CASE AUTH/2079/1/08 and CASE AUTH/2080/1/08 *NO BREACH OF THE CODE*

ROCHE and GLAXOSMITHKLINE v SANOFI-AVENTIS and PROCTER & GAMBLE

Actonel exhibition panel

Roche and GlaxoSmithKline alleged that an exhibition panel for Actonel (risedronate) used by Sanofi-Aventis and Procter & Gamble (the Alliance for Better Bone Health, ABBH) contained claims which were inconsistent with the summary of product characteristics (SPC) and used data outwith the product licence.

Actonel 5mg was for once daily administration and Actonel 35mg was for once weekly administration. Both products were indicated for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral fractures and treatment of established postmenopausal osteoporosis, to reduce the risk of hip fractures. In addition Actonel 5mg was indicated in the prevention of osteoporosis in postmenopausal women with increased risk of osteoporosis and in postmenopausal women undergoing long-term systemic corticosteroid treatment. Actonel 35mg was indicated for the treatment of osteoporosis in men at high risk of fracture. Roche and GlaxoSmithKline co-marketed Bonviva (ibandronate) for the treatment of postmenopausal osteoporosis.

Bisphosphonates had a well established safety profile and their effects on the gastrointestinal tract were understood. The SPCs for all the bisphosphonates included a statement under special warnings and precautions for use relating to GI tolerability. The relevant section of the Actonel SPC stated:

'Some bisphosphonates have been associated with oesophagitis and oesophageal ulcerations. Therefore patients should pay attention to the dosing instructions (see section 4.2). In patients who have a history of oesophageal disorders which delay oesophageal transit or emptying e.g. stricture or achalasia, or who are unable to stay in the upright position for at least 30 minutes after taking the tablet, risedronate sodium should be used with special caution because of limited clinical experience in these patients. Prescribers should emphasise the importance of the dosing instructions to these patients.'

Roche and GlaxoSmithKline alleged that the exhibition panel contradicted the warnings and special precautions for use within the Actonel SPC. Although the exhibition panel had the statement from the SPC within it, it appeared as a footnote, in small text within a box dedicated to a single trial rather than prominent and associated with the high level claims made in the exhibition panel.

Taggart *et al* was a pooled analysis of 9 studies that used Actonel 5mg daily. Very little Actonel 5mg was prescribed in the UK; the significant majority of patients took 35mg once weekly. Unlike efficacy measures, safety data could not simply be bridged from one formulation to another, particularly in the case of bisphosphonates which had been specifically formulated in longer interval dose formulations to avoid the adverse effects and inconvenience associated with dosing. Of specific concern was that the data presented included a proportion (1.7%) of patients in which Actonel could not be prescribed because, inter alia, they were either male or premenopausal.

Overall Roche and GlaxoSmithKline believed that the ABBH had used inconsistent safety messages in promotional material that could potentially mislead prescribers and adversely impact patient safety.

The Panel examined the exhibition panel which was headed 'In postmenopausal osteoporosis' followed by 'Tailor your osteoporosis therapy to your individual patients' needs'. This was followed by a section referring to patients taking concomitant medication (aspirin/NSAID/proton pump inhibitor (PPI)) or having a history of or current GI illness (excluding conditions which delayed oesophageal transit or emptying). The subject of the exhibition panel was thus a specific subset of patients with postmenopausal osteoporosis. A large box headed 'Actonel 5mg daily' stated that in patients who regularly took acetyl salicylic acid or NSAIDs on 3 or more days per week the incidence of upper GI adverse events in such patients was similar to that in control patients. This statement, which appeared in both the Actonel 5mg and 35mg SPCs, was followed by a bar chart referenced to Taggart *et al* headed 'Actonel's upper GI tolerability profile in patients at risk of upper GI side effects in clinical trials of up to 3 years duration'. A footnote to the bar chart stated that Taggart *et al* included 1.7% of the population that were men or premenopausal women and that these patient groups were not licensed for treatment with Actonel 5mg. Beside the bar chart was a prominent statement that in the Actonel 5mg Phase III trials, patients were not excluded because of previous or current GI illness or use of medicines associated with GI intolerance such as NSAIDs or aspirin, (Reginster *et al* 2000 and Harris *et al* 1999). The box also included the bisphosphonates class warning which again appeared in both Actonel SPCs.

Taggart *et al* concluded that treatment with 5mg risedronate did not result in higher frequency of

upper GI tract events amongst patients who had active GI tract disease or required treatment with gastric antisecretory medicines or patients who were receiving concomitant treatment with aspirin or NSAIDs. To establish the applicability of these findings to clinical practice it would be important to have comprehensive postmarketing data on risedronate.

The Panel noted that neither the Actonel 5mg SPC nor the Actonel 35mg SPC included any warnings advising against concomitant use of NSAIDs, whereas Section 4.4 of the Bonviva (150mg) SPC stated 'Since NSAIDs and bisphosphonates are both associated with gastrointestinal irritation, caution should be taken during concomitant administration'.

The Panel noted that the exhibition panel referred generally to patients taking concomitant medicine likely to cause GI problems or with a history of or current GI illness. It then went on to refer only to the 5mg dose. Health professionals would be aware of the dosing instructions for bisphosphonates and in that regard noted the complainants' submission that the effects of biphosphonates on the GI tract were well understood.

The Panel considered that the exhibition panel was clear that the data related to Actonel 5mg. It noted the complainants' view that this was a rarely used dose. The Panel did not accept that the exhibition panel stated or implied that data from the 5mg applied to the 35mg dose as alleged even though in some cases it did for example, the class warning and the statement regarding regular acetyl salicylic acid or NSAID users. There was no mention of the 35mg dose. The 35mg Actonel SPC stated that in a one year study of postmenopausal women with osteoporosis the overall safety and tolerability profiles of the 5mg daily dose and the 35 mg weekly dose were similar. It added, however, that investigators reported a greater incidence in GI disorder (1.6% vs 1%) for 35mg Actonel compared to the 5mg dose.

The Panel noted that Taggart *et al* included patients (1.7% of the population) who were not within the licensed indication for Actonel 5mg. The data was used in relation to tolerability not efficacy. The exhibition panel only included photographs of older (ie postmenopausal) women and was headed 'In postmenopausal women …' in the circumstances the Panel did not consider that the data promoted the use of Actonel 5mg in unlicensed patient populations as alleged. The Panel ruled no breach of the Code.

The Panel considered the exhibition panel was not inconsistent with the Actonel 5mg SPC; no breach of the Code was ruled.

The Panel did not consider that the information about side effects failed to reflect current evidence. The SPC warning was included. Nor did it fail to encourage rational use. Thus no breach of the Code was ruled.

The Panel considered that the bisphosphonate class warning about special caution when using Actonel in certain patients might have been more prominent, ie appear in the same section as the information about patients who regularly used aspirin and NSAIDs, nonetheless it did not consider that in the circumstances it was misleading for it to appear where it had. No breach of the Code was ruled.

Roche Products Limited and GlaxoSmithKline UK Ltd complained about an exhibition panel (ref ACT 3664) for Actonel (risedronate) used by Sanofi-Aventis and Procter & Gamble Pharmaceuticals UK Ltd (the Alliance for Better Bone Health, ABBH). The exhibition panel was displayed at the British Society of Geriatrics meeting held in Harrogate (21-23 November 2007) and the National Osteoporosis Society meeting in Edinburgh (26-28 November 2007).

Actonel 5mg was for once daily administration and Actonel 35mg was for once weekly administration. Both products were indicated for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral fractures and treatment of established postmenopausal osteoporosis, to reduce the risk of hip fractures. In addition Actonel 5mg was indicated in the prevention of osteoporosis in postmenopausal women with increased risk of osteoporosis and in postmenopausal women undergoing long-term systemic corticosteroid treatment. Actonel 35mg was indicated for the treatment of osteoporosis in men at high risk of fracture.

Roche and GlaxoSmithKline co-marketed Bonviva (ibandronate) for the treatment of postmenopausal osteoporosis.

COMPLAINT

The claims in question related to the use of Taggart *et al* (2002) and the inappropriate use of safety data in high level promotional claims which were originally noted in an Actonel leavepiece (ACT3543).

The basis of the concerns remained around the use of claims about safety that were inconsistent with the Actonel summary of product characteristics (SPC) and the use of data in promotional material that contained data outside the product's licence.

Bisphosphonates as a class were associated with a well established safety profile. The effects of bisphosphonates on the gastrointestinal tract were well understood. The SPCs for all the bisphosphonates included a statement under special warnings and precautions for use relating to GI tolerability. The relevant section of the Actonel SPC stated:

> 'Some bisphosphonates have been associated with oesophagitis and oesophageal ulcerations. Therefore patients should pay attention to the dosing instructions (see section 4.2). In patients who have a history of oesophageal disorders which delay oesophageal transit or emptying e.g. stricture or achalasia, or who are unable to stay in the upright position for at least 30 minutes after taking the tablet, risedronate sodium should be used with

special caution because of limited clinical experience in these patients. Prescribers should emphasise the importance of the dosing instructions to these patients.'

Roche and GlaxoSmithKline alleged that the leavepiece and the exhibition panel, contradicted the warnings and special precautions for use within the Actonel SPC. It was recognised that the exhibition panel had the statement from the SPC within it however it was a footnote, in small text within a box dedicated to a single trial rather than prominent and associated with the high level claims made in the exhibition panel. The companies did not believe that this small footnote met the assurances or their concerns and was not in keeping with the spirit of the Code when ABBH stated that it would review the materials in the light of discussions.

Taggart *et al* was a pooled analysis of 9 studies that used Actonel 5mg daily. This 5mg dose made up a very small proportion of the actual Actonel prescribed in the UK. The significant majority of patients took 35mg once weekly. In 'quarter 2' of 2007 IMS data showed that 96.6% of scripts written in the community were for the weekly preparation and only 3.4% for the daily 5mg dose. Unlike standard or surrogate efficacy measures, safety data could not simply be bridged from one formulation to another, particularly in the case of bisphosphonates which had been specifically formulated in longer interval dose formulations to avoid the adverse effects and inconvenience associated with dosing. Of specific concern was that the data presented included a proportion (1.7%) of patients in which Actonel could not be prescribed, ie they were either male or premenopausal. The licensed indications for Actonel 5mg daily did not include the treatment of osteoporosis in either of these patient groups. Additionally the following groups included in Taggart *et al* were out of licence for Actonel 35mg weekly: pre- and postmenopausal women with, or at risk of, corticosteroid-induced osteoporosis, males with, or at risk of, corticosteroid-induced osteoporosis.

The ABBH asserted that stating these facts within the material, in very small font as a footer, allowed it to use these data and address Roche and GlaxoSmithKline's previous concerns. The ABBH also believed that this was permissible as it related to safety. Roche and GlaxoSmithKline accepted in the context of balanced material or material that was non promotional, that such data were valid and assisted the prescriber. In this case however these data were being used to support prominent and high level claims for the use of a medicine in patients who would in all probability receive the weekly rather than the daily dose and in whom special consideration for the GI adverse effects of bisphosphonates must be considered. Roche and GlaxoSmithKline believed the addition of a small footer on a large exhibition panel with a prominent claim did not meet the assurances given in intercompany dialogue.

Overall Roche and GlaxoSmithKline believed that the ABBH had used inconsistent safety messages in promotional material that could potentially mislead prescribers and adversely impact patient safety.

Breaches of Clauses 3.2, 7.2, 7.9 and 7.10 of the Code were alleged.

RESPONSE

Sanofi-Aventis and Procter & Gamble submitted a joint response as the ABBH.

The ABBH noted that Roche and GlaxoSmithKline referred to two meetings but they only referred to one exhibition panel ACT3664. In fact, ACT3664 was shown at the Harrogate meeting and an amended exhibition panel, ACT3599 was shown at the Edinburgh meeting.

At both meetings, which were national scientific congresses, these exhibition panels were shown at the Actonel booth, which was in an exhibition hall, and amongst those from other companies involved in osteoporosis management. The exhibition panels were certified solely for use at these congresses and were thus no longer in use.

The ABBH had taken every opportunity to enter into dialogue with Roche and GlaxoSmithKline including sending copies of the exhibition panel for them to review. This was clear evidence of transparency. The ABBH considered it had done everything possible to maintain a healthy intercompany dialogue and had not misled Roche and GlaxoSmithKline.

The ABBH noted that the main basis for the allegation that tolerability data in the exhibition panels was inconsistent with the SPC for Actonel (specifically in relation to Section 4.4 of the SPC) appeared to be what Roche and GlaxoSmithKline inappropriately referred to as a 'footnote'. This explanatory text was immediately adjacent to the bar chart presenting data and appeared in the same field of vision for the reader. The text was taken directly from Section 4.4 of the Actonel SPC and provided necessary information for health professionals to make an informed decision on their choice of therapy:

'Bisphosphonates have been associated with oesophagitis and oesophageal ulcerations. Therefore patients should pay attention to the dosing instructions. In patients who have a history of oesophageal disorders which delay oesophageal transit or emptying e.g. stricture of achalasia, or who are unable to stay in the upright position for at least 30 minutes after taking the tablet, risedronate sodium should be used with special caution because of limited clinical experience in these patients. Prescribers should emphasise the importance of the dosing instructions to these patients'.

Given the prominence of this text within the exhibition panel used in Harrogate and the overall size of the panel (1.95 metres high x 3.28 metres wide), the text in question was very clear (font size of 1.11cm and the height of the paragraph in question was approximately 0.15 metres). The same could be said for the exhibition panel used in Edinburgh (an overall size of 2.4 metres

high x 4 metres wide, with a font size of the text in question of 1.86cm and the height of the paragraph in question was approximately 0.25 metres).

Additionally, from the wording, health professionals were advised to exclude postmenopausal women with osteoporosis with conditions which delayed oesophageal transit or emptying when considering whether treatment was appropriate.

It should also be noted that Section 5.2 of the SPC for Actonel also stated that 'Among regular acetyl salicylic acid or NSAID users (3 or more days per week) the incidence of upper gastrointestinal adverse events in Actonel treated patients was similar to that in control patients'.

The ABBH considered that sharing these tolerability data in the exhibition panels was not inconsistent with the Actonel SPC and therefore not in breach of the Code.

The ABBH noted that Roche and GlaxoSmithKline had alleged that the tolerability data in the exhibition panels referred to some patients who were outside of the terms of the Actonel licence and also that safety data could not be bridged from one formulation to another.

The ABBH noted that this latter point had not been raised during the intercompany dialogue, nor had the ABBH made or inferred bridging of safety data between dosages. The data included in both exhibition panels was for the Actonel 5mg dosage only and was clearly labelled so.

That said, the Actonel 35mg SPC stated:

> '… comparing risedronate sodium 5mg daily … and risedronate 35mg weekly … in postmenopausal women with osteoporosis, the overall safety and tolerability profiles were similar'.

Given that these data had been reviewed by the regulatory authorities which approved the text in the SPC and the ABBH had not made any bridging statements on safety, the complainants' comments were inappropriate and the ABBH considered that the Code had not been breached.

With regard to the issue that the data presented included a proportion of patients not currently within the licence for Actonel (1.7% of the population were either male or premenopausal women), the ABBH stated that these were tolerability data, not efficacy. It was important to ensure health professionals saw balanced and robust data and it would be inconceivable to prohibit sharing of an analysis such as that by Taggart *et al* when 98.3% of the overall population was within the product licence.

Taggart *et al* conducted a pooled analysis including 9 randomised, double-blind, placebo-controlled, parallel group, Phase 3 studies of the risedronate clinical program. This included over 10,000 patients.

It was clearly stated on the exhibition panels that 1.7% of the population included in Taggart *et al*, were male or premenopausal women and that these were not patient populations included in the product licence for Actonel 5mg.

The exhibition panels did not encourage the prescription of Actonel to patient populations outside the product licence. To clarify this point, the top of the exhibition panel stated that the population referred to was postmenopausal osteoporosis.

It was clear that in the context of a piece about tolerability that this information was included for transparency to allow health professionals to fully assess the validity of the data and was obviously not presented to encourage use of Actonel in these populations.

The ABBH strongly believed it had done all it could to have open and transparent intercompany dialogue and regretted that Roche and GlaxoSmithKline had considered it necessary to escalate this to the Authority.

The ABBH hoped it had addressed all the elements that suggested breaches of Clauses 3.2, 7.2, 7.9 and 7.10 with regard to exhibition panels at issue.

PANEL RULING

The Panel examined exhibition panel ACT3664. There was no complaint regarding ACT3599. Exhibition Panel ACT3664 was headed 'In postmenopausal osteoporosis' followed by 'Tailor your osteoporosis therapy to your individual patients' needs'. This was followed by a section referring to patients taking concomitant medication (aspirin/NSAID/proton pump inhibitor (PPI)) or having a history of or current GI illness (excluding conditions which delayed oesophageal transit or emptying). The subject of the exhibition panel was thus a specific subset of patients with postmenopausal osteoporosis. A large box headed 'Actonel 5mg daily' stated that in patients who regularly took acetyl salicylic acid or NSAIDs on 3 or more days per week the incidence of upper GI adverse events in such patients was similar to that in control patients. This statement, which appeared in both the Actonel 5mg and 35mg SPCs, was followed by a bar chart referenced to Taggart *et al* headed 'Actonel's upper GI tolerability profile in patients at risk of upper GI side effects in clinical trials of up to 3 years duration'. A footnote to the bar chart stated that Taggart *et al* included 1.7% of the population that were men or premenopausal women and that these patient groups were not licensed for treatment with Actonel 5mg. Beside the bar chart was a prominent statement that in the Actonel 5mg Phase III trials, patients were not excluded because of previous or current GI illness or use of medicines associated with GI intolerance such as NSAIDs or aspirin, (Reginster *et al* 2000 and Harris *et al* 1999). The box also included the bisphosphonates class warning which again appeared in both Actonel SPCs.

Taggart *et al* concluded that treatment with 5mg risedronate did not result in higher frequency of upper GI tract events amongst patients who had active GI tract disease or required treatment with gastric

antisecretory medicines or patients who were receiving concomitant treatment with aspirin or NSAIDs. To establish the applicability of these findings to clinical practice it would be important to have comprehensive postmarketing data on risedronate.

The Panel noted that neither the Actonel 5mg SPC nor the Actonel 35mg SPC included any warnings advising against concomitant use of NSAIDs, whereas Section 4.4 of the Bonviva (150mg) SPC stated 'Since NSAIDs and bisphosphonates are both associated with gastrointestinal irritation, caution should be taken during concomitant administration'.

The Panel noted that the exhibition panel referred generally to patients taking concomitant medicine likely to cause GI problems or with a history of or current GI illness. It then went on to refer only to the 5mg dose. Health professionals would be aware of the dosing instructions for bisphosphonates and in that regard noted the complainants' submission that the effects of biphosphonates on the GI tract were well understood.

The Panel considered that the exhibition panel was clear that the data related to Actonel 5mg. It noted the complainants' view that this was a rarely used dose. The Panel did not accept that the exhibition panel stated or implied that data from the 5mg applied to the 35mg dose as alleged even though in some cases it did for example, the class warning and the statement regarding regular acetyl salicylic acid or NSAID users. There was no mention of the 35mg dose. The 35mg Actonel SPC stated that in a one year study of postmenopausal women with osteoporosis the overall safety and tolerability profiles of the 5mg daily dose and the 35 mg weekly dose were similar. It added, however, that investigators reported a greater incidence in GI disorder (1.6% vs 1%) for 35mg Actonel compared to the 5mg dose.

The Panel noted that Taggart *et al* included patients (1.7% of the population) who were not within the licensed indication for Actonel 5mg. The data was used in relation to tolerability not efficacy. The exhibition panel only included photographs of older (ie postmenopausal) women and was headed 'In postmenopausal women …' In the circumstances the Panel did not consider that the data promoted the use of Actonel 5mg in unlicensed patient populations as alleged. The Panel ruled no breach of Clause 3.2.

The Panel considered the exhibition panel was not inconsistent with the Actonel 5mg SPC; no breach of Clause 3.2 was ruled.

The Panel did not consider that the information about side effects failed to reflect current evidence. The SPC warning was included. Nor did it fail to encourage rational use. Thus no breaches of Clauses 7.9 and 7.10 were ruled.

The Panel considered that the bisphosphonate class warning about special caution when using Actonel in certain patients might have been more prominent, ie appear in the same section as the information about patients who regularly used aspirin and NSAIDs, nonetheless it did not consider that in the circumstances it was misleading for it to appear where it had. No breach of the Code was ruled.

Complaint received 17 January 2008

Case completed 29 February 2008