PHARMACOSMOS/DIRECTOR v VIFOR

Alleged breach of undertaking

Pharmacosmos alleged that a Ferinject (ferric carboxymaltose) advertisement issued by Vifor Pharma breached two previous undertakings. Pharmacosmos marketed Cosmofer (iron dextran). Cosmofer and Ferinject were both indicated for the treatment of iron deficiency when oral preparations were ineffective or could not be used.

As the complaint was about an alleged breach of undertaking it was taken up by the Director as it was the Authority's responsibility to ensure compliance with undertakings.

Pharmacosmos noted that in Case AUTH/2442/10/11 Vifor was ruled in breach of a previous undertaking for continuing to link the dextran shell of Cosmofer to safety concerns by referring to 'dextran-induced hypersensitive reactions' in press releases on the Vifor website. In Case AUTH/2422/7/11, Vifor was ruled in breach for two claims which linked the dextran shell of Cosmofer with safety concerns by highlighting that Vifor was free from 'dextran-induced hypersensitivity reactions since it is free of dextran and dextran derivatives'.

In the advertisement now at issue, Pharmacosmos alleged that the claim 'Non dextran carboxymaltose shell' implied that there was merit to be gained by not being dextran based and that there must be a safety concern with the dextran base and that without it, Ferinject was safer. Pharmacosmos acknowledged that Ferinject did not contain dextran, however it cited certain serious side effects that might occur with the medicine.

The detailed response from Vifor is given below.

The Panel noted that Pharmacosmos had stated that Vifor had been previously ruled in breach of the Code because of claims which raised safety concerns about the dextran shell of Cosmofer. This was not so. In Case AUTH/2422/7/11 the Panel upheld Pharmacosmos's allegation that the claim 'Ferinject avoids dextran-induced hypersensitive reactions' was misleading about Ferinject itself; the ruling was not made on the basis that the claim raised concerns about Cosmofer. Similarly in Case AUTH/2442/10/11, Pharmacosmos had referred to claims which had wrongly implied that Ferinject was free of hypersensitivity reactions.

The Panel noted that neither the claim now at issue, 'Non dextran carboxymaltose shell' nor the other two bullet points in the advertisement ('Effective in increasing haemoglobin when inflammation is present' and '1000mg can be administered in 15 minutes by IV injection and IV infusion') referred to hypersensitivity reactions. In the Panel's view, neither the claim of itself nor the advertisement sought to minimise concerns about such reactions with Ferinject. The Panel did not consider that the claim was covered by the previous undertakings and thus it ruled no breach of the Code including no breach of Clause 2.

Pharmacosmos A/S alleged that a Ferinject (ferric carboxymaltose) advertisement (ref UK/FER/12/0163c), issued by Vifor Pharma UK and published in Gastrointestinal Nursing, January 2013, breached the undertakings given in Cases AUTH/2422/7/11 and AUTH/2442/10/11. The advertisement at issue featured the photograph of a leaping ballerina together with three bullet points, the second of which read 'Non dextran carboxymaltose shell'.

Pharmacosmos marketed Cosmofer (iron dextran). Cosmofer and Ferinject were both indicated for the treatment of iron deficiency when oral preparations were ineffective or could not be used.

As the complaint was about an alleged breach of undertaking it was taken up by the Director as it was the Authority's responsibility to ensure compliance with undertakings.

COMPLAINT

Pharmacosmos alleged that the claim 'Non dextran carboxymaltose shell' was the latest attempt by Vifor to use the molecular structure as a differentiating safety feature between Ferinject and Cosmofer which was a dextran-based molecule.

Pharmacosmos noted that in Case AUTH/2442/10/11 Vifor was ruled in breach of Clause 25 for continuing to link the dextran shell of Cosmofer to safety concerns by referring to 'dextran-induced hypersensitive reactions' in press releases on the Vifor website. In Case AUTH/2422/7/11, Vifor was ruled in breach of Clause 7.2 for two claims which linked the dextran shell of Cosmofer with safety concerns by highlighting that Vifor was free from 'dextran-induced hypersensitivity reactions since it is free of dextran and dextran derivatives'.

Pharmacosmos considered that the advertisement now at issue continued to imply that there was merit to be gained by not being dextran based. The only reasonable conclusion that physicians could draw from the bullet point was that there must be a safety concern with the dextran base and therefore leaving it out must mean that Ferinject was safer. Pharmacosmos acknowledged that Ferinject did not contain dextran, however it cited certain serious side effects that might occur with the medicine. These risks must be mentioned if albeit indirectly referring to the safety of competing products in promotional material. Pharmacosmos referred to a recent Rapporteur report to the European Medicines Agency (EMA).

Pharmacosmos alleged that the claim was a continuation of the previous attempts to raise concerns about the safety profile of the dextran molecule in Cosmofer, in breach of the undertakings given in Cases AUTH/2442/10/11 and AUTH/2422/7/11.

When writing to Vifor, the Authority asked it to respond in relation to the requirements of Clause 2 in addition to Clause 25 cited by Pharmacosmos.

RESPONSE

Vifor stated that it was committed to adhering to the Code and that it took allegations of a breach of undertaking extremely seriously. However, Pharmacosmos had raised new and additional concerns that fell outside the undertakings previously given and, as such, there was no automatic right to circumvent the complaints process. The undertakings in Cases AUTH/2442/10/11 and AUTH/2422/7/11 referred to the claim 'Ferinject avoids dextran-induced hypersensitivity reactions' which was ruled in breach of the Code because it was misleading about the safety of Ferinject. Vifor noted that Pharmacosmos had now alleged that the claim 'non dextran carboxymaltose shell' was a breach of those undertakings. This was a new complaint. Vifor submitted that where new complaints arose that did not fall under a breach of Clause 25, Paragraph 5.3 of the Constitution and Procedure required inter-company dialogue first, ie 'that the company concerned has previously informed the company alleged to have breached the Code that it proposed to make a formal complaint and offered inter-company dialogue at a senior level in an attempt to resolve the matter, but that this offer was refused or dialogue proved unsuccessful'. Vifor stated that Pharmacosmos had made no such offer and Vifor viewed this as an abuse of process.

Following the ruling of a breach in Case AUTH/2422/7/11, almost all of the promotional material used by the sales teams was withdrawn. Additionally, all the materials held by the sales teams were collected and destroyed. As a consequence of the breach, a comprehensive internal review was undertaken and all material along with internal approval and material withdrawal processes were reviewed. Two press releases which were prepared globally were not part of this review, a regrettable oversight by Vifor that resulted in Case AUTH/2442/10/11. Following the second case, the boiler plate which contained the claim at issue provided by Vifor Pharma International was replaced and an additional step was added into the standard operating procedure (SOP) for material withdrawal to ensure this did not happen again. Vifor reiterated that all material was now rigorously reviewed before release.

With regard to the claim now at issue, Vifor considered that 'Non dextran carboxymaltose shell' was not about the safety of Ferinject but about its physiochemical properties, completely in line with Section 4.2 of the Ferinject summary of product characteristics (SPC), which allowed up to 1000mg of Ferinject to be administered in 15 minutes. The claim referred exclusively to the physiochemical properties of Ferinject and linked that to its administration according to its SPC. There was no direct or indirect reference to any safety aspects of Cosmofer or, indeed, any other product. Neither the claim in question nor the advertisement referred (directly or indirectly) to safety, adverse events or hypersensitivity reactions, dextran-induced or not (dextran-induced hypersensitivity reaction was the subject of the previous undertakings). As stated above, Vifor did not consider that there was a breach of undertaking and consequently there was no breach of Clauses 25 or 2. The claim was simply about the physiochemical properties of Ferinject rather than its safety.

Vifor was particularly concerned that Pharmacosmos had referred to an EMA report. While it was public knowledge that a Europe wide review of all intravenous iron preparations was in progress, the contents of interim reports generated as part of that process were not. Disclosure of the EMA's preliminary documents was a clear breach of trust within the context of the EMA's referral procedure, where all parties involved (EMA, Rapporteurs, marketing authorization holders, experts) must be able to exchange preliminary views without fear of those views being disclosed prior to the final decision. The EMA clearly recognised that publication of reports should occur only once the final opinion had been adopted. Disclosure of such preliminary documents before a final decision was made had potential serious public health consequences.

Vifor was extremely concerned that Pharmacosmos' intention was to manipulate the complaints process to ensure that an out of context element of a confidential, preliminary EMA statement was included in the case report with the specific intent of making this selective incomplete information public.

In summary, Vifor strenuously denied a breach of Clause 25 and hence Clause 2, based on the narrow, tenuous and misleading points raised and considered that the complaints process had been abused by Pharmacosmos.

PANEL RULING

The Panel noted that in Case AUTH/2422/7/11 the material at issue had been a leavepiece which in a section headed 'How quickly can Ferinject be administered?', featured the claim 'Ferinject avoids dextran-induced hypersensitive reactions'. In Case AUTH/2422/7/11 the Panel noted that the Ferinject SPC 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'. Hypersensitivity including anaphylactoid reactions was listed as an uncommon side effect. The only reference to this possible side effect to Ferinject in the leavepiece was in the prescribing information. The Panel did not accept Vifor's submission that the prescribing information provided all the relevant safety information about hypersensitivity reactions. Claims 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. In the Panel's view, the claim 'Ferinject avoids dextran-induced hypersensitive reactions' highlighted the hypersensitivity issue and sought to minimise the prescriber's concerns about such reactions with Ferinject 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 which was accepted by Vifor.

Case AUTH/2442/10/11 involved two press releases. The Panel considered that the claim in one of the press releases '…not associated with dextran-induced hypersensitivity reactions' was covered by the undertaking in Case AUTH/2422/7/11. 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 Clause 25 was ruled as acknowledged by Vifor.

Although the claim in the other 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 further breach of Clause 25 was ruled as acknowledged by Vifor.

The Panel noted that in the case now at issue, Case AUTH/2589/3/13, Pharmacosmos had stated that Vifor had been previously ruled in breach of the Code because of claims which raised safety concerns about the dextran shell of Cosmofer. This was not so. In Case AUTH/2422/7/11 Pharmacosmos had alleged that the claim 'Ferinject avoids dextran-induced hypersensitive reactions' was misleading about Ferinject itself; not that it raised concerns about Cosmofer. Similarly in Case AUTH/2442/10/11, Pharmacosmos had referred to claims which had wrongly implied that Ferinject was free of hypersensitivity reactions.

The Panel noted that neither the claim now at issue, 'Non dextran carboxymaltose shell' nor the other two bullet points in the advertisement ('Effective in increasing haemoglobin when inflammation is present' and '1000mg can be administered in 15 minutes by IV injection and IV infusion') referred to hypersensitivity reactions. In the Panel's view, neither the claim of itself nor the advertisement as a whole sought to minimise concerns about such reactions with Ferinject. The Panel did not consider that the claim was covered by the previous undertakings and thus it ruled no breach of Clause 25. Given its ruling of no breach of Clause 25, the Panel subsequently ruled no breach of Clause 2.

Complaint received **25 March 2013**

Case completed **24 April 2013**