CASE AUTH/2442/10/11

PHARMACOSMOS/DIRECTOR v VIFOR

Breach of undertaking

Pharmacosmos AS alleged that Vifor Pharma UK had breached its undertaking given in Case AUTH/2422/7/11 by using the claim 'Ferinject avoids dextran-induced hypersensitivity reactions' in two press releases which were available on the company's website in October 2011. Pharmacosmos noted that the claim had been ruled in breach of the Code because it wrongly implied that Ferinject was free of hypersensitivity reactions. The undertaking given in Case AUTH/2422/7/11 was dated 30 August 2011.

One press release, dated 13 June, was about the approval by the Scottish Medicines Consortium (SMC) for the use of Ferinject for the treatment of iron deficiency anaemia. The other was about the Medicines and Healthcare products Regulatory Agency (MHRA) approval for a simplified dosing regimen for the treatment of iron deficiency.

The case was taken up by the Director as the Authority was responsible for ensuring compliance with undertakings.

The detailed response from Vifor is given below.

The Panel noted that an undertaking was an important document. It included an assurance that all possible steps 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.

In Case AUTH/2422/7/11 the claim at issue, 'Ferinject avoids dextran-induced hypersensitive reactions' had appeared in a leavepiece. In that case, the Panel noted that Section 4.4 of the Ferinject SPC, Special warnings and precautions for use, stated that 'Parenterally administered iron preparations can cause hypersensitivity reactions including anaphylactoid reactions, which may be potentially fatal …. Therefore, facilities for cardio-pulmonary resuscitation must be available'. Section 4.8, Undesirable effects listed hypersensitivity including anaphylactoid reactions as an uncommon side effect. The only reference to this possible side effect to Ferinject in the leavepiece at issue was in the prescribing information. The Panel did not accept Vifor's submission that the prescribing information on the back page of the leavepiece provided all the relevant safety information about hypersensitivity reactions. Claims in promotional material had to be capable of standing alone without reference to, *inter alia*, prescribing information to correct an otherwise misleading impression.

The Panel did not accept Vifor's submission in Case AUTH/2422/7/11 that the potential for hypersensitivity reactions with Ferinject *per se* was a separate issue. The claim at issue highlighted the issue of hypersensitivity reactions and in the Panel's view, without a counter-balancing statement with regard to the possibility of hypersensitivity reactions with Ferinject, sought to minimise the prescriber's concerns about such reactions and in that regard might compromise patient safety. A breach of the Code was ruled.

Turning to Case AUTH/2442/10/11, the Panel considered that the claim that Ferinject was '…not associated with dextran-induced hypersensitivity reactions' in the MHRA approval press release was covered by the undertaking in Case AUTH/2422/7/11 although unlike the leavepiece, the press release was not aimed solely at prescribers. The claim highlighted the issue of hypersensitivity reactions and in the Panel's view, without a counter-balancing statement with regard to the possibility of hypersensitivity reactions with Ferinject, sought to minimise the concerns about such reactions. A breach of the Code was ruled as acknowledged by Vifor.

Although the claim in the SMC approval press release that Ferinject was '…not associated with dextran-induced hypersensitivity reactions since it is free of dextran and dextran derivatives…' gave more details it again implied that there was no need to be concerned about hypersensitivity reactions with Ferinject. In the Panel's view this was similarly covered by the undertaking in Case AUTH/2422/7/11. A breach of the Code was ruled as acknowledged by Vifor.

The Panel considered that high standards had not been maintained and ruled a breach of the Code. The Panel considered that failing to comply with the undertaking brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

Pharmacosmos AS alleged that Vifor Pharma UK Limited had breached its undertaking given in Case AUTH/2422/7/11 in which the claim 'Ferinject avoids dextran-induced hypersensitivity reactions' in a leavepiece was ruled in breach of the Code. The undertaking given in that case was dated 30 August 2011. The material now at issue was two press releases on the Vifor UK website.

The case was taken up by the Director as the Authority was responsible for ensuring compliance with undertakings.

COMPLAINT

Pharmacosmos provided screen shots of the Vifor UK website taken on Tuesday, 4 October. Two press releases on the website included the claim at issue in a paragraph of supporting information headed

'About Ferinject'. Pharmacosmos noted that the claim had been ruled in breach of the Code because it wrongly implied that Ferinject was free of hypersensitivity reactions.

A press release dated 13 June about the approval by the Scottish Medicines Consortium (SMC) for the use of Ferinject in the treatment of iron deficiency anaemia stated:

> 'Ferinject is an innovative I.V. iron replacement product discovered and developed by Vifor Pharma. Ferric carboxymaltose, the active pharmaceutical ingredient of Ferinject, overcomes the unmet clinical needs of I.V. iron therapy as Ferinject is not associated with dextran-induced hypersensitivity reactions since it is free of dextran and dextran derivatives, and has a low potential for iron toxicity. Ferinject, in doses up to 1000 mg iron, can be administered in a 15 minute drip infusion in patients with iron deficiency associated with a variety of clinical conditions.'

A September press release about the Medicines and Healthcare products Regulatory Agency (MHRA) approval for a simplified dosing regimen for the treatment of iron deficiency stated:

> 'Ferinject is an innovative intravenous iron replacement product discovered and developed by Vifor Pharma. Ferric carboxymaltose, the active pharmaceutical ingredient of Ferinject, meets the unmet clinical need for an intravenous (I.V.) iron therapy that is not associated with dextran-induced hypersensitivity reactions with a low iron toxicity potential. Ferinject can be administered in doses up to 1000mg iron in a 15-minute drip infusion or I.V. injection in patients with iron deficiency associated with a variety of clinical conditions.'

On the basis of the above, Pharmacosmos alleged a breach of Clause 25.

When writing to Vifor, the Authority asked it to consider the requirements of Clauses 2 and 9.1 in addition to Clause 25 as cited by Pharmacosmos.

RESPONSE

Vifor submitted that following Cases AUTH/2422/7/11 and AUTH/2423/7/11 the leavepieces at issue (refs 0148/FER/2011 and 0090A/FER/2011 respectively) were withdrawn as per the undertakings given. This resulted in almost all of the promotional material used by the sales teams, 58 different items, being withdrawn from circulation on 31 August 2011 in line with the company's standard operating procedure (SOP) for the withdrawal of promotional material (a list of the materials withdrawn was provided). Vifor submitted that this process meant that there were no new materials available to order. Additionally, all the materials that were held by the sales teams were collected and destroyed according to the SOP for the withdrawal of promotional material.

A new sales aid and four further leavepieces which did not include the claims at issue were sent to the sales teams on 22 September 2011 and had been used ever since. As a consequence of the two cases, Vifor undertook a comprehensive review of all of its materials in addition to the approval and withdrawal processes.

As this review was undertaken solely on materials in circulation, the two press releases that were prepared globally for two important company announcements were, unfortunately, missed. Vifor acknowledged this oversight and noted that as soon as the matter was brought to its attention, it withdrew the press releases from its website.

The two press releases in question were signed off before the claims were ruled in breach of the Code and before the undertaking given on 30 August 2011. The SMC approval press release was approved for release on 13 April 2011 and the MHRA approval press release was approved for release on 13 July. The claims at issue were part of the press release boiler plate provided to affiliates by Vifor Pharma International. The boiler plate had since been changed and a new one that did not include the claim at issue had been given to all Vifor Pharma affiliates.

Despite the press release on the revised Ferinject summary of product characteristics (SPC) being approved on 13 July, it was only posted on the Vifor website on 7 September, the day the new SPC was available in the UK. Vifor noted that the press release was not prepared or approved after the undertaking was given.

Nonetheless, Vifor acknowledged that not checking the press release was an oversight on its part which it regretted and for which it apologised. However, this oversight notwithstanding, it submitted that comprehensive steps were followed at considerable cost to the company in order to comply with the undertaking given in Case AUTH/2422/7/11.

Vifor stated that it had since added an additional step in its SOP for the withdrawal of promotional material in order to ensure this did not happen again.

In response to a request for clarification regarding the date of issue of the two press releases Vifor stated that the SMC approval press release was signed off on 13 June 2011. It was distributed on 13 June to the medical media by a public relations agency. A distribution list was provided. It was put on the Vifor UK website on 14 June and as a result of the breach was taken off the website on 12 October 2011. The date of 13 April above was a typing error and Vifor apologised for the confusion caused.

With regard to the MHRA approval press release Vifor explained that the MHRA was the reference member state for Ferinject. When the MHRA approved the label changes in July 2011, a press release was prepared to communicate the information globally.

The MHRA approval press release was approved for media release on 13 July 2011. The approval was via email as the signatories were not available in the office and a copy of the electronic approval was added to the job bag. As the Vifor signatories were out of the office on 13 July the job bag itself was therefore not physically signed off until 21 July 2011 and 4 August respectively, by the two final signatories. This press release was distributed on 13 July to the medical media by Vifor's public relations agency which released it via email to the same distribution list as for the SMC approval press release.

After several minor iterations, the final wording of the UK SPC reflecting the full MHRA label update was made available to Vifor Pharma UK from Vifor global regulatory in early September 2011. The global press release was therefore placed on the Vifor UK website on 7 September 2011 and when the company realised it was in breach it was taken off the website on 12 October 2011.

There had been a subsequent further variation to the Ferinject SPC that came into effect on 29 September 2011 and so a revised version of the Ferinject SPC was issued on 29 September. The current SPC was supplied to the Authority as requested, ie the 29 September 2011 version.

PANEL RULING

The Panel noted that an undertaking was an important document. It included an assurance that all possible steps 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.

Case AUTH/2422/7/11

The material at issue in this case was a claim in a leavepiece (ref 0148/FER/2011) that 'Ferinject avoids dextran-induced hypersensitive reactions'. The claim appeared as the second bullet point in a section headed 'How quickly can Ferinject be administered?'.

The Panel noted that Section 4.4 of the Ferinject SPC, Special warnings and precautions for use, stated that 'Parenterally administered iron preparations can cause hypersensitivity reactions including anaphylactoid reactions, which may be potentially fatal …. Therefore, facilities for cardio-pulmonary resuscitation must be available'. Section 4.8, Undesirable effects listed hypersensitivity including anaphylactoid reactions as an uncommon side effect. The only reference to this possible side effect to Ferinject in the leavepiece at issue was in the prescribing information. The Panel did not accept Vifor's submission that the prescribing information on the back page of the leavepiece provided all the relevant safety information about hypersensitivity reactions. Claims in promotional material had to be capable of standing alone without reference to, *inter alia*, prescribing information to correct an otherwise misleading impression.

The Panel did not accept Vifor's submission that the potential for hypersensitivity reactions with Ferinject *per se* was a separate issue. The claim at issue highlighted the issue of hypersensitivity reactions and in the Panel's view, without a counter-balancing statement with regard to the possibility of hypersensitivity reactions with Ferinject, sought to minimise the prescriber's concerns about such reactions and in that regard might compromise patient safety.

The Panel considered that the claim was misleading and a breach of Clause 7.2 was ruled.

The case had also involved another claim which the Panel considered was misleading with regard to adverse events. The Panel considered that both of the claims at issue would minimise a prescriber's concerns about Ferinject's safety profile and as activities which were prejudicial to patient safety were regarded as serious matters it reported Vifor to the Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure. The Appeal Board decided that Vifor should be audited and following receipt of the audit report the Appeal Board would consider whether further action was necessary.

Case AUTH/2442/10/11

Turning to the case now before it, the Panel noted that the material at issue was two press releases. The SMC approval press release had been signed off on 13 June 2011 according to the 'Job Bag Item Approval Form' and the form stating that the material was 'Approved as compliant with Vifor Pharma Policies and SOPs and with the requirements of the ABPI Code of Practice for the Pharmaceutical Industry 2011' and not 13 April as stated in Vifor's first response. This apparent inconsistency was followed up with Vifor which acknowledged that its first submission included a typographical error and the SMC approval press release was signed off on 13 June. It had been published on the Vifor website on 14 June 2011. There was no reference on the SMC approval press release provided by Vifor unlike the certificate which bore the reference 0229A/FER/2001. The reference did appear in the version provided by Pharmacosmos.

The second press release was dated 13 July 2011 and referred to the MHRA approval. The certificate bore the reference 0265/FER/2011 and according to the documentation it was signed off on 21 July and 4 August as being compliant with Vifor Policies, SOPs and the Code. The final sign off of the job bag approval form was dated 21 July and not 13 July as stated in Vifor's first response. The Panel noted that Vifor's second submission explained that the MHRA approval press release had been approved by email and the job bag had been signed when the signatories were next in the office. The Panel noted that the MHRA press release was placed on the Vifor website on 7 September.

The Panel considered that the claim that Ferinject was '…not associated with dextran-induced hypersensitivity reactions' in the MHRA approval press release was covered by the undertaking in Case AUTH/2422/7/11 although unlike the leavepiece,

the press release was not aimed solely at prescribers. The claim now at issue highlighted the issue of hypersensitivity reactions and in the Panel's view, without a counter-balancing statement with regard to the possibility of hypersensitivity reactions with Ferinject, sought to minimise the concerns about such reactions. A breach of Clause 25 was ruled as acknowledged by Vifor.

Although the claim in the SMC approval press release that Ferinject was '…not associated with dextran-induced hypersensitivity reactions since it is free of dextran and dextran derivatives…' gave more details it again implied that there was no need to be concerned about hypersensitivity reactions with Ferinject. In the Panel's view this was similarly covered by the undertaking in Case AUTH/2422/7/11. A breach of Clause 25 was ruled as acknowledged by Vifor.

The Panel considered that high standards had not been maintained and ruled a breach of Clause 9.1. Failing to comply with an undertaking and assurance was cited as an example of an activity likely to be in breach of Clause 2. The Panel considered that failing to comply with the undertaking brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

Complaint received **11 October 2011**

Case completed **18 November 2011**