CASE AUTH/1925/12/06

NOVARTIS v APOPHARMA

Breach of undertaking

Novartis alleged that a promotional piece for Ferriprox (deferiprone) was clearly in breach of the undertaking given in Case AUTH/1822/4/06. Novartis further alleged that a claim about survival data was unsubstantiated. As the complaint involved an alleged breach of undertaking the matter was taken up with ApoPharma by the Director as it was the Authority's responsibility to ensure compliance with undertakings. Novartis supplied Desferal (desferoxamine).

Novartis noted that an animated Ferriprox banner advertisement which appeared as a link on the website of the British Journal of Haematology, contained the claim 'New Cardioprotection and Survival Data Now Available'. The statement 'For reference or prescribing information please click here' linked to another website 'Ferriprox.com' and the landing page was headed with the claim 'Life is Getting Longer … in thalassaemia major patients'. There was a link to a summary of product characteristics and a link marked 'for information on Ferriprox and cardioprotection, please click here'. When this link was followed, it took the reader to the Pub Med listing for the abstract of Borgna-Pignatti et al (2006).

Novartis alleged that the claim 'Life is Getting Longer … in thalassaemia major patients' found in breach recently was a hanging comparison. As this was previously found to be in breach for exactly the same reasons it also represented a breach of undertaking.

Secondly, Borgna-Pignatti et al did not provide survival data of any form that could support this claim. The paper discussed cardiac events but there was no analysis of survival. This represented a failure to substantiate a claim and also, by directing the reader to this paper, it was also a misrepresentation of data.

The Panel noted that in Case AUTH/1822/4/06 a Ferriprox banner advertisement, in the electronic version of the British Journal of Haematology, which claimed that 'Life is Getting Longer' was ruled in breach of the Code because it was a hanging comparison. In error, as acknowledged by ApoPharma, the claim had been used again and in breach of the undertaking given in Case AUTH/1822/4/06. The Panel ruled breaches of the Code. The Panel further considered that ApoPharma, by not doing all that it could have done to comply with its undertaking had brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

The Panel noted that the banner advertisement on the British Journal of Haematology website stated 'New Cardioprotection and Survival Data Now Available'. The data available was Borgna-Pignatti *et al*, an epidemiological, natural history study conducted in Italy which compared cardiac morbidity and mortality in deferoxamine- or deferiprone-treated patients with thalassemia major. The authors reported that deferiprone therapy was associated with significantly greater cardioprotection than desferoxamine. The authors, however, noted that the study was not randomized and so treatment groups might not have been comparable. Further, there might have been a bias against deferiprone because in the early stages of the 9 year study it was experimental and given to patients with a higher body iron load. Conversely, because deferiprone was not licensed in Italy until mid-way through the trial, some doctors might have been reluctant to prescribe it for their sicker patients thus introducing a bias in favour of the medicine. The authors commented that neither consideration appeared to have strongly biased the results. The authors further noted that the study had potential for length bias in that in order to have received deferiprone, patients would have had to survive long enough to receive it. Thus the sickest patients, possibly, who had cardiac events, were those who did not have the opportunity to receive deferiprone, and the observations on deferiprone might not have been long enough for cardiac events to occur. There were two deaths reported in the deferiprone group (1.3%) compared with 24 in the desferoxamine group (6.7%). Of the 24 deaths in the desferoxamine group, 15 were cardiac related; neither death in the deferiprone group was cardiac related. The authors calculated a hazard ratio of 0.38 (CI 0.9, 1.6) of death on deferiprone but given the small number of events the study did not have sufficient power to test this question.

The Panel considered that the claim 'New Cardioprotection and Survival Data Now Available' implied that there was positive data in this regard. The Panel considered that, in view of the limitations noted by Borgna-Pignatti et al, such a claim was too strong and could not be substantiated. A breach of the Code was ruled.

Upon appeal by ApoPharma the Appeal Board noted that the claim appeared as a banner on a specialist website – ie the website of the British Journal of Haematology. By clicking on the banner the reader was taken to Borgna-Pignatti et al as cited on Pub Med. The Appeal Board considered that, as presented, the claim 'New Cardioprotection and Survival Data Now Available' was a statement of fact and not a claim for positive data for Ferriprox in this regard. No breach of the Code was ruled.

Novartis Pharmaceuticals UK Ltd alleged that a promotional piece for Ferriprox (deferiprone) which appeared as a link on the website of the British Journal of Haematology was clearly in breach of the undertaking given in Case AUTH/1822/4/06. Novartis further alleged that a claim about survival data was unsubstantiated. As the complaint involved an alleged breach of undertaking the matter was taken up with ApoPharma Inc by the Director as it was the Authority's responsibility to ensure compliance with undertakings. Novartis supplied Desferal (desferoxamine).

COMPLAINT

Novartis noted that the material at issue, an animated Ferriprox banner advertisement, contained the claim 'New Cardioprotection and Survival Data Now Available'. The statement 'For reference or prescribing information please click here' linked to another website 'Ferriprox.com' and the landing page was headed with the claim 'Life is Getting Longer … in thalassaemia major patients'. There was a further link to a summary of product characteristics following a further link marked 'for information on Ferriprox and cardioprotection, please click here', the reader was taken to the Pub Med listing for the abstract of Borgna-Pignatti *et al* (2006).

Novartis did not believe that including the statement on the landing page that the website was intended for Hong Kong residents only made it any more acceptable under the Code given that UK readers of the journal had been directed to these pages from a UK journal site.

Novartis considered that the material breached the Code in several areas. The first was the retention of the claim 'Life is Getting Longer … in thalassaemia major patients' found in breach recently. This still remained a hanging comparison, in breach of Clause 7.2, as there was no explanation as to what Ferriprox was being compared with. As this was previously found to be in breach for exactly the same reasons it also represented a breach of undertaking (Clause 22).

Secondly, Borgna-Pignatti *et al* did not provide survival data of any form that could support this claim. The paper discussed cardiac events but there was no analysis of survival. This represented a failure to substantiate a claim and also, by directing the reader to this paper, it was also a misrepresentation of data. Novartis alleged a breach of Clause 7.4.

Novartis considered that ApoPharma had failed to comply with the Authority's previous ruling and the undertaking associated with it.

When writing to ApoPharma, the Authority asked it, in addition to those clauses cited by Novartis, to respond to Clauses 2 and 9.1.

RESPONSE

ApoPharma stated that as per its undertaking, it had stopped using the 'Life is Getting Longer' banner advertisement in the British Journal of Haematology on 25 August 2006. The advertisement was replaced with another that did not make any claims, but did provide a notification of published data pertaining to the effects of deferiprone on the heart ('Cardioprotection and Survival Data Now Available'). As noted by Novartis, a link in the banner advertisement allowed the reader to access prescribing information for Ferriprox.

However, this was not the Hong Kong website for Ferriprox as stated by Novartis. It was a link to enable readers to access information specified in the advertisement, and it also served as a portal for entry into the Hong Kong Ferriprox website for Hong Kong residents, if they so chose. A copy of the site was provided, demonstrating the need to follow another link to enter the Hong Kong website.

The page attached differed in one important aspect from that viewed by Novartis at the time of its complaint. While the current introductory line read, 'Life is waiting', the previous line stated 'Life is Getting Longer'. Removal of this statement from all European advertising had been executed, as stated. However, in error, it was not removed from this link, which UK physicians might access. In this regard, ApoPharma had failed through oversight, not defiance. This oversight did not appear in an advertisement in the UK.

Since the current advertisement in the British Journal of Haematology did not make a claim of increased survival, the complaint by Novartis regarding the adequacy of the references was irrelevant. However, the view expressed by Novartis regarding a lack of adequate data on survival in the reference was incorrect, as revealed by a review of the extensive data presented in the article, which was summarized unequivocally by Borgna-Pignatti *et al* as follows, 'The results of the current study demonstrate that patients with thalassemia major who switched to deferiprone therapy had a remarkably lower prevalence of cardiac disease and cardiac death than patients chelated with [deferoxamine] only'.

Now there was yet another publication which had also demonstrated a dramatic decline in cardiac deaths in thalassemia patients in the whole of Cyprus since the introduction of deferiprone, used primarily in combination therapy in that country (Telfer *et al* 2006).

ApoPharma hoped that this provided the information necessary to demonstrate that no further breach had occurred, but if additional information was required it would readily provide it.

ApoPharma noted that the Authority had asked it for details of the steps it had taken to comply with the undertaking given in Case AUTH/1822/4/06. With regards to the banner advertisement in the British Journal of Haematology: the phrase, 'Life is getting longer' was removed on 25 August 2006: a direct link to Ferriprox prescribing information was introduced; a replacement line, educational in nature, was used to inform clinicians of important information on studies relating to thalassemia, cardiac iron, cardiac disease

and survival ('Cardioprotection and Survival Data Now Available') and a link to Ferriprox prescribing information was provided for readers of the banner advertisement in the British Journal of Haematology.

ApoPharma confirmed that it would comply with the Authority's ruling and ensure that there was no further occurrences that breached the Code. Furthermore ApoPharma was committed to providing a first class service and enhancing the reputation of the pharmaceutical industry with its customers, both with the medical profession and with their patients.

PANEL RULING

The Panel considered that an undertaking was an important document. It included an assurance that all possible stops would be taken to avoid similar breaches of the Code in future. It was very important for the reputation of the industry that companies complied with undertakings.

The Panel noted that in Case AUTH/1822/4/06 a Ferriprox banner advertisement, in the electronic version of the British Journal of Haematology, which claimed that 'Life is Getting Longer' was ruled in breach of Clause 7.2 because it was a hanging comparison. In error, as acknowledged by ApoPharma, the claim had been used again. Although the claim did not appear on the British Journal of Haematology website it did appear on a direct link from the Ferriprox banner advertisement on that site. The Panel considered that the linked page was covered by the Code and thus the use of the claim 'Life is Getting Longer' was in breach of the undertaking given in Case AUTH/1822/4/06. The Panel ruled breaches of Clauses 7.2 and 22. High standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel further considered that ApoPharma, by not doing all that it could have done to comply with its undertaking had brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled. These rulings were not appealed.

The Panel noted that the banner advertisement on the British Journal of Haematology website stated 'New Cardioprotection and Survival Data Now Available'. The data available was Borgna-Pignatti *et al*, an epidemiological, natural history study conducted in Italy which compared cardiac morbidity and mortality in deferoxamine- or deferiprone-treated patients with thalassemia major. The authors reported that deferiprone therapy was associated with significantly greater cardioprotection than desferoxamine. The authors, however, noted that the study was not randomized and so treatment groups might not have been comparable. Further, there might have been a bias against deferiprone because in the early stages of the 9 year study it was experimental and given to patients with a higher body iron load. Conversely, because deferiprone was not licensed in Italy until mid-way through the trial, some doctors might have been reluctant to prescribe it for their sicker patients thus introducing a bias in favour of the medicine. The authors commented that neither consideration appeared to have strongly biased the results. The authors further noted that the study had potential for length bias in that in order to have received deferiprone, patients would have had to survive long enough to receive it. Thus the sickest patients, possibly, who had cardiac events, were those who did not have the opportunity to receive deferiprone, and the observations on deferiprone might not have been long enough for cardiac events to occur. There were two deaths reported in the deferiprone group (1.3%) compared with 24 in the desferoxamine group (6.7%). Of the 24 deaths in the desferoxamine group, 15 were cardiac related; neither death in the deferiprone group was cardiac related. The authors calculated a hazard ratio of 0.38 (CI 0.9, 1.6) of death on deferiprone but given the small number of events the study did not have sufficient power to test this question.

The Panel considered that the claim 'New Cardioprotection and Survival Data Now Available' implied that there was positive data in this regard. The Panel considered that, in view of the limitations noted by Borgna-Pignatti *et al*, such a claim was too strong and could not be substantiated. A breach of Clause 7.4 was ruled. This ruling was appealed.

APPEAL BY APOPHARMA

ApoPharma submitted that it was critical that it addressed a misconception of the Panel regarding the banner and one of the two studies listed in its links. Data on cardioprotection and survival relating to the use of deferiprone had appeared in the medical literature prior to the appearance of the new data to which the banner referred. The link associated with the new banner lead the reader to the abstracts of two studies published in Blood ie 'Randomized controlled trial of deferiprone or deferoxamine in beta-thalassemia major patients with asymptomatic myocardial siderosis' (Pennell *et al* 2006) and 'Cardiac morbidity and mortality in deferoxamine- or deferiprone-treated patients with thalasseamia major' (Borgna-Pignatti *et al*). It appeared that the Panel considered that the latter study did not substantiate the statement 'New Cardioprotection and Survival Data Available'. The study had contained new data relating to cardioprotection and survival.

ApoPharma noted that the Panel had considered that the limitations noted by Borgna-Pignatti *et al*, particularly that the sickest patients, who had cardiac events, were those who did not have the opportunity to receive deferiprone, would bias the results of this study in favour of deferiprone. The consideration was incorrect. In fact, to avoid this potential bias, the study enrolled only patients who had not had cardiac events at the start of the observation period: 'The analysis included all patients treated for thalassemia major at the 7 centers participating in this study who were born between 1970 and 1993 and who on January 31, 1995, were alive, on follow-up, had not undergone bone marrow transplantation, **and had not had a cardiac event'** (Borgna-Pignatti *et al*) (emphasis added by ApoPharma).

ApoPharma submitted that the assessment of potential biases in this study had been evaluated in the editorial that accompanied the publication of Borgna-Pignatti *et al*: 'Although potential bias could easily arise in a retrospective study of unmatched groups, the authors have examined possible biases in a comprehensive fashion, controlling for as many as possible, and explaining the rest with admirable clarity and near-perfect patient ascertainment' (Neufeld, 2006).

The Panel had concluded that Borgna-Pignatti *et al* was unable to show a significant difference between treatments by referring to the Cox regression analysis of total deaths between the two groups (p=0.19). However, ApoPharma noted that since the only two deaths that occurred in patients on deferiprone were neither cardiac- nor deferiprone-related, the authors conducted further analyses, which revealed a significant difference, as described in the publication: 'In addition, we performed a Cox regression that included the noncardiac deaths as failure events in addition to the cardiac events (ie, redefining the failure event as cardiac event or death, whichever occurred first). This analysis included the 2 deaths on deferiprone and provided an estimated hazard ratio of a cardiac event or death of .078 (CI .010, .56; P = .011) on deferiprone relative to [deferoxamine]'.

ApoPharma submitted that as described above, Novartis had claimed that Borgna-Pignatti *et al* did not provide survival data of any form that could support this claim. The paper discussed cardiac events but there was no analysis of survival, this was incorrect. Having considered the limitations of their study, Borgna-Pignatti *et al* concluded that '… this epidemiologic study demonstrated a **significant difference in cardiac morbidity and mortality between thalassemia patients treated with deferiprone and those treated with [deferoxamine]. In contrast to patients treated with [deferoxamine], the patients on this study treated with deferiprone did not have cardiac events'** (emphasis added by ApoPharma).

ApoPharma submitted that the editorial that accompanied the publication also concurred with the conclusion of the authors by stating 'This stunning finding, coupled with similar but less rigorous data from other sites, is hard to ignore. The results confirmed a smaller retrospective analysis of Piga *et al*' (Neufeld).

ApoPharma submitted that Borgna-Pignatti *et al* and Pennell *et al*, published in August 2006, were indeed new data on the role of deferiprone in protecting the heart; iron-related cardiac disease was responsible for approximately 70% of deaths in patients with thalassemia.

COMMENTS FROM NOVARTIS

Novartis continued to maintain that the website was in breach of Clause 7.4 because the reference cited to substantiate a claim of overall survival improvement did not substantiate the claim.

The website in its original form was clearly headed with the claim 'Life is getting longer … in thalassemia major patients'. This was clearly a claim for overall survival benefit from treatment with deferiprone irrespective of cause. This claim was a hanging comparison as ruled by the Panel as it was not clear to what treatment deferiprone was being compared. Below this claim appeared a series of options for the reader including a bullet point with the following direction: 'For information on Ferriprox and survival, please click here'. The link led the reader to the Pub Med citation for Borgna-Pignatti *et al*, which was then evidently intended to substantiate the key claim at the head of the website that 'Life is getting longer …' and the reader was led to believe that it contained robust data to demonstrate a survival benefit from treatment with deferiprone.

Novartis alleged, however, that the study did not demonstrate any such overall survival benefit. As the Panel noted in its ruling, the hazard ratio for death for patients on deferiprone was 0.38 (CI 0.9, 1.6) (p=0.19) which was not statistically significant and indeed the authors concluded that the study did not have sufficient power to test the question of survival.

It was incorrect and misleading to make such a bold claim for increased survival and only discuss cardiac causes of death. Thus, irrespective of the criticisms of the trial design which the Panel and ApoPharma had commented on, the fact remained that the results of the study were insufficient to substantiate an overall survival advantage of treatment with deferiprone over treatment with deferoxamine.

APPEAL BOARD RULING

The Appeal Board noted that the claim 'New Cardioprotection and Survival Data Now Available' appeared as a banner on a specialist website – ie the website of the British Journal of Haematology. By clicking on the banner the reader was taken to Borgna-Pignatti et al as cited on Pub Med. The Appeal Board considered that, as presented, the claim 'New Cardioprotection and Survival Data Now Available' was a statement of fact and not a claim for positive data for Ferriprox in this regard. No breach of Clause 7.4 was ruled. The appeal was successful.

Complaint received	**1 December 2006**
Case completed	**19 April 2007**