).

The SPC for Aranesp recognised that the doses for IV darbepoetin and SC darbepoetin were equivalent. However, data suggested that there was a dose reduction required when transferring patients from IV erythropoietin stimulating agents (ESAs) to SC epoetin beta. This suggested that there would be

expected to be a dose reduction between SC darbepoetin and SC NeoRecormon. Locatelli *et al* (2003) reported a 9% increase in darbepoetin dose when switching from SC epoetin beta to SC darbepoetin.

Amgen suggested that excluding Tolman *et al* from the data presented at the congress was misleading but, since it was the only paper that indicated that a higher dose of NeoRecormon than darbepoetin was required in order to achieve the same clinical effect, and the design had not been replicated at any other centre to Roche's knowledge, using as it did a complicated and unique computerised algorithm for determining dose rarely used elsewhere. Thus the balance of evidence supported the claim at issue. Additionally there were a number of other anomalies in the design of this study: it did not compare like with like, with darbepoetin being administered via pre-filled syringes, and yet (despite the availability of prefilled syringes of NeoRecormon) multidose vials of NeoRecormon were used, allowing for a greater degree of dosing error in this group. Tolman *et al* was a single centre study without a true control arm. Once patients had been stabilised on NeoRecormon three times weekly, all patients were then randomised to the once weekly regimen, leaving no patients on the three times weekly dose. Further, two thirds of the patients in the epoetin beta arm were male, while the genders were equally split in the darbepoetin arm.

Interestingly, other studies (Locatelli *et al* 2002 and Weiss *et al* 2000) had demonstrated no dose penalties when changing from thrice weekly to once weekly epoetin beta, and yet Tolman *et al* again stood out as not reflecting the balance of evidence, since patients required a significant dose increase. This had been an ongoing source of inter-company dialogue.

Roche also noted that the majority of the results presented in Tolman *et al* and all presented in abstracts and presentations had been from the per protocol analysis, and although the publication referred to a 'modified' intention to treat only population (ITT), an ITT analysis had, to Roche's knowledge, never been presented. It was well accepted that presenting data only on those patients that completed the study and not on the ITT population led to bias in the results. The lead author of this study was, at the time of acceptance for publication, (as he remained) an Amgen employee although he was not recognised as such in the publication.

Roche therefore refuted the assertion that the use of Goldsmith *et al* was not accurate, balanced, fair and unambiguous. It was indeed an up-to-date and a fair reflection of the evidence available and not in breach of Clause 7.2.

PANEL RULING

The Panel noted that the exhibition panel was headed 'NeoRecormon' in logo format, followed by 'Energy to make a difference. NeoRecormon SC is a cost efficient option for treatment of anaemia'. The claim at issue 'In a retrospective study, a 24% dose reduction has been demonstrated with NeoRecormon SC compared with darbepoetin alfa SC', was referenced to the Revised European Best Practice Guidelines 2004 (EBPG) and appeared as a bullet point immediately above a table, referenced to Goldsmith *et al*, which compared the mean weekly IV and SC doses of NeoRecormon and darbepoetin alfa.

The Panel noted that Goldsmith *et al*, a poster presentation, was a retrospective analysis which assessed anaemia management and current treatment practices with erythropoietins in patients on haemodialysis with particular emphasis on the impact that different erythropoietins and their routes of administration had on haemoglobin (Hb) control. Mean Hb levels were similar between the three cohorts: NeoRecormon, darbepoetin alfa and epoetin alfa. Hb control was defined as the proportion of Hb values within the target range of 10-12g/dl. Mean weekly SC doses for darbepoetin alfa and for epoetin beta were 10,210 IU and 7,890 IU respectively. A 24% dose reduction was possible with SC epoetin beta vs SC darbepoetin alfa.

Tolman *et al* was an open label, prospective, randomized, 9 month study which compared the clinical effectiveness of SC weekly NeoRecormon and darbepoetin alfa on conversion from thrice weekly SC NeoRecormon. There was no control group. Patients were managed according to their Hb levels. Over the course of the study maintenance of Hb levels was associated with a need to increase NeoRecormon doses whilst darbepoetin alfa doses fell. The Hb target range was 11-12g/dl. The mean weekly epoetin beta dose at 9 months was 44% higher than the mean darbepoetin alfa dose (133 IU/kg vs 92 IU/kg). The study authors noted that they had failed to observe complete dose and Hb stabilization in both arms until at least week 28 after conversion.

The Panel noted that Roche had referred to a number of other studies which it considered supported its claim eg Locatelli *et al* (2003), Locatelli *et al* (2001) and Vanrenterghem *et al*. Although these studies showed that lower doses of SC epoetin beta were required than SC darbepoetin the differences between the two were less than the 24% reported by Goldsmith *et al* and ranged from 12.3% to 16.4%. Locatelli *et al* (2003) reported that the dose increase seen in patients on darbepoetin appeared to be due to the fact that they had been sub-optimally controlled whilst on SC epoetin. The studies all differed in the Hb targets which they set.

Overall the Panel considered that the data was such that the claim at issue was an oversimplification of the situation and thus did not represent the balance of the evidence. The claim was misleading as alleged. A breach of Clause 7.2 was ruled.

The Panel noted that the slide depicting the bar chart entitled 'Route of Administration Dose Saving with Epoetin ß SC vs IV' was referenced to data on file and made no comparison with darbepoetin alfa. The subsequent bar chart compared the achievement of Hb target range of all ESAs. The Panel did not know how the slide was presented at the symposium. On the evidence before it the Panel did not consider the slide constituted a misleading comparison with darbepoetin alfa and thus on this narrow point considered that it was not misleading as alleged; no

breach of Clause 7.2 was ruled.

The slide was also reproduced in the brochure alongside the abstract entitled 'Hb Control: Current Clinical Practice'. The Panel did not consider that it invited a comparison with darbepoetin alfa as alleged and on this narrow point no breach of Clause 7.2 was ruled.

2 Treatment of target haemogloblin levels

An exhibition panel headed 'NeoRecormon achieves Hb stability in practice' featured the claims 'In a retrospective study (n=1098) NeoRecormon SC controls Hb levels within a 10-12g/dl range in 75% of haemodialysis patients' and 'Significantly more haemodialysis patients treated with NeoRecormon achieve constant Hb control within a 10-12g/dl range compared with darbepoetin alfa' appeared on a Roche exhibition stand referenced to Goldsmith *et al*.

In connection with a Roche sponsored satellite symposium entitled 'Anaemia Management : from Targets to Reality', Roche distributed a brochure which included a bar chart based on Goldsmith *et al*. The bar chart was headed 'Staying Within Hb Target Range. Are all ESAs Equal' which Amgen stated purportedly showed that Aranesp enabled fewer patients to reach the Hb target range of 10-12g/dl than NeoRecormon.

COMPLAINT

Amgen stated that Roche's claims were misleading in their treatment of target haemoglobin levels. Specifically, the target haemoglobin level (10-12g/dl) used in Goldsmith *et al* did not have real clinical relevance and was inconsistent with the European Best Practice Guidelines (EBPG) that were widely applied in clinical practice throughout Europe. The EBPG recommended that, in general, patients with chronic kidney disease should maintain a target haemoglobin concentration > 11g/dl. Erythropoiesis-stimulation agents should be given to all chronic kidney disease patients with haemoglobin levels consistently < 11g/dl where all other causes of anaemia had been excluded.

Roche accepted this since, in the same Roche-sponsored brochure circulated in connection with its satellite symposium, a haemoglobin level ≥ 11g/dl was said to be 'recommended'. Applying the EBPG, it could be seen, even with Goldsmith at al, that more patients achieved the target level with Aranesp than with NeoRecormon: 58% of Aranesp patients reached Hb > 11g/dl, whereas only 46% of NeoRecormon patients achieved Hb target > 11g/dl. Bizarrely, however, the brochure referred to Goldsmith *et al* which was based on a target haemoglobin of 10-12g/dl, purportedly to demonstrate greater efficacy of NeoRecormon in comparison to Aranesp. A copy of an abstract Hb control: Current Clinical Practice from the brochure was provided. Amgen did not consider that it represented a balanced representation of the evidence. Amgen alleged that this piece misled the reader both by distortion and undue emphasis.

The failure to draw readers' attention either in the exhibition panel claims or the Roche brochure to the fact that Goldsmith *et al* was not consistent with the EBPG was a distortion and directly misled the audience by undue emphasis. The material was not sufficiently complete to enable the reader to form their own opinion of the therapeutic value of the medicine. These claims, therefore, breached Clause 7.2 of the Code.

RESPONSE

Roche stated that the current UK Renal Association guidelines referred to the target haemoglobin level of ≥ 10g/dl with anaemia being diagnosed when haemoglobin levels fell below 12g/dl. This led to the target range of 10-12g/dl being included the protocol for Goldsmith *et al*. The updated EBPG had been published since the initiation of Goldsmith *et al*, but the UK Renal Association continued to recommend that individual patients' Hb levels should be maintained about 10g/dl. It would clearly be misleading and distortion to present the data from this study by using a target Hb level not included within the protocol. Notwithstanding that Roche did when appropriate refer to the EBPG.

Goldsmith *et al* was designed to identify haemodialysis patients who maintained stable haemoglobin levels within a target range of 10-12g/dl. Whilst Amgen stated that 58% of darbepoetin alfa patients reached Hb > 11g/dl compared with 46% of NeoRecormon patients, this end point was not included in the study. When presented and understood within the right context, neither the materials nor the symposia speaker distorted or misrepresented the results of Goldsmith *et al*.

Reference was made at the Roche sponsored symposium to the Goldsmith data and the target range that was included in the protocol as discussed above. The data presented in the brochure therefore did not seek to mislead by either distortion or undue emphasis. Further the brochure was only available to those attending the symposium who therefore were subject to the complete oral programme. Amgen had, Roche believed, been somewhat disingenuous by selecting only one page from the brochure provided rather than leaving it in context. Roche firmly considered that the symposium brochure did not breach Clause 7.2 as alleged.

PANEL RULING

The Panel noted that the EBPG Section II 'Targets for anaemia treatment' discussed appropriate haemoglobin targets for anaemia treatment: this was dependent upon patient population and was recommended in general to be > 11g/dl. Goldsmith *et al* stated that Hb control was defined as the proportion of the Hb values within the target range of 10-12g/dl during the 12 month study period. This range reflected current licences and was based on reports relating to clinical outcomes to provide acceptable variability (±1g/dl) around the EBPG Hb target of 11g/dl. The Panel noted Amgen's submission that if the EBPG were applied to the Goldsmith *et al* data more patients achieved the target level with darbepoetin alfa than with NeoRecormon; 58% of darbepoetin alpha patients reached Hb >

11g/dl compared to 46% of NeoRecormon.

The Panel considered that the exhibition panel was not sufficiently complete to enable the reader to form their own opinion of the therapeutic value of the medicine as alleged. The EBPG recommended target was not mentioned. A breach of Clause 7.2 was ruled.

In relation to the brochure the Panel noted that the bar chart at issue depicting data from Goldsmith *et al* accompanied an abstract headed 'Hb Control: Current Clinical Practice'. The abstract began by stating 'International studies and registry data have shown consistent improvement in the management of CKD [chronic kidney disease] related anaemia, with an increasing proportion of patients achieving recommended Hb levels ≥11g/dl with erythropoiesis stimulating agents (ESAs)'.

The accompanying bar chart depicting the results of Goldsmith *et al*, however, referred to an Hb target range of 10-12g/dl and showed that more patients hit this range with NeoRecormon than darbepoetin alpha. The Panel considered that to refer to one target level in the text but to depict results relating to another was inconsistent and thus misleading. A breach of Clause 7.2 was ruled.

3 Claim 'Guidelines favour SC administration for both clinical and economic reasons'

COMPLAINT

Amgen alleged that the statement 'Guidelines favour SC administration for both clinical and economic reasons' was referenced to EBPG was misleading. The EBPG only made such a statement regarding epoetin alfa [sic] (NeoRecormon) and only in CKD patients not undergoing dialysis and in transplant patients. Yet this qualification was not included.

Moreover by placing this statement directly under the comparison with darbepoetin alfa regarding SC dose requirements, this statement amounted to a claim relying on an implicit comparison with Aranesp which was misleading and incapable of substantiation. More specifically under the heading 'Recommendation' the relevant parts of the EBPG stated:

> 'The recommended route of administration is dependent on the patient group being treated and the ESA being used.
>
> - For patients on HD [haemodialysis], the intravenous (i.v.) route may be preferable for comfort and convenience, but the subcutaneous (s.c.) route can substantially reduce the dose requirements of ESA.
> - In CKD patients not undergoing dialysis and in transplant patients, epoetin beta should preferably be given s.c. for both economic and practical reasons.
> - Epoetin alfa (Eprex, Erypo) is not licensed for s.c. administration in all CKD patients in many European countries (including all member states of the European Union) due to the risk of pure red cell aplasia (PRCA).
> - Darbepoetin alfa can be given either i.v. or s.c. without dose adjustments in all CKD patients. In HD patients, darbepoetin alfa may be easier to administer i.v., but the s.c. route is preferable in all other CKD patients.'

Therefore the statement that SC was recommended for economic and practical reasons was only true and capable of substantiation for epoetin alfa and epoetin beta. It was not true or capable of substantiation for darbepoetin alfa. With darbepoetin alfa, the IV route of administration was as cost efficient as SC administration. Accordingly, the EBPG specifically pointed out that darbepoetin alfa, in contrast to NeoRecormon, could be administered either IV or SC without dose adjustments. Again this directly relevant fact was noticeably absent on the exhibition panel.

Amgen alleged a breach of Clauses 7.2, 7.3 and 7.4 of the Code.

RESPONSE

Roche stated that Amgen had mistakenly referred to NeoRecormon as epoetin alfa, but the guidelines did state that in CKD epoetin beta (NeoRecormon) should be administered preferably via the SC route. However the above statement used at the congress referred to the overall position of the EBPG. Guideline III.II referred to the route of administration of epoetin, suggesting that:

- 'For patients on HD the intravenous route (IV) may be preferable for comfort and convenience, but the subcutaneous route (SC) may substantially reduce the dose requirements of ESA' (Evidence level A)
- 'In CKD patients not undergoing dialysis and in transplant patients epoetin beta should preferably be given subcutaneously for both economic and practical reasons'
- 'Patients on dialysis should preferably be given epoetin beta subcutaneously for economic reasons' (Evidence level A)
- 'Epoetin alfa (Eprex, Erypo) is not licensed for SC administration in all CKD patients in many European countries (including all member states of the European Union) due to the risk of pure red cell aplasis (PRCA)' (Evidence level B)
- 'Darbepoetin alfa can be given either IV or SC without dose adjustments in all CKD patients. In HD patients, darbepoetin alfa may be easier to administer but the SC route is preferable in all other CKD patients' (Evidence level B).

Roche therefore believed that the EBPG fully supported its statement that they favoured SC administration for both clinical and economic reasons and Roche completely refuted the suggestion that this statement was in breach of Clauses 7.2, 7.3 and 7.4 of the Code, being neither inaccurate, unbalanced, unfair, unobjective nor ambiguous. It did not mislead and did not seek to compare NeoRecormon with Aranesp.

PANEL RULING

The Panel noted that the claim at issue appeared on the same exhibition panel as the comparative bullet

point at issue at point 1 above and immediately beneath a table comparing the mean weekly SC and IV dose of NeoRecormon and darbepoetin alfa. The exhibition panel also featured some claims which were clearly only about NeoRecormon. Given the context in which it appeared it was unclear as to whether the claim 'Guidelines favour SC administration for both clinical and economic reasons' related only to NeoRecormon or was a comparison of NeoRecormon with darbepoetin alfa.

The Panel noted that the introductory paragraph of Guideline III.II of the EBPG read 'The recommended route of administration is dependent on the patient group being treated and the type of ESA used'. The Panel noted the economic, clinical and practical points listed in relation to the route of administration and choice of epoetin for each patient group. Economic reasons were mentioned in relation to NeoRecormon SC for patients on dialysis, CKD patients not undergoing dialysis and in transplant patients. A table summarizing the recommendations gave SC administration as the recommended route for all patient types.

The guidelines stated that darbepoetin alfa could be given either IV or SC without dose adjustment in all CKD patients. In HD patients, darbepoetin alfa might be easier to administer IV but the SC rate was preferable in all other CKD patients. Given that there was no dose difference between IV and SC darbepoetin there was no economic reason to use the SC route. The Panel considered that given the context in which it appeared, the claim 'Guidelines favour SC administration for both clinical and economic reasons' was misleading about the guidelines' recommendations for darbepoetin alfa and not capable of substantiation in this regard. Breaches of Clauses 7.2, 7.3 and 7.4 were ruled.

Complaint received **27 July 2006**

Case completed **4 December 2006**