CASE AUTH/2115/4/08

ROCHE v GLAXOSMITHKLINE

Press releases for Tykerb/Tyverb on corporate website

Roche complained about two press releases for Tykerb/Tyverb (lapatinib) posted on GlaxoSmithKline's corporate website (www.gsk.com). Tykerb was already licensed in the US. Tyverb was the registered brand name for lapatinib in Europe and the proposed trade name in certain other markets pending regulatory approval. Lapatinib was used in the treatment of advanced or metastatic breast cancer.

Roche alleged that a press release titled 'GlaxoSmithKline reviews positive EMEA opinion for a conditional approval of Tyverb', dated 14 December 2007, was promotional, unbalanced and did not accurately and fairly reflect available evidence, in breach of the Code. In particular Roche was concerned at the selective representation of lapatinib efficacy data, and misleading downplaying of adverse events.

Roche was concerned that a quotation from Piccart, '… this is just the beginning given the ongoing clinical programme investigating the potential use of lapatinib in earlier stages of the disease' implied an unsubstantiated claim for activity of lapatinib in early breast cancer.

Roche alleged that the press release implied that lapatinib was effective for the treatment of brain metastases and that additional data to be presented at an international meeting would substantiate this. GlaxoSmithKline claimed that the use of words such as 'potential' made this acceptable. Roche considered that this did not make the section balanced and fair in that it was speculative and implied lapatinib activity where there was no substantiation. Roche noted that on one hand, GlaxoSmithKline argued that the press release solely concerned the data relevant to the conditional positive opinion from the European Medicines Evaluation Agency (EMEA), and used this as a justification for not including a full and balanced picture of lapatinib's data in brain metastases.

Conversely, however, the press release unduly emphasised data from a retrospective brain metastases analysis and advertised the fact that further data would be presented. This was not relevant to the purpose of the press release and constituted promotion prior to licence. Furthermore, a full and balanced picture of the brain metastases data (ie that studies in this area had failed to meet their primary endpoints) had not been provided.

Roche alleged that the statement 'The majority of adverse events were mild to moderate in severity and were not significantly higher than those seen with capecitabine' was misleading and did not give a fair and balanced impression of the additional side effects associated with lapatinib. The press release inaccurately implied that toxicity with lapatinib was negligible. It was important to provide information about the additional toxicity attributable to lapatinib (ie a significant increase in diarrhoea, dyspepsia and rash) to provide balance alongside claims of additional efficacy. Roche further noted that this was not a straight comparison since a lower dose of capecitabine was used in the combination arm of the study compared with the capecitabine monotherapy arm. The company was also concerned at the lack of reference to more serious adverse events, such as cardiac toxicity. Roche alleged that downplaying of serious adverse events potentially prejudiced patient safety.

Roche also considered that it was inappropriate to place the press release on an open-access UK website; it was on GlaxoSmithKline's homepage not the investors' section of the website. GlaxoSmithKline had claimed that the intended audience for the press release was business journalists, but Roche considered that this was ambiguous in terms of both content and placement of the press release.

The Panel noted that the press release had been issued in the UK and that it referred to Tyverb, the proposed brand name for lapatinib in the UK. The Panel thus considered that the press release came within the scope of the Code.

The press release was principally about the positive opinion given by the EMEA with regard to the use of lapatinib, in combination with capecitabine, in the treatment of patients with advanced or metastatic breast cancer whose tumours over-expressed HER2. The EMEA had recommended that a conditional marketing authorization be granted. Patients had to have progressive disease despite prior therapy with other antineoplastic agents. Piccart had welcomed the positive opinion and stated that lapatinib represented an important new treatment option for a group of patients in real need of alternative therapies. Piccart further stated 'Not only that, but this is just the beginning given the ongoing clinical programme investigating the potential use of lapatinib in earlier stages of the disease'. The Panel did not consider that, within the context in which it appeared, the statement implied activity of lapatinib in early breast cancer as alleged. No breaches of the Code were ruled.

The press release gave details of the data upon

which the EMEA had based its positive opinion. Readers were then told that, in addition to the achievement of the primary endpoint, results had demonstrated the associated potential to reduce the incidence of brain metastases as the first site of recurrence in metastatic breast cancer. The Tyverb summary of product characteristics (SPC) was cited in support of a statement that progression of brain metastases was 2% in the combination arm compared with 6% in the capecitabine alone arm. It was further noted that central nervous system metastases were a major burden for breast cancer patients and that the latest data on the use of lapatinib and capecitabine in brain metastases would be presented at a major breast cancer symposium on 16 December 2007 (two days after the press release was issued).

The press release explained that a conditional marketing authorization was granted to a medicine that fulfilled an unmet medical need when the benefit to public health of immediate availability outweighed the risk inherent in the fact that additional data were still required. In the case of lapatinib, GlaxoSmithKline was to provide further data from the pivotal study and also additional demonstration of decreased incidence of relapse in the central nervous system, for which a study would be conducted. It was further explained that the conditional marketing authorization would be valid for one year and thereafter might be renewed annually.

The Panel did not consider that undue emphasis had been given to the brain metastases data as alleged. The press release was factual and low key in this regard. The data was topical, given that it was about to be discussed at a major breast cancer symposium, and was not irrelevant to the conditional marketing authorization recommended by the EMEA. It was clear that the results were preliminary and were the basis of ongoing research. The data was included in the draft Tyverb SPC. No breaches of the Code were ruled. The Panel did not consider that the press release constituted promotion of lapatinib prior to the grant of a marketing authorization as alleged. No breaches of the Code were ruled.

The Panel noted that the press release stated that the most common adverse events during therapy with lapatinib plus capecitabine were gastrointestinal (diarrhoea, nausea and vomiting) or skin disorders (rash and hand and foot syndrome). It was further stated that the majority of adverse events were mild to moderate in severity and were not significantly higher than those seen with capecitabine monotherapy. There was no reference to more serious adverse events such as cardiac toxicity. In that regard the Panel noted that decreased left ventricular ejection fraction (LVEF) was listed in the draft Tyverb SPC as a common cardiac disorder adverse reaction associated with therapy. The SPC further stated that LVEF should be evaluated in all patients prior to initiation of treatment and that it should continue to be evaluated during treatment to ensure that it did not decline to an unacceptable level.

The Panel considered that the brief reference to adverse effects in the press release was misleading as alleged and did not reflect the available evidence. In that regard the risk benefit profile of lapatinib had not been presented fairly. Breaches of the Code were ruled.

The Panel noted that the material at issue was a press release specifically aimed at business journalists and analysts/investors. In that regard the Panel did not consider that the press release constituted an advertisement to the public for lapatinib. No breach of the Code was ruled.

Despite undertakings in inter-company dialogue from GlaxoSmithKline that it would remind its corporate colleagues not to use names excessively in press releases, Roche was concerned that a press release dated 18 March 2008 and titled 'Tyverb (lapatinib) European regulatory update' had been posted on the www.gsk.com website which breached the Code by using the stylized brand name more than ten times in the opening five paragraphs.

The Panel noted that the press release had been issued in the UK and that it referred to Tyverb, the proposed brand name for lapatinib in the UK. The Panel thus considered that the press release came within the scope of the Code.

The Panel noted that Tyverb was referred to ten times in the first five paragraphs of text. There were, however, twelve paragraphs of text and in all Tyverb was referred to twelve times. Although each reference to the product name was in italics the Panel noted that the text was not emboldened; the product name did not appear in logo type. Lapatinib was referred to seven times. The press release was about a delay in the regulatory procedure for Tyverb due to reports of hepatotoxicty. The Panel considered that although it would have been preferable not to have mentioned Tyverb so frequently, taking all the circumstances into account, it did not consider that the references to Tyverb were excessive or in a style such as to make the press release promotional as alleged. No breach of the Code was ruled which was upheld on appeal by Roche.

Roche Products Ltd complained about two press releases for Tykerb/Tyverb (lapatinib) posted on GlaxoSmithKline's corporate website (www.gsk.com). Tykerb was already licensed in the US. Tyverb was the registered brand name for lapatinib in Europe and the proposed trade name in certain other markets pending regulatory approval. Lapatinib was used in the treatment of advanced or metastatic breast cancer.

GlaxoSmithKline noted that the corporate press releases at issue were available on www.gsk.com

via the 'Media Centre', which was aimed at business journalists and the investor/analyst community. The following statement on the 'Media Centre' home page (available at www.gsk.com/media/index.htm) made it very clear the audience for which the information was intended: 'These press releases are intended for business journalists and analysts/investors. Please note that these releases may not have been issued in every market in which GSK operates.' In addition, each press release bore the following explicit wording at the top: 'This press release is intended for business journalists and analysts/investors. Please note that this release may not have been issued in every market in which GlaxoSmithKline operates.'

GlaxoSmithKline acknowledged that links to latest press releases appeared on the GlaxoSmithKline home page but under the heading 'Corporate press releases'. Clicking the title of a particular release opened the release itself within the 'Media Centre' with the header described above. Thus, whilst the content of www.gsk.com, including the 'Media Centre', could be accessed by the public, GlaxoSmithKline considered that the intended audience of these releases was clear and unambiguous.

1 Press release dated 14 December 2007: 'GlaxoSmithKline receives positive EMEA opinion for a conditional approval of Tyverb'

COMPLAINT

Roche alleged that the press release was promotional, unbalanced and did not accurately and fairly reflect available evidence, in breach of Clauses 3.1, 3.2, 7.2, 7.3, 7.4, 7.9, 7.10, 9.1 and 20.2. In particular Roche was concerned at the selective representation of lapatinib efficaty data, and misleading downplaying of adverse events:

- **Use of a quotation from Piccart:** Roche was concerned about the language used in this quotation, particularly the sentence '… this is just the beginning given the ongoing clinical programme investigating the potential use of lapatinib in earlier stages of the disease'. Clause 7.10 of the Code clearly stated that 'Claims should not imply that a medicine or an active ingredient has some special merit, quality or property unless this can be substantiated'. The quotation implied activity of lapatinib in early breast cancer – a claim which could not be substantiated. Roche further alleged a breach of Clause 7.4.

- **Data on progression with brain metastases:** Roche alleged that the information presented implied that lapatinib was effective for the treatment of brain metastases and that additional data to be presented at an international meeting would substantiate this. GlaxoSmithKline claimed that the use of words such as 'potential' made this acceptable. Roche considered strongly that this did not make the section balanced and fair, but in fact constituted a further breach of Clause 7.10 in that it was speculative and implied lapatinib activity where there was no substantiation. Roche noted that on one hand, GlaxoSmithKline argued that the press release solely concerned the data relevant to the conditional positive opinion from the EMEA, and used this as a justification for not including a full and balanced picture of lapatinib's data in brain metastases. Conversely, however, the press release unduly emphasised the retrospective brain metastases analysis from the EGF 100151 trial and advertised the fact that further data would be presented at an international meeting. By GlaxoSmithKline's own admission, this was not relevant to the purpose of the press release and Roche alleged that this constituted promotion prior to licence, in breach of Clauses 3.1 and 3.2. Furthermore, Roche alleged that a full and balanced picture of the brain metastases data (ie that specific studies in this area had failed to meet their primary endpoints) had not been provided, in breach of Clauses 7.2, 7.10, 9.1 and 20.2.

- **Adverse event data:** Roche considered that the statement 'The majority of adverse events were mild to moderate in severity and were not significantly higher than those seen with capecitabine' was misleading and did not give a fair and balanced impression of the additional side effects associated with lapatinib. The press release inaccurately implied that toxicity with lapatinib was negligible. It was important to provide information about the additional toxicity attributable to lapatinib (ie a significant increase in diarrhoea (60% vs 39%, $p<0.001$), dyspepsia (11% vs 3%, $p=0.014$) and rash (27% vs 15%, $p=0.011$)) to provide balance alongside claims of additional efficacy. Roche further noted that this was not a straight comparison since a lower dose of capecitabine was used in the combination arm of the study compared with the capecitabine monotherapy arm. Roche alleged breaches of Clauses 7.2, 7.3, 7.4 and 7.9. The company was also concerned at the lack of reference to more serious adverse events, such as cardiac toxicity, with lapatinib in the press release. The Code required information to be fair and balanced (Clause 7.2) and reflect available evidence (Clause 7.10) and so it was not sufficient to simply list the most common adverse events, as this ignored less common adverse events which might be more serious or clinically significant. This general principle was supported by Clause 4.2 which stated that information should include common side-effects, serious side-effects and precautions and contraindications. Since cardiac safety was an important clinical issue in breast cancer management Roche considered that it was inappropriate to downplay the cardiac toxicity seen with lapatinib. Since the US prescribing information for lapatinib (ie available evidence) referred to the need for regular cardiac monitoring, decreases in left ventricular ejection

fraction (LVEF) and prolongation of the QT interval under 'Warnings and Precautions' (and in light of the warning letter from the Food and Drug Administration (FDA) to GlaxoSmithKline regarding the company's omission of the most serious and important risk information in the lapatinib-related literature) Roche considered that the UK company should include such important information. Roche alleged that downplaying of serious adverse events breached Clauses 7.2 and 7.9 and potentially prejudiced patient safety.

Roche also considered that it was inappropriate to place the press release on an open-access UK website; it was placed on GlaxoSmithKline's homepage not on the investors' section of the website. Roche noted that GlaxoSmithKline claimed that the intended audience for the press release was business journalists, but considered that this was ambiguous in terms of both content and placement of the press release.

Roche considered that the press release fell within the scope of the Code since it was freely accessible to the UK public, related to a prescription only medicine, had been placed on the Internet by a UK company (issued in London) and referred to the availability or use of lapatinib in Europe, which included the UK (see Case AUTH/2046/9/07). Roche alleged a breach of Clause 20.1.

RESPONSE

GlaxoSmithKline explained that the purpose of the press release was to highlight positive European Medicines Evaluation Agency (EMEA) opinion for the conditional approval of lapatinib (in combination with capecitabine). Communication of such business-important information was expected and appropriate for the business/financial audience for which this release was intended.

Use of the Piccart quotation: GlaxoSmithKline noted that the sentence referred to by Roche was the last in a four-sentence quotation by Piccart, and should not therefore be considered in isolation. The full quotation was:

'This positive opinion is fantastic news for eligible women with ErbB2-positive [HER2-positive] breast cancer across the European Union. Thousands of women are diagnosed every year in Europe with ErbB2-positive breast cancer and are at a greater risk of disease progression and death compared to women with tumours that do not over-express this protein,' said Dr Martine Piccart, Professor of Oncology, Université Libre de Bruxelles and Department Head, Medicine, Jules Bordet Institute, Brussels. *'Lapatinib represents an important new treatment option for a group of patients in real need of alternative therapies and I look forward to the day that I can prescribe lapatinib. Not only that, but this is just the beginning given the ongoing clinical programme investigating the potential use of lapatinib in earlier stages of the disease.'*

GlaxoSmithKline considered that the sentence highlighted by Roche was acceptable and balanced when read in the context of the whole quotation and the preceding paragraphs of the press release. Indeed, the opening paragraph of the release clearly and explicitly referred to the indication for lapatinib (ie patients with advanced or metastatic breast cancer whose tumours overexpressed HER2 and who had progressive disease following prior therapy with anthracyclines, taxanes and therapy with trastuzumab in the metastatic setting) so that there was no ambiguity as to which patients it would be licensed for and therefore had demonstrated activity in.

GlaxoSmithKline did not accept that this final sentence of the quotation suggested definitive activity or efficacy for lapatinib in earlier stages of breast cancer. It most certainly did not imply that lapatinib had some special merit, quality or property. It was a statement of fact that trials evaluating lapatinib in earlier stages of breast cancer were ongoing. This reflected the usual sequence of oncology medicine development, in which efficacy was established in advanced/metastatic disease before progressing to trials in earlier stages of disease. The sentence was accurate and fair in acknowledging that the clinical development was *'ongoing'* and was investigating the *'potential'* for lapatinib in this setting.

In summary, GlaxoSmithKline firmly considered that this closing sentence was fair and balanced in the context of the whole quotation, which was primarily concerned with welcoming the good news regarding the positive opinion for lapatinib as a new treatment option for women with HER2-positive advanced breast cancer who had progressed on trastuzumab, an area of unmet clinical need for which there were currently no specifically licensed treatment options. It was entirely appropriate, given the intended audience, to highlight that not only had a positive opinion been reached for lapatinib in a late-stage setting but that further development work in earlier settings was ongoing. GlaxoSmithKline denied breaches of Clauses 7.4 and 7.10 of the Code.

Data on progression with brain metastases: As stated in the opening paragraph of the release, the indication for which lapatinib had received positive opinion for a conditional approval was for use in combination with capecitabine for patients with advanced or metastatic breast cancer whose tumours overexpressed HER2. Patients should have progressive disease following prior therapy which must include anthracyclines and taxanes, and therapy with trastuzumab in the metastatic setting. Thus, GlaxoSmithKline emphasised that any patient with advanced/metastatic breast cancer, including those with brain metastases from breast cancer, would be eligible to receive lapatinib in combination with capecitabine providing they had received the specified pre-treatments in the correct settings.

GlaxoSmithKline noted Roche's allegation that undue emphasis was given to the retrospective brain metastases analysis from the EGF100151 trial, the pivotal study supporting this indication. In addition, the company had asserted that the use of the word *'potential' ('associated potential to reduce the incidence of brain metastases as first site of recurrence .....')* was speculative and implied lapatinib activity where there was no substantiation, in breach of Clause 7.10.

GlaxoSmithKline did not accept that these data were overly emphasised. They were germane to the positive opinion from the EMEA for the use of lapatinib in combination with capecitabine and therefore appropriate to include in the press release. Further, given that the management of breast cancer with brain metastases was a major clinical challenge for which few treatments were available and new options were urgently required, any new data in this area was of high clinical and scientific interest and relevant to the business/investor community to whom the release was directed. GlaxoSmithKline had taken great care to represent the data in a balanced and transparent manner. The information was presented separately from and following the study's primary endpoint results. The word *'potential'* was deliberately included to accurately reflect the volume of evidence to date and, as discussed in a later paragraph of the release, a requirement of lapatinib's conditional marketing authorization was additional demonstration of reduced incidence of relapse in the central nervous system. In addition, it was fairly acknowledged that these data were *'preliminary'* and were the *'basis of ongoing research in this area'*. Nevertheless, the inclusion of these data in section 5.1 of the lapatinib draft summary of product characteristics (SPC) surely indicated some evidence of activity in this regard, as well as evidence of the clinical importance of such data in this area of high unmet medical need. GlaxoSmithKline therefore did not accept that the statements were misleading and incapable of substantiation and denied the alleged breaches of Clauses 7.2 and 7.10.

GlaxoSmithKline disagreed with Roche's allegation that these data were not relevant to the purpose of the press release and therefore constituted promotion prior to licence in breach of Clauses 3.1 and 3.2. As explained above, the data on brain metastases provided in the release were from the pivotal EGF100151 trial underpinning the registration of lapatinib plus capecitabine and were therefore pertinent to the positive opinion that formed the prime focus of the release. It was entirely appropriate to give the business/investor community this information given the high level of interest and unmet medical need in this area.

Finally, GlaxoSmithKline noted that Roche had alleged that the press release did not provide a full and balanced picture of data regarding lapatinib in brain metastases by not referring to two studies in this area that had failed to meet their primary endpoint, constituting breaches of Clauses 7.2, 7.10, 9.1 and 20.2.

The studies in question were both by Lin *et al* (CTEP 6969 and EGF 105084); they evaluated lapatinib monotherapy as treatment for patients with progressive brain metastases following trastuzumab and cranial radiotherapy, and hence, were not relevant to the press release which was concerned with the positive opinion for the lapatinib plus capecitabine combination. However, in the extension phase of EGF105084, some patients went on to receive the same lapatinib plus capecitabine combination with which the press release was concerned, and therefore, GlaxoSmithKline considered that it was appropriate to refer to the fact that latest data for this combination were to be presented at the forthcoming international meeting. For the above reasons, GlaxoSmithKline denied the alleged breaches. In particular, since the press release was not directed to the public the company strongly refuted the alleged breach of Clause 20.2.

Adverse event data: Roche had asserted that the statement *'The majority of adverse events were mild to moderate in severity and were not significantly higher that those on capecitabine monotherapy'* was misleading and gave an inaccurate impression of the additional side effects associated with lapatinib. Roche further stated that the important information to provide was what additional toxicity was attributable to lapatinib.

GlaxoSmithKline disagreed. The company considered that it was more important and relevant to highlight the safety profile of the lapatinib plus capecitabine combination that patients would receive in clinical practice rather than focus on that of lapatinib *per se*. Indeed, the preceding sentence in the press release appropriately described the most common adverse events associated with this combination as being *'gastrointestinal (diarrhoea, nausea and vomiting) or skin disorders (rash and hand and foot syndrome)'*.

The sentence at issue correctly referred to the *'majority'* of adverse events not being significantly higher in the combination arm versus capecitabine alone. Indeed, the adverse event table presented in the Geyer publication listed 18 adverse events, of which only 3 (diarrhoea, rash, dyspepsia) were significantly greater with the combination. This amounted to 15 of 18 events (the great majority) for which there was not a significant difference between the combination and capecitabine monotherapy.

In addition, whilst the total incidence of diarrhoea, rash and dyspepsia (ie at any grade) was higher in the combination arm, the difference was mainly accounted for by an increase in grade 1 and 2 events; for each, the incidence of grade 3 or 4 events was very similar between treatment groups.

Thus, GlaxoSmithKline continued to believe that the paragraph in the press release correctly and fairly

reflected the adverse event profile reported for lapatinib plus capecitabine compared with capecitabine alone in the pivotal EGF100151 study. The company strongly denied breaches of Clauses 7.2, 7.3, 7.4 and 7.9 of the Code.

GlaxoSmithKline noted Roche's concern at the lack of reference to more serious events, such as cardiac toxicity.

As discussed earlier, the purpose of the release was to communicate positive EMEA opinion for conditional approval of lapatinib (in combination with capecitabine) to the business/investor community. It was not intended to provide comprehensive safety information on the product for clinicians/prescribers. The release therefore listed only those adverse events that were most commonly observed with lapatinib plus capecitabine therapy in the pivotal registration study.

GlaxoSmithKline accepted that cardiac safety was an important clinical issue in breast cancer management and believed that it was relevant to discuss such events and cardiac monitoring requirements in materials directed at health professionals once the product was licensed and commercially available.

In conclusion, GlaxoSmithKline did not accept that the press release was misleading with respect to the safety information provided, given its focus on the positive EMEA opinion, and the company denied breaches of Clauses 7.2, 7.9 and 7.10. GlaxoSmithKline strongly refuted the allegation that the press release potentially prejudiced patient safety given the audience for which it was intended and the fact that lapatinib was currently only available in the UK through a clinical trials programme with guidance on cardiac monitoring; it was not commercially available.

PANEL RULING

The Panel noted that the press release had been issued in the UK and that it referred to Tyverb, the proposed brand name for lapatinib in the UK. The Panel thus considered that the press release came within the scope of the Code.

The press release was clearly marked as being intended for business journalists and analysts/investors and not for distribution to US media. The press release also stated that it might not have been issued in every market in which GlaxoSmithKline operated. The supplementary information to Clause 20.2, Financial Information, stated that information made available in order to inform shareholders, the Stock Exchange and the like by way of annual reports and announcements etc, might relate to both existing medicines and those not yet marketed. Such information must be factual and presented in a balanced way. Business press releases should identify the business importance of the information.

The press release was principally about the positive opinion given by the EMEA with regard to the use of lapatinib, in combination with capecitabine, in the treatment of patients with advanced or metastatic breast cancer whose tumours over-expressed HER2. The EMEA had recommended that a conditional marketing authorization be granted. Patients had to have progressive disease despite prior therapy with other antineoplastic agents. Piccart had welcomed the positive opinion and stated that lapatinib represented an important new treatment option for a group of patients in real need of alternative therapies. Piccart further stated 'Not only that, but this is just the beginning given the ongoing clinical programme investigating the potential use of lapatinib in earlier stages of the disease'. The Panel did not consider that, within the context in which it appeared, the statement implied activity of lapatinib in early breast cancer as alleged. No breaches of Clauses 7.4 and 7.10 were ruled.

The Panel was concerned that the press release referred to the positive opinion being '… fantastic news …' as this might not meet the requirements of the Code with regard to balance etc. Nevertheless there was no specific complaint on this point. It requested that GlaxoSmithKline be advised of its concerns in this regard.

The press release gave details of the data upon which the EMEA had based its positive opinion. Readers were then told that, in addition to the achievement of the primary endpoint, results had demonstrated the associated potential to reduce the incidence of brain metastases as the first site of recurrence in metastatic breast cancer. The Tyverb SPC (GlaxoSmithKline data on file) was cited in support of a statement that progression of brain metastases was 2% in the combination arm compared with 6% in the capecitabine alone arm. It was further noted that central nervous system metastases were a major burden for breast cancer patients and that the latest data on the use of lapatinib and capecitabine in brain metastases would be presented at a major breast cancer symposium on 16 December 2007 (two days after the press release was issued).

The press release explained that a conditional marketing authorization was granted to a medicine that fulfilled an unmet medical need when the benefit to public health of immediate availability outweighed the risk inherent in the fact that additional data were still required. In the case of lapatinib, GlaxoSmithKline was to provide further data from the pivotal study and also additional demonstration of decreased incidence of relapse in the central nervous system, for which a study would be conducted. It was further explained that the conditional marketing authorization would be valid for one year and thereafter might be renewed annually.

The Panel did not consider that undue emphasis

had been given to the brain metastases data as alleged. The press release was factual and low key in this regard. The data was topical, given that it was about to be discussed at a major breast cancer symposium, and was not irrelevant to the conditional marketing authorization recommended by the EMEA. It was clear that the results were preliminary and were the basis of ongoing research. The data was included in the draft Tyverb SPC. No breaches of Clauses 7.2, 7.10, 9.1 and 20.2 were ruled. The Panel did not consider that the press release constituted promotion of lapatinib prior to the grant of a marketing authorization as alleged. No breaches of Clauses 3.1 and 3.2 were ruled.

The Panel noted that the press release stated that the most common adverse events during therapy with lapatinib plus capecitabine were gastrointestinal (diarrhoea, nausea and vomiting) or skin disorders (rash and hand and foot syndrome). It was further stated that the majority of adverse events were mild to moderate in severity and were not significantly higher than those seen with capecitabine monotherapy. There was no reference to more serious adverse events such as cardiac toxicity. In that regard the Panel noted that decreased LVEF was listed in the draft Tyverb SPC as a common cardiac disorder adverse reaction associated with therapy. Under special warnings and precautions for use (section 4.4 of the SPC) it was stated that LVEF should be evaluated in all patients prior to initiation of treatment and that it should continue to be evaluated during treatment to ensure that it did not decline to an unacceptable level.

The Panel considered that the brief reference to adverse effects in the press release was misleading as alleged and did not reflect the available evidence. In that regard the risk benefit profile of lapatinib had not been presented fairly. Breaches of Clauses 7.2, 7.3, 7.4, 7.9 and 7.10 were ruled.

The Panel noted that the material at issue was a press release specifically aimed at business journalists and analysts/investors. In that regard the Panel did not consider that the press release constituted an advertisement to the public for lapatinib. No breach of Clause 20.1 was ruled.

2 Press Release – 18 March 2008: 'Tyverb (lapatinib) European regulatory update'

COMPLAINT

Despite receiving undertakings in inter-company dialogue from GlaxoSmithKline that it would remind its corporate colleagues not to use names excessively in press releases, Roche was concerned that the press release of 18 March had subsequently been posted on the www.gsk.com website which again breached Clause 3.1 by using the stylized brand name more than ten times in the opening five paragraphs.

Again, Roche considered that this press release fell within the scope of the Code since it was freely accessible to the UK public, related to a prescription only medicine, had been placed on the Internet by a UK company (issued in London) and referred to the availability or use of the medicine in Europe, which included the UK, again Clause 3.1.

RESPONSE

GlaxoSmithKline accepted that the frequent use of the brand name was regrettable and this had been addressed with its corporate colleagues. However, the intent of this corporate press release was not promotional but to provide an update on the regulatory status for lapatinib in Europe. Marketing authorization for lapatinib in combination with capecitabine had been expected from the EU Commission between 22 February and 8 March 2008. However, the provision of new data by GlaxoSmithKline (arising from a standard pharmacovigilance review) relating to possible hepatotoxicty during treatment with lapatinib had prompted the Commission to refer lapatinib back to the Committee for Medicinal Products for Human Use (CHMP) for further discussion, thereby delaying the marketing authorization.

GlaxoSmithKline did not believe that any pharmaceutical company would set out to communicate a potential safety issue associated with its product in a promotional manner. GlaxoSmithKline put out a press release to be transparent about these new data and the reason for the regulatory delay. The company considered it entirely appropriate to keep the business community and investors appraised of such important information on a medicine in which they might have a material interest. The coverage that was generated from the release was confined to the business/financial media.

In summary GlaxoSmithKline submitted that intent of the press release was not promotional but to communicate the reason for lapatinib's regulatory delay. In addition, there was no doubt as to the intended audience for the item given the explicit statement on www.gsk.com's 'Media Centre' homepage and on the top of the item.

PANEL RULING

The Panel noted that the press release had been issued in the UK and that it referred to Tyverb, the proposed brand name for lapatinib in the UK. The Panel thus considered that the press release came within the scope of the Code.

The press release was clearly marked as being intended for business journalists and analysts/investors and not for distribution to US media. The press release also stated that it might not have been issued in every market in which GlaxoSmithKline operated. The supplementary

information to Clause 20.2, Financial Information, stated that information made available in order to inform shareholders, the Stock Exchange and the like by way of annual reports and announcements etc, might relate to both existing medicines and those not yet marketed. Such information must be factual and presented in a balanced way. Business press releases should identify the business importance of the information.

The Panel noted that Tyverb was referred to ten times in the first five paragraphs of text. There were, however, twelve paragraphs of text and in all Tyverb was referred to twelve times. Although each reference to the product name was in italics the Panel noted that the text was not emboldened; the product name did not appear in logo type. Lapatinib was referred to seven times. The press release was about a delay in the regulatory procedure for Tyverb due to adverse data regarding hepatotoxicty. The Panel considered that although it would have been preferable for the press release not to mention Tyverb so frequently, taking all the circumstances into account, it did not consider that the references to Tyverb were excessive or in a style such as to make the press release promotional as alleged. No breach of Clause 3.1 was ruled.

APPEAL BY ROCHE

Roche noted that the Code clearly stated that 'the brand name of the product may be included in moderation but it should not be stylized or used in excess'. Roche submitted that it had raised similar concerns to GlaxoSmithKline twice before and on both occasions received an undertaking to address this with its corporate colleagues. Whilst Roche accepted that the subject of the press release was a safety issue with lapatinib, this did not negate the requirement to comply with the Code. Roche alleged that the press release breached Clause 3.1 by using italics which stylized the brand name 'Tyverb' and it was unnecessary and a breach of the Code to use the brand name ten times in the first five paragraphs and twelve times in total. Roche considered that the current ruling would set a precedent that was in conflict with the Code.

COMMENTS FROM GLAXOSMITHKLINE

GlaxoSmithKline submitted that the press release at issue was not intended to be promotional but to provide an update on the regulatory status for lapatinib in Europe. The marketing authorization for lapatinib in combination with capecitabine had been expected from the EU Commission between 22 February and 8 March 2008. However the provision of new data by GlaxoSmithKline arising from a standard pharmacovigilance review relating to possible hepatotoxicty during lapatinib treatment had prompted the Commission to refer lapatinib back to the CHMP for review of these data, thereby delaying the marketing authorization. Clause 20.2 of the Code allowed information to be made available in order to inform shareholders and the like about both existing medicines and those not yet marketed. Such information must be factual and presented in a balanced way. The press release should identify the business importance of the information. The press release clearly met these requirements.

GlaxoSmithKline submitted that the press release itself was clearly aimed at business journalists and analysts/investors (it was headed with: 'This press release is intended for business journalists and analysts/investors'). In addition, the press release was placed in the 'Media Centre' on www.gsk.com, the home page of which also clearly stated the nature of the audience for which the information was intended.

GlaxoSmithKline submitted that it was entirely appropriate and responsible to have informed the business/financial/investor community of new data relating to possible hepatotoxicity associated with lapatinib and the impact on its regulatory status, a medicine from a company in which they might have had a material interest, particularly in an environment where there was increased interest in understanding the risks as well as the benefits of new medicines. In this context, GlaxoSmithKline strongly refuted the implication that this activity amounted to promotion prior to the grant of marketing authorization, particularly as communicating these adverse safety data might have a potentially negative impact on future sales of lapatinib and hence shareholder return. GlaxoSmithKline issued the press release to be transparent about these new data and the reasons for the regulatory delay.

As discussed above, the press release was clearly not aimed at health professionals who might have been responsible for the prescription or the supply of lapatinib. Furthermore, GlaxoSmithKline would not have informed the clinical community of a potential safety issue with one of its products via a press release. Indeed, a 'Dear Investigator' letter explaining the situation had been approved by the EMEA and sent to all investigators involved in lapatinib clinical trials.

GlaxoSmithKline noted as highlighted by Roche, that the Code stated in the supplementary information to Clause 3.1 that 'the brand name of the product may be included in moderation but it should not be stylized or used to excess'. However, this requirement applied to the provision of advance planning information to health authorities, health boards, trust hospitals and primary care trusts to assist them in estimating the budgetary impact of a new product. A press release on a product's regulatory delay did not constitute advance budgetary notification, and as such, this clause did not apply.

Given the circumstances, GlaxoSmithKline did not consider the use of the Tyverb brand name twelve times in twelve paragraphs of text to be excessive.

The product name was not emboldened and did not appear in logo type and therefore was not in a style such as to make the press release promotional as alleged. In addition, given the nature of the release it was important for the business media and investor community to be entirely clear as to what product the release referred to. The UK operating company had repeatedly advised corporate colleagues that brand names should be used in moderation in press releases, irrespective of their nature or intent. GlaxoSmithKline noted that the latest lapatinib press release (provided) concerning its recent EU marketing authorization reflected this advice.

FINAL COMMENTS FROM ROCHE

Roche had no further comments to add to those previously submitted.

APPEAL BOARD RULING

The Appeal Board noted that the press release had been issued to inform investors/business analysts and the like that the marketing authorization for Tyverb might be delayed due to a review of hepatoxicity data. It was not a good news story. The press release was not directed to clinicians or patients. The Appeal Board noted that there appeared to be a discrepancy between the companies as to how the press release was accessed on www.gsk.com. The intended audience was made clear at the start of the press release. The Appeal Board considered that it was not unacceptable to issue such a press release as long as it complied with the Code. Press releases should be factual and informative and not promote a product.

The Appeal Board considered that although the supplementary information referred to by Roche was specific to the provision of information about the advance notification of products with significant budgetary implication, and thus did not apply to the press release at issue, it nonetheless provided helpful guidance.

The Appeal Board noted that the brand name had appeared in italics in the press release; it was not unusual for brand names to be differentiated in this way from generic names. The brand name was not emboldened, enlarged, or in any other way distinctive from the surrounding text except by the use of italics. The Appeal Board, however, was concerned about the frequency with which the brand name had been used; in its view it would have been preferable if it had been used less often. Companies were obliged to comply with both the spirit and the letter of the Code. Nonetheless, taking all the circumstances into account, the Appeal Board did not consider that the references to Tyverb were excessive or in a style such as to make the press release promotional as alleged. The Appeal Board upheld the Panel's ruling of no breach of Clause 3.1. The appeal was unsuccessful.

Complaint received **15 April 2008**

Case completed **16 July 2008**