CASES AUTH/2061/10/07 and AUTH/2062/10/07

WYETH v LILLY and BOEHRINGER INGELHEIM

Cymbalta detail aid

Wyeth complained about the claim 'Cymbalta vs venlafaxine XL – Cymbalta 60mg OD had similar efficacy to venlafaxine XL 150mg OD' in a primary care detail aid for Cymbalta (duloxetine) issued by Lilly and Boehringer Ingleheim. Cymbalta was indicated, *inter alia*, for the treatment of major depressive episodes. Wyeth supplied Efexor XL (venlafaxine).

Wyeth noted that the claim at issue was referenced to Perahia *et al* (2007). As could be seen from the graph on the relevant page, Lilly was making a claim that the efficacy [of venlafaxine XL] was similar to that of Cymbalta. Wyeth asserted that such a claim needed to be backed by robust scientific evidence, such as a positive non-inferiority analysis.

Perahia *et al* included a non-inferiority efficacy analysis but it was negative. As the authors stated 'Duloxetine 60mg/day failed to meet the a priori-defined non-inferiority criteria for the comparison with venlafaxine 150mg/day at study period II and study periods II and III'. Thus as no robust statistical evidence to demonstrate that venlafaxine and Cymbalta had similar efficacy had been presented, Wyeth asserted that the claim should not have been made. Wyeth did not consider that Lilly's suggestion to change the wording above the graph to 'The efficacy of Cymbalta 60mg OD has not been shown to be different from venlafaxine 150mg XL OD', changed anything, as the impression was still that the medicines were equivalent even if it was only by implication.

Wyeth alleged that the current (and proposed) claim was misleading and exaggerated; to the extent that it had not been substantiated, there was a further breach. Wyeth also suggested that the graph did not conform to the spirit of the Code, which was also a breach.

The Panel noted that Wyeth had complained to Lilly and Boehringer Ingelheim about a detail aid. Following inter-company discussions the detail aid and others sales material had been withdrawn. The Director considered that it appeared that the inter-company discussion on the original detail aid had been successful in that the original claim had been withdrawn and thus the Panel was not required to rule on this detail aid. The new Cymbalta detail aid at issue 'Simplifying the approach to a difficult patient journey' described briefly on page 6 the design, objectives and results of Perahia *et al*. The section concluded with 'The primary objective was not met, however, on the outcome analysis, no statistical difference was seen between venlafaxine XL and duloxetine'. The page featured a graph showing the decrease (improvement) in HAM-D17 scores of Cymbalta 60mg once a day and venlafaxine XL 150mg once a day. The two lines of the graph were almost superimposed on one another. A heading to the graph stated 'In this study, the efficacy of Cymbalta 60mg OD has not been shown to be different from venlafaxine 150mg XL OD (response and return to normal functioning as measured by HAM-D17) – secondary endpoint'. The claim was referenced to Perahia *et al*. The bullet point 'With no direct evidence of difference in efficacy to venlafaxine XL 150mg OD' appeared beneath the graph.

The Panel noted that Perahia *et al* was the only published, peer reviewed, direct comparison of Cymbalta and venlafaxine. The authors had noted a number of limitations to their study. The authors stated that the results of the Global Benefit Risk assessment (the primary endpoint) suggested that Cymbalta and venlafaxine had a similar benefit-risk profile. Similarly the secondary efficacy measures also demonstrated little difference between the two. The authors concluded that additional head-to-head studies, including trials of longer duration, were warranted to determine if patients might have a better benefit-risk profile with one medicine compared with the other.

Overall the Panel considered that Perahia *et al* was a useful first comparison of Cymbalta and venlafaxine but that it had not proven the equivalence of Cymbalta and venlafaxine. More studies were needed. In that regard the Panel noted supplementary information to the Code which stated that where a clinical or scientific issue existed which had not been resolved in favour of one generally accepted viewpoint, particular care must be taken to ensure that the issue was treated in a balanced manner.

The Panel considered that the detail aid at issue implied that Cymbalta and venlafaxine had been shown, beyond doubt, to have equivalent efficacy which was not so. The detail aid was misleading in that regard. Breaches of the Code ruled. The unequivocal claim could not be substantiated. A further breach was ruled.

Wyeth Pharmaceuticals complained about a primary care detail aid (ref CYM 1008) for Cymbalta (duloxetine) issued by Eli Lilly and Company Limited and Boehringer Ingleheim Limited. Cymbalta was indicated, *inter alia*, for the treatment of major depressive episodes. Wyeth supplied Efexor XL (venlafaxine).

COMPLAINT

Wyeth complained about the claim 'Cymbalta vs venlafaxine XL – Cymbalta 60mg OD had similar efficacy to venlafaxine XL 150mg OD'. The claim was referenced to Perahia *et al* (2007). As could be seen from the graph on the relevant page, Lilly was making a claim that the efficacy was similar to that of Cymbalta. Wyeth asserted that such a claim needed to be backed by robust scientific evidence, such as a positive non-inferiority analysis.

Perahia *et al* included a non-inferiority efficacy analysis but it was negative. As the authors stated, 'Duloxetine 60mg/day failed to meet the a priori-defined non-inferiority criteria for the comparison with venlafaxine 150mg/day at study period II and study periods II and III'.

As Lilly had presented no robust statistical evidence to demonstrate that venlafaxine and Cymbalta had similar efficacy, Wyeth asserted that it should not be making such a claim. Wyeth did not consider that Lilly's suggestion to change the wording above the graph to 'The efficacy of Cymbalta 60mg OD has not been shown to be different from venlafaxine 150mg XL OD', changed anything, as the impression that doctors would receive, especially in the context of a promotional item, was that the medicines were equivalent even if it was only by implication.

Thus Wyeth alleged that the current (and proposed) promotion was misleading and exaggerated, in breach of Clauses 7.2 and 7.3. To the extent that the claim referred to above had not been substantiated, there was a breach of Clause 7.4. Wyeth also suggested that the graph did not conform to the spirit of the Code, which was a breach of Clause 7.8.

RESPONSE

Lilly and Boehringer Ingleheim (the Alliance) submitted similar responses.

The companies submitted that the claim 'Cymbalta 60mg OD had similar efficacy to venlafaxine XL 150mg OD' could be supported, Perahia *et al*. However, in the spirit of inter-company dialogue and in an effort to reach an acceptable resolution, the companies offered an amendment to clarify further that there was no difference between the treatment groups. This commitment was communicated to Wyeth on 7 September. The companies also committed to highlight that this claim was a secondary endpoint of the study.

The Alliance therefore offered to stop using this particular claim in sales material and all materials produced for use from 4 October had been amended with the new claim '… the efficacy of Cymbalta 60mg OD has not been shown to be different from venlafaxine 150mg XL OD (response and return to normal functioning as measured by HAM-D17) – secondary endpoint'.

Wyeth was not satisfied with this response and at a meeting in September attended by representatives from all three companies, it was clear that Wyeth did not believe that the Alliance should use this study in any promotional materials and that the new proposed wording was not acceptable.

Perahia *et al* described two pooled studies of similar study design. The pre-defined primary objective of these studies was to test the hypothesis that duloxetine 60mg/daily was statistically superior to venlafaxine XL 150mg/daily after 6 weeks of treatment using the GBR (Global Benefit Risk) measure. Whilst the primary endpoint did not demonstrate superiority of duloxetine 60mg/daily to venlafaxine 150mg/daily there was however no statistically significant difference between the GBR scores for the two treatment groups.

Secondary endpoints of the pooled studies included efficacy measures looking at response and remission rates as measured by the HAM-D17. The studies showed that although duloxetine failed to meet a further secondary endpoint of non-inferiority based upon change in HAM-D17 from baseline the response and remission rates were not significantly different between duloxetine 60mg/daily and venlafaxine XL 150mg/daily at 6 weeks (response rate of 51.6% and 54.5%; and remission rates of 31.4% and 35.2% respectively) and at 12 weeks (response rates of 62.6% and 69.1%; and remission rates of 48.1% and 50.3% respectively). It should be noted that response and remission rates were determined as a priori secondary objectives of this study.

Perahia *et al* was the only fully published peer-reviewed direct comparison of duloxetine and venlafaxine. Therefore this study represented the full balance of evidence to support the aforementioned claims relating to comparative efficacy of these two anti-depressants.

Wyeth submitted only one page of the detail aid, which only showed the graph and the efficacy claims without the study descriptor that was an important component of this detail aid. To be able to fully assess whether this material met the requirements of the Code, the Alliance believed that the detail aid needed to be considered in the context that it was presented to a health professional. The detail aid was specifically designed so that the adjacent page provided relevant information about the design and outcomes of the study.

The objective of the study descriptor 'Cymbalta vs Venlafaxine XL' page in the detail aid was to highlight the actual study design and describe the primary objective of the pooled studies as published; state upfront that the primary objective of the study was not met. (The GBR assessment did not demonstrate Cymbalta 60mg OD to be superior to venlafaxine XL 150mg) and detail the tolerability profile demonstrated for the anti-depressants.

Therefore this descriptor provided relevant information and context to the health professional when viewing the following adjacent page that outlined the secondary endpoint and related efficacy graph. Thus the Alliance did not agree that the graph used to

illustrate the secondary outcome of the study was misleading when coupled with the study descriptor.

In any event, the graph was a true and accurate representation of the graph shown in Perahia *et al* and therefore gave a fair and balanced view of the comparison between these two anti-depressants. The claim and graph were also clearly referenced. For this reason alone, the Alliance did not agree that the graph was misleading as alleged. In addition the claim, 'Cymbalta 60mg OD had similar efficacy to venlafaxine XL 150mg OD (response and return to normal functioning as measured by HAMD-17)' was fully substantiated by Perahia *et al*.

As this was the only published peer-reviewed paper that described a direct head-to-head comparison between Duloxetine and venlafaxine, and hence represented the full balance of evidence when directly comparing the efficacy and tolerability of these two treatments, the Alliance disagreed with Wyeth's assertion that there was a lack of robust scientific evidence to support this claim. Nonetheless, in an effort to resolve this issue at an inter-company level the Alliance committed to modify its promotional claims to: 'In this study, the efficacy of Cymbalta 60mg OD has not been shown to be different from venlafaxine 150mg XL OD (response and return to normal functioning as measured by HAM-D17) – secondary endpoint'.

The companies confirmed that the detail aid had now been updated accordingly. In the interest of inter-company dialogue a copy of this updated page was sent to Wyeth on 19 September. Hence the companies were very disappointed to note Wyeth's complaint about the former material.

The detail aid accurately stated that Cymbalta 60mg OD had not been shown to be different from venlafaxine XL 150mg OD (response and return to normal functioning as measured by HAM-D17) as a secondary endpoint since there was no statistically significant difference between response and remission rates. Also in the current detail aid the primary objective was clearly stated and the outcome detailed clearly upfront before the secondary outcome was illustrated.

Venlafaxine and duloxetine were the only two serotonin and noradrenalin reuptake inhibitors (SNRIs) currently available in the UK. The Alliance's sales team were frequently asked for any comparative data on the class of anti-depressant treatment by health professionals wishing to make informed treatment choices. Perahia *et al*, as previously stated, was the only published peer reviewed paper that described a direct head-to-head comparison between duloxetine and venlafaxine and hence represented the full balance of evidence when directly comparing the efficacy and tolerability of the two treatments.

The Alliance disagreed with Wyeth's assertion that such a claim needed to be backed by robust scientific evidence such as a positive non-inferiority analysis. The claim was an accurate reproduction of the results from Perahia *et al* that was considered worthy of publication in a psychiatric peer-reviewed journal and the pertaining evidence had not been challenged or contradicted by any subsequent evidence based studies.

The companies believed the aforementioned claims presented in both primary care details aids, CYM 1008 and 1072, accurately and fairly reflected the results of Perahia *et al*. Hence the companies did not believe that the claims were misleading or exaggerated and in breach of Clauses 7.2 and 7.3.

In addition the Alliance did not agree that the graph used to illustrate the secondary outcome of the study was misleading as alleged, as it was a true and accurate representation of the graph in Perahia *et al*. The Alliance did not agree, therefore, that this graph was in breach of Clause 7.8.

In this respect the Alliance believed that its primary care detail aid in its entirety had accurately represented the data to enable health professionals to interpret, evaluate and draw their own conclusions about the study and how it related to their own clinical practice.

PANEL RULING

The Panel noted that Wyeth had complained to Lilly and Boehringer Ingelheim about a detail aid (CYM 1008). Following inter-company discussions the detail aid and others sales material had been withdrawn. The Director considered that it appeared that the inter-company discussion on the original detail aid (CYM 1008) had been successful in that the original claim had been withdrawn and thus the Panel was not required to rule on this detail aid.

The Panel noted that the new Cymbalta detail aid at issue (CYM 1072) 'Simplifying the approach to a difficult patient journey' described briefly on page 6 the design, objectives and results of Perahia *et al*. The section concluded with 'The primary objective was not met, however, on the outcome analysis, no statistical difference was seen between venlafaxine XL and duloxetine'. The page featured a graph showing the decrease (improvement) in HAM-D17 scores of Cymbalta 60mg once a day and venlafaxine XL 150mg once a day. The two lines of the graph were almost superimposed on one another. A heading to the graph stated 'In this study, the efficacy of Cymbalta 60mg OD has not been shown to be different from venlafaxine 150mg XL OD (response and return to normal functioning as measured by HAM-D17) – secondary endpoint'. The claim was referenced to Perahia *et al*. The bullet point 'With no direct evidence of difference in efficacy to venlafaxine XL 150mg OD' appeared beneath the graph.

The Panel noted that Perahia *et al* was the only published, peer reviewed, direct comparison of Cymbalta and venlafaxine. The authors had noted a number of limitations to their study. The authors stated that the results of the GBR assessment (the primary endpoint) suggested that Cymbalta and venlafaxine had a similar benefit-risk profile. Similarly the

secondary efficacy measures also demonstrated little difference between the two. The authors concluded that additional head-to-head studies, including trials of longer duration, were warranted to determine if patients might have a better benefit-risk profile with one medicine compared with the other.

Overall the Panel considered that Perahia *et al* was a useful first comparison of Cymbalta and venlafaxine but that it had not proven the equivalence of Cymbalta and venlafaxine. More studies were needed. In that regard the Panel noted the supplementary information to Clause 7.2 of the Code which stated that where a clinical or scientific issue exists which has not been resolved in favour of one generally accepted viewpoint, particular care must be taken to ensure that the issue is treated in a balanced manner in promotional material.

The Panel considered that the detail aid at issue implied that Cymbalta and venlafaxine had been shown, beyond doubt, to have equivalent efficacy which was not so. The detail aid was misleading in that regard. Breaches of Clauses 7.2, 7.3 and 7.8 were ruled. The unequivocal claim could not be substantiated. A breach of Clause 7.4 was ruled.

Complaint received	**24 October 2007**
Case completed	**3 December 2007**