CASE AUTH/3345/5/20

HEALTH PROFESSIONAL v SOBI

Promotion of Alprolix in the British Medical Journal

A complainant, who described him/herself as a concerned UK heath professional, complained about an advertisement for Alprolix (eftrenonacog alfa) placed by Swedish Orphan Biovitrum Ltd (Sobi) on a website hosted by the BMJ. Alprolix was indicated for the treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency).

The section at issue was headed 'Alprolix was generally well tolerated in patients of all ages in clinical studies' followed by 'Confidence for the long-term: The tolerability profile of Alprolix was studied over 5 years in the B-YOND extension study'. Below this were three highlighted boxes in a row, the last one of which was headed 'No anaphylaxis or allergic reactions'; this heading was referenced to Powell et al (2013) and drew the reader's attention to a footnote which read 'The B-YOND study and its parent trial included previously treated patients. The safety of Alprolix in previously untreated patients is currently being investigated'. Both the reference and the footnote could be accessed from a link just below the three boxes. The complainant drew attention to the first two of the three bullet points in the last highlighted box which read: 'No serious hypersensitivity or anaphylaxis events were reported in clinical studies' and 'Hypersensitivity or allergic reactions have been observed rarely in a post-marketing setting and may in some cases progress to severe anaphylaxis (including shock)'.

The complainant drew attention to two other footnotes which like the footnote referred to above were accesed by clicking a link. The two footnotes referred to by the complainant read 'From the start of B-LONG until the end of B-YOND', 'Clinical trial programme only'. [These two footnotes were linked to other parts of the material and not to the highlighted box headed 'No anaphylaxis or allergic reactions and its three bullet points.]

The complainant alleged that the bold headings stated one thing but that the detail in the last highlighted box directly contradicted it; and this was misleading and the data clearly could not substantiate the incorrect statement.

The complainant noted that the footnotes were hidden on a separate web page. The footnotes were important qualifiers to the more visible statements and considerably changed the data that was displayed.

Overall, the complainant alleged that the material provided the data in a misleading manner which could lead to a situation where patient safety was placed at risk.

The detailed response from Sobi is given below.

Firstly, the Panel considered the immediate and overall impression of the claim 'No anaphylaxis or allergic reactions' as it would appear to a health professional. In the Panel's view the claim implied that the reader did not have to be concerned about the occurrence of anaphylaxis or allergic reactions in patients treated with Alprolix. Whilst the Panel noted that the heading to the section referred to clinical studies, the position was more complicated than the impression given. Sobi had further qualified the claim by the use of a footnote and bullet points beneath the claim which contradicted the claim. The first bullet point stated that no serious hypersensitivity or anaphylaxis events were reported in clinical studies whereas the second bullet point, referenced to the Alprolix summary of product characteristics (SPC), stated that allergic reactions or hypersensitivity had been observed rarely in the post marketing setting and might in some cases progress to severe anaphylaxis. The footnote accessed via a link below the highlighted box explained that the B-YOND study and its parent trial only included previously treated patients and the safety of Alprolix in previously untreated patients was currently being investigated. The Panel noted that the Alprolix SPC stated that the safety and efficacy of Alprolix in previously untreated patients had not yet been established and that no data were available. It appeared to the Panel that the section of the material in question was reporting the results of the clinical studies without making this sufficiently clear. Further the outcomes described were inconsistent with the Alprolix SPC. Insuffficient explanation and context was provided.

The Panel noted its comments above and considered that the claim 'No anaphylaxis or allergic reactions' was misleading and ruled a breach of the Code as acknowledged by Sobi. The claim could not be substantiated and did not reflect the available information about adverse events. The Panel therefore ruled breaches of the Code.

The Panel considered that Sobi had failed to maintain high standards and a breach of the Code was ruled.

The Panel further considered that the failure to include accurate information about a product's side effects was such as to bring discredit upon and reduce confidence in the pharmaceutical industry. It was crucial that health professionals could rely upon the industry for up-to-date and accurate information about their medicines. A breach of Clause 2 was ruled.

A complainant, who described him/herself as a concerned UK heath professional, complained about an advertisement for Alprolix (eftrenonacog alfa) placed by Swedish Orphan Biovitrum Ltd (Sobi) on a website hosted by the BMJ. Alprolix was indicated for the treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency).

The section of the advertisement at issue was headed 'Alprolix was generally well tolerated in patients of all ages in clinical studies' followed by 'Confidence for the long-term: The tolerability profile of Alprolix was studied over 5 years in the B-YOND extension study'. Below this were three highlighted boxes in a row, the last one of which was headed 'No anaphylaxis or allergic reactions'; this heading was referenced to Powell *et al* (2013) and drew the reader's attention to a footnote which read 'The B-YOND study and its parent trial included previously treated patients. The safety of Alprolix in previously untreated patients is currently being investigated'. Both the reference and the footnote could be accessed from a link just below the three boxes. The complainant drew attention to the first two of the three bullet points in the last highlighted box which read: 'No serious *hypersensitivity* or anaphylaxis events were reported in clinical

studies' and '*Hypersensitivity* or allergic reactions have been observed rarely in a post-marketing setting and may in some cases progress to severe anaphylaxis (including shock)'. (Emphasis added by complainant).

The complainant further drew attention to another two footnotes which like the footnote referred to above were accessed by clicking a link. The two footnotes referred to by the complainant read 'From the start of B-LONG until the end of B-YOND', 'Clinical trial programme only'. [These two footnotes were linked to other parts of the material and not to the highlighted box headed 'No anaphylaxis or allergic reactions and its three bullet points.]

COMPLAINT

The complainant alleged that the bold headings stated one thing but that the detail in the last highlighted box directly contradicted it; and this was misleading and the data clearly could not substantiate the incorrect statement.

The complainant noted that the footnotes were hidden on a separate web page. The footnotes were important qualifiers to the more visible statements and considerably changed the data that was displayed.

Overall, the complainant alleged that the material provided the data in a misleading manner which could lead to a situation where patient safety was placed at risk.

When writing to Sobi, the Authority asked it to consider the requirements of Clauses 2, 7.2, 7.4, 7.9 and 9.1.

RESPONSE

Sobi noted that the webpage in question was hosted on BMJ.com in its 'hosted' content section, accessed via the BMJ.com homepage. The material went live on 9 January 2020 and had had 393 unique visitors. Readers could access the webpage in two ways:

1. Via BMJ.com (via BMJ.com URL) and selecting the 'Hosted' button in the top bar navigation on the BMJ homepage. Readers then clicked the Alprolix page thumbnail within the hosted section to access the page.

2. Via certified Alprolix promotional channels ie promotional emails that clicked through to the Aplrolix page on BMJ.com or online advertising where Alprolix banner advertisements appeared on medical publisher websites that directed traffic to the BMJ hosted page.

Sobi stated that on receipt of the complaint it immediately contacted the BMJ to request that the hosted content be taken down so that the company could conduct a full investigation. Confirmation that this had been done was received on the same day.

Sobi explained that the section of the advertisement headed 'Alprolix was generally well-tolerated in patients of all ages in clinical studies' set out to represent the overall tolerability in long-term clinical studies, including from an extension study of up to 5 years.

The emboldened sub-heading, at the top of the highlighted box sat below and in proximity to the heading described above, which provided the context of clinical studies. The emboldened sub-

heading read ‘No anaphylaxis or allergic reaction’ and the reference was provided. Underneath the emboldened sub-heading, within the highlighted box, was text contained within three bullets, each given similar prominence. The complainant had drawn attention to the first two bullets points:

> ‘No hypersensitivity or anaphylaxis’ [sic, the claim was ‘No serious hypersentivity or anaphylaxis events …] which was specifically presented in the context of clinical studies, with references and
>
> ‘hypersensitivity or allergic reactions have been observed rarely’, information which was described as coming from the post- marketing setting, with reference to the summary of product characteristics (SPC).

Sobi submitted that the intention of this section was to demonstrate the wealth of data from long-term studies, in relation to all patient age groups and the tolerability reported in these studies. However, in order to ensure a complete representation of the safety profile, information from post-marketing experience was also included on the page. Sobi noted that this information was presented in the same font size as the information relating to clinical study information to ensure they were given similar prominence. Each of the bullet point clearly described the context of the information presented therein, and each statement was accurate and capable of substantiation, with references given. Sobi denied a breach of Clause 7.4.

Sobi noted, however, that whilst it intended to represent the available information in relation to anaphylaxis and hypersensitivity from both the clinical trial setting and the post-marketing experience in a transparent and balanced way, it acknowledged that due to the wording used in the sub-heading this did not accurately represent the content of the bulleted information beneath it, and that that could be misleading. Sobi therefore acknowledged a breach of Clause 7.2.

However, as the information provided on safety referred to in the complaint reflected the available evidence both in the context of long-term clinical studies and from the post-marketing setting, the company denied a breach of Clause 7.9.

Sobi noted that the Alprolix webpage hosted by the BMJ contained six key content sections. The webpage was constructed in a single-scrolling linear page style. A highly visible button with the wording ‘Click here for references and footnotes’ was included at the bottom of each content section to give the viewer a clear signpost to the footnotes and references that were directly related to the content viewed on that page. That approach in having the specific references and footnotes readily available for viewing in close proximity to the related content was chosen as an easy and clear approach compared with, for example, scrolling to the bottom of the full page to access references.

The Code required that when promotional material referred to published studies, clear references must be given. There was no guidance on where these references should be positioned on the page and there was no guidance on the positioning of footnotes.

The footnotes on the section in question included more detail about the clinical studies from the start of B-LONG study to the end of the B-YOND study but they did not change the meaning and the message remained consistent with the Alprolix SPC. Sobi disagreed that the data had been presented in a misleading way as a consequence of the footnotes. The company submitted that each claim was accurate and substantiated, and it had included up-to-date

information, including congress data from 2019, which was not inconsistent with the SPC. Sobi thus denied any breach of Clauses 7.2, 7.4 or 7.9.

Given the presentation of information relating to clinical studies and post-marketing experience, as well as the prescribing information with obligatory information and the black triangle warning, Sobi submitted advertisement could not adversely affect patient safety.

Sobi regretfully acknowledged that the sub-header was potentially misleading, in breach of Clause 7.2 as alleged and as stated above. Sobi stated that it had promptly reviewed all other Alprolix materials currently in use in the UK and had withdrawn all digital materials that presented the relevant information in the same manner. Throughout the preparation of its materials the company intended to accurately represent all the available information and submitted that its acceptance of the breach of Clause 7.2, and its immediate actions to correct it, including the withdrawal of all similar current Alprolix materials, demonstrated the high standards by which the company operated. In that regard the company submitted that the material at issue did not warrant a breach of Clause 9.1. In addition to the above, the information about hypersensitivity and allergic reactions had been presented in a complete way on the webpage, ensuring that the reader could make a full assessment and so the advertisement would not discredit the pharmaceutical industry. Sobi submitted that a ruling of a breach of Clause 2 was not warranted.

PANEL RULING

The Panel noted the headline of the section of the advertisement at issue 'Alprolix was generally well tolerated in patients of all ages in clinical studies'. Below the heading were three highlighted boxes in a row, the last one of which was headed 'No anaphylaxis or allergic reactions' and drew the reader's attention to a footnote which read 'The B-YOND study and its parent trial included previously treated patients. The safety of Alprolix in previously untreated patients is currently being investigated'. Both the reference and the footnote could be accessed from a link just below the three boxes. The Panel noted that the first two of the three bullet points in the box highlighted by the complainant read: 'No serious hypersensitivity or anaphylaxis events were reported in clinical studies' and 'Hypersensitivity or allergic reactions have been observed rarely in a post-marketing setting and may in some cases progress to severe anaphylaxis (including shock)'.

Firstly, the Panel considered the immediate and overall impression of the claim 'No anaphylaxis or allergic reactions' as it would appear to a health professional. In the Panel's view the claim implied that the reader did not have to be concerned about the occurrence of anaphylaxis or allergic reactions in patients treated with Alprolix. Whilst the Panel noted that the heading to the section referred to clinical studies, the position was more complicated than the impression given. Sobi had further qualified the claim by the use of a footnote and bullet points beneath the claim which contradicted the claim. The first bullet point stated that no serious hypersensitivity or anaphylaxis events were reported in clinical studies whereas the second bullet point, referenced to the Alprolix SPC, stated that allergic reactions or hypersensitivity had been observed rarely in the post marketing setting and might in some cases progress to severe anaphylaxis. The footnote accessed via a link below the highlighted box explained that the B-YOND study and its parent trial only included previously treated patients and the safety of Alprolix in previously untreated patients was currently being investigated. The Panel noted that the Alprolix SPC stated that the safety and efficacy of Alprolix in previously untreated patients had not yet been established and that no data were available. The supplementary information

to Clause 7 stated that claims must be capable of standing alone and that, in general, they should not be qualified by the use of footnotes. It appeared to the Panel that the section of the material in question was reporting the results of the clinical studies without making this sufficiently clear. Further the outcomes described were inconsistent with the Alprolix SPC. Insuffficient explanation and context was provided.

The Panel noted its comments above and considered that the claim 'No anaphylaxis or allergic reactions' was misleading and ruled a breach of Clause 7.2 as acknowledged by Sobi. The claim could not be substantiated and did not reflect the available information about adverse events. The Panel therefore ruled a breach of Clauses 7.4 and 7.9.

The Panel considered that Sobi had failed to maintain high standards and a breach of Clause 9.1 was ruled.

The Panel further considered that the failure to include accurate information about a product's side effects was such as to bring discredit upon and reduce confidence in the pharmaceutical industry. It was crucial that health professionals could rely upon the industry for up-to-date and accurate information about their medicines. A breach of Clause 2 was ruled.

Complaint received **6 May 2020**

Case completed **23 September 2020**