ROCHE v GLAXOSMITHKLINE

Promotion of Tykerb

Roche complained about the promotion of Tykerb (lapatinib) by GlaxoSmithKline. Roche noted that a pre-licence advertisement for lapatinib ('Coming soon … Tykerb') was published in the January 2007 issue of 'The Oncologist', including its UK circulation. GlaxoSmithKline claimed that this was an 'inadvertent error' and attributed to its US colleagues placing the advertisement without its knowledge in the UK. Nevertheless, the impact was made.

The Panel noted that supplementary information to the Code stated that advertisements published in professional journals came within the scope of the Code if they were produced in the UK and/or intended for a UK audience. International journals that were produced in English in the UK were subject to the Code even if only a small proportion of their circulation was to a UK audience.

The Oncologist was published by AlphaMed Press, Carolina, USA, and AlphaMed Europe based in Northern Ireland. The Panel noted GlaxoSmithKline's submission that when commissioning the advertisement, the US company was unaware of any non US print runs for The Oncologist and did not specify any particular run for the advertisement. Further the journal had no separate European run. GlaxoSmithKline thus submitted that the issue of the journal in question was obtained in the US. The Panel noted that had the advertisement appeared in a separate run of the journal that had been produced in the UK or had otherwise been intended for a UK audience it would have come within the scope of the Code. However, on the basis of GlaxoSmithKline's submission the Panel decided that the run of The Oncologist at issue did not satisfy the criteria and thus the matter was outside the scope of the Code. No breach was ruled.

Roche's ongoing media monitoring had shown high levels of Tykerb/lapatinib coverage. Roche had had correspondence with GlaxoSmithKline on this matter, specifically relating to an article in the Sunday Express on 17 September in which a GlaxoSmithKline source was quoted as saying that the medicine would achieve better results than Herceptin. Although Roche received assurances from GlaxoSmithKline that this had not arisen from GlaxoSmithKline briefings, it was clearly attributed to GlaxoSmithKline. Tykerb was unlicensed in the UK and no head-to-head comparative data existed against Herceptin. Should this statement have come via a GlaxoSmithKline supported agency, GlaxoSmithKline was still responsible.

Evidence of an engineered campaign of pre-marketing was supported by the consistency of wording of claims that were appearing in the media, including regular comparisons with Herceptin. More specifically, there had been several mentions that lapatinib might be 'better than Herceptin', that lapatinib might be effective in 'Herceptin resistant' patients, that lapatinib might be effective in brain metastases, and that lapatinib might have less cardiotoxicity than Herceptin. There was no evidence to support the above claims and whilst Roche accepted that there might be an element of misunderstanding amongst the media, the consistency with which such messages had been conveyed in the media strongly suggested that there must be some origin for these unfounded claims. It seemed a totally improbable coincidence that this could originate from a source other than GlaxoSmithKline. Totally unfounded statements over safety were of particular concern and should be viewed as a breach of Clause 2.

The Panel noted that the article in question in the Sunday Express referred to the superiority of lapatinib over Herceptin. The article stated that 'GlaxoSmithKline claims the drug will achieve better results than Herceptin, a rival treatment …'. Complaints about articles in the media were judged on the information provided by the company to the journalist. The Panel noted GlaxoSmithKline's submission that neither it nor its agency had spoken to the journalist in question. GlaxoSmithKline had however issued a corporate press release about the Tykerb US filing and thereafter answered a question from a different journalist at the Sunday Express about when the filing was due to take place. GlaxoSmithKline had surmised that this second journalist had relayed this information to the author of the article and that it was possible that the Sunday Express article may have been prompted by the embargoed press release.

The press release was headed 'GlaxoSmithKline seeks US approval for Tykerb (lapatinib ditosylate) for the treatment of advanced breast cancer'. The date of issue was Monday, 18 September. The press release described the product's proposed US licensed indication – in combination with Xeloda for the treatment of advanced or metastatic HER2 (ErbB2) positive breast cancer in women who had received prior therapy, including Herceptin. The compound had been granted fast track status by the FDA in this patient population. The press release made it clear that Tykerb was an investigational medicine and had not been approved for marketing by any regulatory body. The trial on which the application was based, was described and referenced to Data on file, King of Prussia. It was noted that an interim analysis showed that relevant women in whom the disease progressed following treatment with Herceptin and other cancer therapies when transferred either to Tykerb and

Xeloda or Xeloda alone, the combination of Tykerb and Xeloda nearly doubled median time to progression (36.7 weeks [8.5 months] in the combination arm vs 19.1 weeks [4.4 months] versus Xeloda alone, p= 0.00008). The press release also stated that in March 2006 an independent data monitoring committee recommended that enrolment ceased based on the early success of the trial. The study met its primary endpoint of time to disease progression and exceeded the predetermined stopping criteria. Enrolment stopped in April 2006. The press release supplied by GlaxoSmithKline did not mention an embargo.

The Panel did not consider that the press release supplied to the Sunday Express implied that Tykerb would achieve better results than Herceptin, nor that head-to-head comparative data existed as alleged. References to Herceptin were within the context of the proposed licensed indication in the US which was clearly stated in the press release. No breach of the Code ruled.

In relation to the allegation about a premarketing campaign involving comparative claims with Herceptin the Panel noted GlaxoSmithKline's submission that any conversations with journalists had been restricted to messages in the approved press releases. The evidential burden was on Roche to establish, on the balance of probabilities that GlaxoSmithKline had supplied material to the media which was misleading or otherwise in breach of the Code as alleged. The Panel noted the series of published articles provided by Roche and a summary of the coverage. Roche cited that Tykerb might be 'better than Herceptin', 'effective in Herceptin resistant patients', 'effective in brain metastases' and 'have less cardiotoxicity than Herceptin'. Nonetheless, the Panel also noted that none of the press releases issued by GlaxoSmithKline or its corporate office featured the comparative claims referred to by Roche.

GlaxoSmithKline had provided copies of press releases dated from May 2006 to December 2006. Two were clearly marked for medical press only, one was a London Stock Exchange announcement. Eight discussed phase III data, one noted its imminent publication. The licensing status was made clear. The Panel was concerned that the intended audience was not always clear on the face of the press release. The Panel was also concerned that the heading to a press release dated 28 December described the phase III data as 'Landmark' data and referred to it changing the 'treatment paradigm'. Other press releases described the phase III trial more modestly as 'positive new data'. However, on the evidence before it the Panel did not consider that the press materials overall amounted to promotion of a medicine prior to the grant of marketing authorization or were otherwise in breach of the Code as alleged. No breach of the Code was ruled.

Roche Products Limited complained about the promotion of Tykerb (lapatinib) by GlaxoSmithKline UK Ltd.

1 Tykerb pre-licence advertisement

COMPLAINT

Roche noted that an advertisement for lapatinib ('Coming soon … Tykerb') was published in the January 2007 issue of 'The Oncologist', including its UK circulation. GlaxoSmithKline claimed that this was an 'inadvertent error' and attributed it to its US colleagues placing the advertisement without its knowledge in the UK. Roche provided GlaxoSmithKline's written response. Nevertheless, the impact was made. Roche alleged that the advertisement breached Clauses 3.1, 9.1 and 9.2 of the Code.

RESPONSE

GlaxoSmithKline submitted that the advertisement in question was placed in the January 2007 issue of 'The Oncologist', an international journal, by GlaxoSmithKline personnel in the US operating company without GlaxoSmithKline UK's prior knowledge or consent. Once this became known to GlaxoSmithKline UK, it contacted US colleagues who promptly withdrew the advertisement and were now fully aware of the importance of regulations relating to information and advertisements in journals with distribution outside the USA.

Nevertheless, 'teaser' advertising was permitted under US Food and Drugs Administration (FDA) regulations and since the journal in question was produced outside of the UK and was not primarily intended for a UK audience (UK readership of The Oncologist was approximately 10% of total circulation), GlaxoSmithKline did not believe that this complaint should fall under the scope of the ABPI Code. GlaxoSmithKline therefore denied breaches of Clauses 3.1, 9.1 and 9.2 of the Code.

In response to a request for further information, GlaxoSmithKline stated that the Oncologist was published monthly by AlphaMed Press, North Carolina USA and AlphaMed Europe Limited, Northern Ireland.

At the time of commissioning the Tykerb piece, GlaxoSmithKline's US colleagues were unaware of any non-US print runs for The Oncologist which was a US-based journal with no separate European print run and had minimal (under 200 copies) international circulation; as a result they did not specify any particular run for the advertisement.

It was therefore most likely that the issue of the journal with the advertisement under discussion was obtained in the US; in which case US regulations applied confirming GlaxoSmithKline UK's position of not having breached the Code.

PANEL RULING

The Panel noted the supplementary information to

Clause 1.1 of the Code, Journals with an International Distribution stated that advertisements published in professional journals came within the scope of the Code if they were produced in the UK and/or intended for a UK audience. International journals that were produced in English in the UK were subject to the Code even if only a small proportion of their circulation was to a UK audience.

The Panel noted that The Oncologist was published by AlphaMed Press, Carolina, USA, and AlphaMed Europe based in Northern Ireland. The Panel noted GlaxoSmithKline's submission that when commissioning the advertisement, the US company was unaware of any non US print runs for The Oncologist and did not specify any particular run for the advertisement. Further the journal had no separate European run. GlaxoSmithKline thus submitted that the issue of the journal in question was obtained in the US. The Panel noted that had the advertisement appeared in a separate run of the journal that had been produced in the UK or had otherwise been intended for a UK audience it would have come within the scope of the Code. However, on the basis of GlaxoSmithKline's submission the Panel decided that the run of The Oncologist at issue did not satisfy the criteria set out in Clause 1.1 and thus the matter was outside the scope of the Code. No breach of Clauses 3.1, 9.1 and 9.2 was accordingly ruled.

2 Tykerb media coverage

COMPLAINT

Roche's ongoing media monitoring had shown high levels of Tykerb/lapatinib coverage. Roche had had correspondence with GlaxoSmithKline on this matter, specifically relating to an article in the Sunday Express on 17 September 2006 in which a GlaxoSmithKline source was quoted as saying that the medicine would achieve better results than Herceptin. Although Roche received assurances from GlaxoSmithKline that this had not arisen from GlaxoSmithKline briefings, it was clearly attributed to GlaxoSmithKline. Hence, Roche alleged breaches of Clauses 3.1, 7.2 and 8.1. Tykerb was unlicensed in the UK and no head-to-head comparative data existed against Herceptin. Should this statement have come via a GlaxoSmithKline supported agency, GlaxoSmithKline was still responsible under Clause 20.6.

Evidence of an engineered campaign of pre-marketing was supported by the consistency of wording of claims that were appearing in the media, including regular comparisons with Herceptin. More specifically, there had been several mentions that lapatinib might be 'better than Herceptin', that lapatinib might be effective in 'Herceptin resistant' patients, that lapatinib might be effective in brain metastases, and that lapatinib might have less cardiotoxicity than Herceptin. There was no evidence to support the above claims and whilst Roche accepted that there might be an element of misunderstanding amongst the media, the consistency with which such messages had been conveyed in the media strongly suggested that there must be some origin for these unfounded claims. It seemed a totally improbable coincidence that this could originate from a source other than GlaxoSmithKline (or an agency working for it) via a written or verbal briefing. Totally unfounded statements over safety were of particular concern and should be viewed as a breach of Clause 2.

RESPONSE

GlaxoSmithKline confirmed that no one at GlaxoSmithKline UK (or other parts of the organisation) or from its PR agency had spoken to the Sunday Express journalist in question. The journalist was not GlaxoSmithKline's usual contact and was not known to it. GlaxoSmithKline could only hypothesise on what might have happened. It was possible that the article might have been prompted by an embargoed press release issued by GlaxoSmithKline corporate media in relation to lapatinib's US filing around the same time. The article did refer to a GlaxoSmithKline spokeswoman in relation to a comment on the US and EU filings for lapatinib, but it believed this arose because a separate journalist from the Sunday Express had contacted GlaxoSmithKline's corporate media team to ask when the filings were due to take place. It was possible that this journalist relayed that information to the author of the article.

The reference to GlaxoSmithKline claiming superiority over Herceptin was not in quotes, nor attributed to a GlaxoSmithKline spokesperson, but was paraphrased. GlaxoSmithKline could only assume that the journalist made her own interpretation of the content of the press release, either in relation to the anticipated licence indication for lapatinib (ie for patients who had previously received Herceptin) and/or in relation to the findings of the pivotal registration trial, as reflecting superiority to Herceptin. The relevant paragraphs from the press release were as follows:

> '…..approval to market Tykerb (lapatinib ditsoylate), in combination with Xeloda (capecitabine), for the treatment of advanced or metastatic HER2 (ErbB2) positive breast cancer in women who have received prior therapy, including Herceptin (trastuzumab).'
>
> 'A planned interim analysis of the Phase III international, multicenter, open-label trial randomized 324 women who had advanced or metastatic breast cancer with documented HER2 overexpression and whose disease progressed following treatment with herceptin and other cancer therapies, to TYKERB and Xeloda or Xeloda alone. In this pivotal trial, the combination of Tykerb and Xeloda versus Xeloda alone nearly doubled median time to progression (36.7 weeks [8.5 months] in the combination arm versus 19.1 weeks [4.4 months] with Xeloda alone, p=0.00008).'

As could be seen, the press release accurately represented the design of the study and the results and clearly did not make a superiority claim against Herceptin. GlaxoSmithKline had been unable to find

any other references to such a claim and could confirm that it had undertaken no media briefings to journalists where such a claim could have been made. GlaxoSmithKline could only conclude that the statement must represent the journalist's own interpretation, either of this press release or of other press coverage, or of data she might have seen at, or reported from, scientific congresses.

GlaxoSmithKline strongly refuted the allegation of an engineered pre-marketing campaign for lapatinib.

GlaxoSmithKline UK activities

GlaxoSmithKline UK's media activities had solely consisted of issuing press releases to the medical press around significant milestones for lapatinib - the presentation of significant new data at a scientific congress (ESMO 2006), and the EU filing. GlaxoSmithKline UK had not organised or undertaken any press briefings with the medical press or health correspondents on the UK national press. As was standard practice upon issuing a press release, journalists had been followed up by phone to check they had received the press release. All such conversations were restricted to only the approved messages in the press releases.

GlaxoSmithKline corporate media activities

GlaxoSmithKline's corporate media team had also issued corporate press releases on key data and on the US and EU filings to the investment community and health correspondents on the national press. Both GlaxoSmithKline's corporate office and its PR agency had confirmed that any conversations with journalists were restricted to the messages in the approved press releases.

The press coverage in relation to lapatinib, alleged by Roche to be part of a campaign, was most likely to have been generated by legitimate corporate activities related to the investment community. This was reinforced by details provided by Roche predominantly featuring coverage generated in the business press.

None of GlaxoSmithKline's press releases (either developed by GlaxoSmithKline UK or by the corporate media team) had contained any of the claims that Roche alleged. No claims had been made relating to superiority of lapatinib over Herceptin, lapatinib having less cardiotoxicity than Herceptin, lapatinib being effective in 'Herceptin resistant' patients or lapatinib being effective in brain metastases.

With reference to the allegation regarding lapatinib in brain metastases, it was important to be aware that brain metastases were an increasing clinical problem in patients with HER2-positive (HER2+) breast cancer, and were associated with significant morbidity, mortality and impaired quality of life. There were very few treatment options available and the management of breast cancer with brain metastases was an elusive clinical challenge. The statements that had appeared regarding brain metastases in press releases sent by GlaxoSmithKline corporate media accurately represented the preliminary nature of the evidence and plans for future studies with lapatinib in this area. GlaxoSmithKline believed this to be a legitimate provision of information given the level of interest in finding new treatments in this area of significant unmet medical need.

GlaxoSmithKline was aware that the area of cancer (particularly breast cancer) was one that had developed a high media profile, and as such, it had provided factual releases to ensure that correct and balanced information was available to investment, medical and health journalists who might write stories relating to these events. The considerable media interest in this area was reflected by the fact that press articles had appeared intermittently and not necessarily around the time when GlaxoSmithKline had issued press releases. Many of the articles might have come out of the release of landmark data per se, rather than a GlaxoSmithKline press release around such data.

In summary, GlaxoSmithKline strongly denied the alleged breaches of the Code. It believed that the information on lapatinib disseminated in these GlaxoSmithKline press releases constituted a legitimate activity to provide information to journalists writing for the medical press and the investment community in an area of high media interest, particularly given the novel nature of lapatinib and the current high unmet need for patients with HER2-positive (HER2+) advanced/metastatic breast cancer who had progressed on Herceptin - the target first indication for lapatinib. The content of all such press releases were an accurate, balanced, fair and objective reflection of the available evidence for lapatinib. GlaxoSmithKline refuted having made any inappropriate statements regarding the safety of lapatinib, and particularly, regarding the comparative safety of lapatinib and Herceptin. There was no evidence that any of the claims cited by Roche had originated from concerted campaign by GlaxoSmithKline, either directly, or from one of its agencies.

GlaxoSmithKline therefore refuted any alleged breach of Clauses 2, 3.1, 7.2, 8.1 and 20.6.

PANEL RULING

The Panel noted that the article in question in the Sunday Express referred to the superiority of lapatinib over Herceptin. The article stated that 'GlaxoSmithKline claims the drug will achieve better results than Herceptin, a rival treatment …'. The Panel noted that complaints about articles in the media were judged on the information provided by the company to the journalist. The Panel noted GlaxoSmithKline's submission that neither it nor its agency had spoken to the journalist in question. GlaxoSmithKline had however issued a corporate press release about the Tykerb US filing and thereafter answered a question from a different journalist at the Sunday Express about when the filing was due to take place. GlaxoSmithKline had surmised that this second journalist had relayed this information to the author of the article and that it was possible that the Sunday

Express article may have been prompted by the embargoed press release.

The Panel noted that the press release was headed 'GlaxoSmithKline seeks US approval for Tykerb (lapatinib ditosylate) for the treatment of advanced breast cancer'. The date of issue was Monday, 18 September. The press release described the product's proposed US licensed indication – in combination with Xeloda for the treatment of advanced or metastatic HER2 (ErbB2) positive breast cancer in women who had received prior therapy, including Herceptin. The compound had been granted fast track status by the FDA in this patient population. The press release made it clear that Tykerb was an investigational medicine and had not been approved for marketing by any regulatory body. The phase III open label trial on which the application was based, was described and referenced to Data on file, King of Prussia. It was noted that an interim analysis showed that relevant women in whom the disease progressed following treatment with Herceptin and other cancer therapies when transferred either to Tykerb and Xeloda or Xeloda alone, the combination of Tykerb and Xeloda nearly doubled median time to progression (36.7 weeks [8.5 months] in the combination arm vs 19.1 weeks [4.4 months] versus Xeloda alone, p= 0.00008). The press release also stated that in March 2006 an independent data monitoring committee recommended that enrolment ceased based on the early success of the trial. The study met its primary endpoint of time to disease progression and exceeded the predetermined stopping criteria. Enrolment stopped in April 2006. The press release supplied by GlaxoSmithKline did not mention an embargo.

The Panel did not consider that the press release supplied to the Sunday Express implied that Tykerb would achieve better results than Herceptin, nor that head-to-head comparative data existed as alleged. References to Herceptin were within the context of the proposed licensed indication in the US which was clearly stated in the press release. No breach of Clauses 3.1, 7.2 and 8.1 was ruled on this point.

In relation to the allegation about a premarketing campaign involving comparative claims with Herceptin, the Panel noted GlaxoSmithKline's submission that any conversations with journalists had been restricted to messages in the approved press releases. The Panel noted that the evidential burden was on Roche to establish, on the balance of probabilities, that GlaxoSmithKline had supplied material to the media which was misleading or otherwise in breach of the Code as alleged. The Panel noted the series of published articles provided by Roche and a summary of the coverage. Roche cited that Tykerb might be 'better than Herceptin', 'effective in Herceptin resistant patients', 'effective in brain metastases' and 'have less cardiotoxicity than Herceptin'. Nonetheless, the Panel also noted that none of the press releases issued by GlaxoSmithKline or its corporate office featured the comparative claims referred to by Roche.

The Panel noted that GlaxoSmithKline had provided copies of press releases dated from May 2006 to December 2006. Two were clearly marked for medical press only, one was a London Stock Exchange announcement. Eight discussed phase III data, one noted its imminent publication. The licensing status was made clear. The Panel was concerned that the intended audience was not always clear on the face of the press release. The Panel was also concerned that the heading to a press release dated 28 December described the phase III data as 'Landmark' data and referred to it changing the 'treatment paradigm'. Other press releases described the phase III trial more modestly as 'positive new data'. However, on the evidence before it the Panel did not consider that the press materials overall amounted to promotion of a medicine prior to the grant of marketing authorization or were otherwise in breach of the Code as alleged. No breach of Clauses 3.1, 7.2 and 8.1 was ruled. Given its ruling there could be no breach of Clause 2.

The Panel noted that Roche had referred to Clause 20.6 which read ' Companies are responsible for information about their products which is issued by their public relations agencies'. The Panel considered that Clause 20.6 was a simple statement of fact which could not be infringed.

Complaint received **27 April 2007**

Case completed **10 July 2007**