

# VOLUNTARY ADMISSION BY SHIRE

## Journal reprint

Shire Pharmaceuticals voluntarily admitted that a reprint from *The Lancet* (Mehta *et al* 2009), which it used to promote Replagal (agalsidase alfa), contained a bar chart which was misleading about Fabrazyme (agalsidase beta) marketed by Genzyme Therapeutics.

When Mehta *et al* was published in December 2009, Genzyme noted the incorrect bar chart. The lead author was contacted and *The Lancet* published a corrected figure in January 2010.

Shire submitted that it circulated official reprints within a reprint carrier, via its sales team and at conferences. The *Lancet* reprints comprised the original article with the correction at the end. Shire noted, however, that neither the reprint nor the reprint cover made it clear that the article contained an error. The uncorrected bar chart was still reproduced and the corrected bar chart was at the end of the article. Shire appreciated that without explicitly drawing attention to it, readers might not notice the correction.

The detailed response from Shire is given below.

The Panel noted that the bar chart at issue depicted decrease in renal function as measured by the mean yearly fall in estimated glomerular filtration rate (GFR) according to stage of chronic kidney disease at baseline in patients with Fabry's disease during five years of treatment with Replagal. One bar of the chart depicted data from Germain *et al* (2007) showing results for Fabrazyme which had been 'plotted for reference and comparison'. The bar for Fabrazyme showed a mean annualised change in GFR of approximately  $-2.8\text{ml}/\text{min}/1.73\text{m}^2$ . The change in GFR for Fabrazyme reported by Germain *et al* was in fact approximately  $-1.1\text{ml}/\text{min}/1.73\text{m}^2$ . Mehta *et al* did not compare Fabrazyme and Replagal in the text of their paper. The *Lancet* published a corrected bar chart on the last page of the reprint; to see the corrected bar chart the reader would have to turn over the last page of the paper although the Panel noted that it was clear from the last page that something was printed on the reverse. The cover of the reprint referred the reader to *The Lancet's* website for WebExtra content. Once on *The Lancet* website, there was a link from Mehta *et al* to the corrected bar chart.

The Panel noted that Shire had distributed Mehta *et al* in a reprint folder together with a four page summary. The reprint folder cited the references for both the original paper and the corrected bar chart as did the front page of the summary. The summary gave a brief overview of Mehta *et al* and made no comparisons with Fabrazyme; neither the original nor the corrected bar chart was included in the summary.

The Panel considered that it was unfortunate that Mehta *et al* had published an incorrect bar chart. Nonetheless, the reprint distributed by Shire had included the corrected bar chart, readers were directed to *The Lancet* website where there was a link to the corrected bar chart and the cover of the reprint carrier cited the reference for both the original paper and the corrected bar chart. Other than in the bar chart, the authors did not compare Replagal with Fabrazyme and the summary of Mehta *et al* drew no comparisons between the two medicines. Taking all the circumstances into account the Panel did not consider that the material at issue was misleading and no breaches of the Code, including Clause 2, were ruled.

Shire Pharmaceuticals Limited voluntarily admitted that a reprint from *The Lancet* (Mehta *et al* 2009) which it used in the promotion of Replagal (agalsidase alfa), contained a bar chart which was misleading about Fabrazyme (agalsidase beta) marketed by Genzyme Therapeutics. Mehta *et al* had analysed 5-year treatment with Replagal in patients with Fabry's disease who were enrolled in the Fabry Outcome Survey observational database. Fabrazyme and Replagal were both indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry's disease.

## COMPLAINT

Shire stated that when Mehta *et al* was published in December 2009, Genzyme noted that the bar chart in question (figure 4) contained an error which related to Fabrazyme. The lead author was contacted and *The Lancet* published a corrected figure in January 2010.

Shire noted that in inter-company dialogue it had stated that it would not deliberately refer to, or use the bar chart in its uncorrected form.

Shire submitted that as Mehta *et al* presented data about Replagal it acquired official reprints and circulated them, within a reprint carrier, via its sales team and at conferences. As was the standard practice when errors had been noted, *The Lancet* reprints comprised the original article with the correction at the end. Shire noted, however, that neither the reprint nor the reprint cover made it clear that the article contained an error. The uncorrected bar chart was still reproduced and the corrected bar chart was at the end of the article as per standard practice. It was possible, therefore, that readers might not notice the correction.

Shire immediately arranged for the sales team to return any remaining copies of the reprint. Shire submitted that while the reprints it used were the official versions obtained from *The Lancet*, it appreciated that in using them without explicitly drawing the readers' attention to the correction, they might not have noticed it.

When writing to Shire, the Authority asked it to respond in relation to Clauses 2, 7.2 and 9.1 of the Code.

## RESPONSE

Shire explained that the Fabry Outcome Survey was a Shire sponsored, long-term, observational study of patients with Fabry's disease who were either not treated or who were receiving Replagal. The survey's international board, which was made up of independent physicians, decided to publish the results in a cohort of patients who had been treated for 5 years. The data was collated by Shire statisticians and presented to the authors. One of the ten authors was a health professional employed by Shire. The authors with writing support from an agency (paid for by Shire), completed the article and submitted it to The Lancet. As with all Shire-sponsored articles that were about one of its products, the article was internally reviewed to ensure accuracy of the Shire data but was not subject to any other editorial review by Shire. The involvement of Shire and Shire personnel was referenced in the article.

Following online publication of the article on 2 December, Shire received a letter from Genzyme which noted an error in the bar chart which referred to Fabrazyme. Genzyme stated that it had already contacted the lead author who was aware of the error and would ask The Lancet to correct it. The Lancet subsequently published a correction in its usual fashion (Department of Error).

In response to Genzyme's letter, Shire stated that it would not deliberately refer to, or use, the bar chart in its uncorrected form. However, it reserved the right to use the article when accompanied by the correction notice or any data including the corrected bar chart.

Shire stated that after the correction had been published it received 220 official reprints from The Lancet to be distributed in a reprint carrier that was certified on 21 August 2012. The reprint carrier also included an insert which the representatives were encouraged to focus on when they discussed the article. This insert did not refer to the bar chart but focussed on the conclusions drawn by the authors from the Fabry Outcome Study data. The reprint carrier referenced the original article and the correction. During the approval and certification process it was considered that the use of the official reprint including the corrected version of the bar chart would satisfy the agreement with Genzyme as to how the reprint would be used.

Shire stated that each of its five representatives received 20 copies of the reprint and carrier and distributed some at various 1:1 meetings and conferences. On 14 February 2013, following an email from Genzyme which had picked up one of these reprints at a meeting, the representatives were emailed and asked to return all remaining copies of the reprint carriers until the company had completed its investigation and resolved the situation.

Approximately 40 copies had been returned. Shire noted that the initial inter-company dialogue was conducted between 11 December 2009 and 8 February 2010 and the latest correspondence started 17 December 2012 and had been ongoing since then. Shire confirmed immediately that it had used the official reprint from The Lancet and not the uncorrected version. Shire accepted that the erratum could have been more clearly referenced although it was the standard reprint from The Lancet; further, the reprint carrier cited both the original reprint and the erratum. Whilst not currently incorrect, given the inability to reach consensus with Genzyme, Shire considered that the most reasonable approach would be to self-refer this issue to the Authority.

## PANEL RULING

The Panel noted that the bar chart at issue depicted decrease in renal function as measured by the mean yearly fall in estimated glomerular filtration rate (GFR) according to stage of chronic kidney disease at baseline in patients with Fabry's disease during five years of treatment with Replagal. One bar of the chart depicted data from Germain *et al* (2007) showing results for Fabrazyme which had been 'plotted for reference and comparison'. The bar for Fabrazyme showed a mean annualised change in GFR of approximated -2.8ml/min per 1.73m<sup>2</sup>. The change in GFR for Fabrazyme reported by Germain *et al* was in fact approximately -1.1ml/min per 1.73m<sup>2</sup>. Mehta *et al* did not compare Fabrazyme and Replagal in the text of their paper and once notified of the error, the lead author asked The Lancet to publish a corrected bar chart which it did. The official reprint of Mehta *et al* included the corrected bar chart on the last page; to see the corrected bar chart the reader would have to turn over the last page of the paper although the Panel noted that it was clear from the last page that something was printed on the reverse. The cover of the reprint referred the reader to The Lancet's website for WebExtra content. Once on The Lancet website, there was a link from Mehta *et al* to the corrected bar chart.

The Panel noted that Shire had distributed Mehta *et al* in a reprint folder together with a four page, A4 summary (ref UK/HG/REP/12/0008a). The reprint folder cited the references for both the original paper and the corrected bar chart as did the front page of the A4 summary. The A4 summary gave a brief overview of Mehta *et al* and made no comparisons with Fabrazyme; neither the original nor the corrected bar chart was included in the summary.

The Panel considered that it was unfortunate that Mehta *et al* had published an incorrect bar chart. Nonetheless, the reprint distributed by Shire had included the corrected bar chart, readers were directed to The Lancet website where there was a link to the corrected bar chart and the cover of the reprint carrier cited the reference for both the original paper and the corrected bar chart. Other than in the bar chart, the authors did not compare Replagal with Fabrazyme and the A4 summary of Mehta *et al* drew no comparisons between the two medicines. Taking all the circumstances into account the Panel did not consider

that the material at issue was misleading. No breach of Clause 7.2 was ruled. The Panel did not consider that there had been a failure to uphold high standards. No breach of Clause 9.1 was ruled. Given these rulings, the Panel also ruled no breach of Clause 2.

**Complaint received**                      **21 March 2013**

**Case completed**                         **16 April 2013**

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