CASE AUTH/2422/7/11

PHARMACOSMOS v VIFOR

Ferinject leavepiece

Pharmacosmos complained about a Ferinject (ferric carboxymaltose) solution for injection/infusion leavepiece issued by Vifor Pharma. Ferinject was indicated for the treatment of iron deficiency when oral preparations were ineffective or could not be used. The claims at issue were both referenced to Geisser (2009).

The detailed responses from Vifor are given below.

Pharmacosmos alleged that the claim 'Ferinject avoids dextran-induced hypersensitive reactions' was not balanced or fair because there was no mention that Ferinject itself might cause hypersensitivity reactions as stated in the Ferinject summary of product characteristics (SPC). The material was not sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine.

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.

In the Panel's view, the claim 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 was ruled.

Pharmacosmos alleged that the claim 'Ferinject has a low molecular weight thus limiting adverse events' which appeared as a bullet point immediately beneath the claim at issue above was misleading. There was no proven link between the molecular weight of Ferinject and the adverse event rate.

The Panel noted that Geisser stated that the tolerability of iron compounds depended not only on the reactivity of the iron and how easily it was released from the carbohydrate but also on the size of the iron-carbohydrate complex and the nature of the carbohydrate moiety. A relationship between release rate and acute toxicity was noted. The Panel considered that the claim implied a simple correlation between molecular weight and side effects. In the Panel's view the situation was more complex than that. The Panel considered that the claim sought to minimise a prescriber's concerns about all side effects with Ferinject and in that regard might compromise patient safety. The Panel ruled that the claim was misleading and in breach of the Code.

During its consideration of the case, the Panel noted that both of the claims at issue had been ruled to be misleading with regard to the safety profile of Ferinject; it considered that each would minimise a prescriber's concerns in that regard. Activities prejudicial to patient safety were regarded as serious matters and so the Panel reported Vifor to the Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

The Appeal Board was extremely concerned about the material at issue; that it had the potential to compromise patient safety was a serious worry. It had been certified as required by the Code. The Appeal Board was concerned that, as in Case AUTH/2411/6/11, this case raised very serious concerns regarding the expertise of Vifor signatories and the role of senior management in compliance matters.

The Appeal Board noted that Vifor had accepted that it had made serious errors and in that regard it had already started to review its policies and procedures. Nonetheless, the Appeal Board decided that Vifor's procedures in relation to the Code should be audited as soon as possible by the Authority. The audit would take place at the same time as that required in Case AUTH/2411/6/11. On receipt of the audit report the Appeal Board would consider whether further sanctions were necessary.

Vifor was first audited in November 2011 and upon receipt of that audit report the Appeal Board was concerned that Vifor had much work to do. It noted from Vifor's response that a preliminary corrective and preventative actions programme had been drawn up. It requested that Vifor be asked to provide timescales. It also decided that Vifor should be asked to provide copies of the correspondence between the company and its head office about the audit report and details about the role of an external consultant.

The Appeal Board was concerned to note that since deciding that Vifor should be audited, another case, which involved a breach of undertaking (Case AUTH/2442/10/11), had been considered by the Panel. On the day of the audit that case was still on going and so was not discussed. The Appeal Board noted, however, that the case had now completed.

The Appeal Board decided that Vifor should be re-audited in March 2012. On receipt of the report for that audit, the Appeal Board would consider if further sanctions were necessary.

Upon receipt of the March 2012 audit report the Appeal Board was disappointed at the lack of progress since the November 2011 audit particularly with regard to the revision of standard operating procedures (SOPs). The Appeal Board noted that new staff were due to be appointed. The Appeal Board considered that Vifor should be re-audited in six months time at which point it expected there to be significant improvement. In the meantime Vifor should provide by the end of June a detailed interim response to the recommendations of the March 2012 audit to include an update on recruitment and SOPs. If the Appeal Board was not satisfied then the re-audit would be brought forward.

Upon receipt of the next audit report, the Appeal Board would decide whether further sanctions were necessary.

On consideration of the interim response from Vifor the Appeal Board decided there was no need to re-audit sooner than the currently arranged date, in October 2012.

Upon receipt of the October 2012 audit report, the Appeal Board noted that good progress had been made since the last audit. New staff had been appointed who would have key roles in compliance. New standard operating procedures had been written and resources had been committed to Code compliance. The Appeal Board considered that on the basis that Vifor's current commitment to compliance was maintained, no further action was required.

Pharmacosmos A/S complained about the promotion of Ferinject (ferric carboxymaltose) solution for injection/infusion by Vifor Pharma UK Limited. Ferinject was indicated for the treatment of iron deficiency when oral preparations were ineffective or could not be used.

The material at issue was a six-page gatefolded leavepiece (ref 0148/FER/2011) entitled 'Dosage and Administration Summary'. The claims at issue were both referenced to Geisser (2009).

1 Claim 'Ferinject avoids dextran-induced hypersensitive reactions'

This claim appeared as the second bullet point in a section headed 'How quickly can Ferinject be administered?

COMPLAINT

Pharmacosmos noted that there was no mention that Ferinject itself might cause hypersensitivity reactions, although it might be correct as it was stated that Ferinject avoided hypersensitivity reactions caused by another iron product.

Pharmacosmos alleged that this did not represent balanced and fair information and the material was therefore not sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine in breach of Clause 7.2.

The Ferinject summary of product characteristics (SPC), Section 4.8 Undesirable effects, clearly stated that hypersensitivity reactions were observed following administration of Ferinject:

> 'Immune system disorders:
>
> Uncommon (>1/1,000, <1/100): Hypersensitivity including anaphylactoid reactions'.

Furthermore, Section 4.4 clearly identified hypersensitivity reactions as a potential adverse event with Ferinject that might have very severe consequences for the patient:

> 'Parenterally administered iron preparations can cause hypersensitivity reactions including anaphylactoid reactions, which may be potentially fatal (see Section 5.3). Therefore, facilities for cardio-pulmonary resuscitation must be available'.

In addition, Pharmacosmos noted that a recent publication from the Swiss Medicines Agency reported 19 serious anaphylactoid reactions caused by Ferinject over a short period of time in Switzerland.

Pharmacosmos stated that it was clearly documented that Ferinject caused hypersensitivity reactions and this information must be adequately addressed when informing about hypersensitivity reactions in relation to Ferinject. These facts underpinned the importance of physicians knowing about this possible serious adverse event before using Ferinject.

In inter-company dialogue Vifor's statement that the claim was a 'statement of fact' concerned Pharmacosmos because firstly, Vifor had completely missed the point that inferences would be drawn from the claim implying that hypersensitivity reactions were not a feature of Ferinject and secondly, the company's response that its claim was a 'statement of fact' was not correct.

RESPONSE

Vifor submitted that the claim 'Ferinject avoids dextran-based hypersensitive reactions' was a statement of fact as ferric carboxymaltose contained no dextran and thus avoided dextran-based hypersensitivity.

The inclusion of dextran in intravenous (IV) iron preparations was an important physician and patient consideration and health authorities had taken a very clear view on this. In May 2010 The European Medicines Agency (EMA) Pharmacovigilance Working Party (PhVWP) looked at safety concerns associated with iron dextran. In addition, a year ago the French national authority for health (Haute Autorité de Santé) report on Ferinject stated clearly that Ferinject was not a dextran and hence it became the first IV iron accepted for reimbursement in

populations other than haemodialysis patients. Furthermore, in 2010 the French agency for the safety of health products (Agence Française de Sécurité Sanitaire des Produits de Santé) issued a report on iron dextran (CosmoFer marketed in the UK by Pharmacosmos) and requested a Dear Doctor letter be sent to all physicians in France by the company that marketed iron dextran in France. Iron dextran had been added to the list of 77 medicines under assessment by the pharmacovigilance commission of the French agency for safety concerns.

The fact that Ferinject avoided dextran-based hypersensitivity was therefore an important consideration for health professionals and it was important for Vifor to highlight this feature in its communications with health professionals.

The potential for hypersensitivity reactions with Ferinject *per se* was a separate issue and all the relevant Ferinject safety information was clearly and appropriately outlined in the prescribing information on the back page of the leavepiece. Vifor denied a breach of Clause 7.2.

Vifor stated that it was not clear from the complaint what (if any) breach of the Code was alleged in the narrative on the potential for anaphylactic reactions with Ferinject. However, the SPC quoted was accurate and the leavepiece complied with the required Ferinject label and SPC requirements.

The reference to the Swiss Medicines Agency report was, unfortunately, very selective as it omitted to mention that only page 15 of the document referred to the number of anaphylactoid cases with Ferinject and suggested caution regarding interpretation as so little specific could be said regarding this data at that time. Furthermore, the data did not refer to dextran-based hypersensitive reactions at all and so it was not relevant to the complaint.

PANEL RULING

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 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.

2 Claim 'Ferinject has a low molecular weight thus limiting adverse events'

The claim appeared as a bullet point immediately beneath the claim at issue in point 1 above.

COMPLAINT

Pharmacosmos stated that there was no proven link between the molecular weight of Ferinject and the adverse event rate; there was no data in the cited reference to support the claim. If anything, some of the unreferenced statements in Geisser seemed to support a lower risk of side effects which related to free iron in iron-carbohydrate molecules with a high molecular weight and Ferinject was characterised in the article as having a high molecular weight. Pharmacosmos alleged that the claim was misleading in breach of Clause 7.2.

RESPONSE

Vifor submitted that Ferinject was similar in structure to ferritin and caused iron to be deposited in the reticuloendothelial system of the liver. It could provide iron without inducing oxidative stress. Its molecular weight of 150,000 Daltons meant that little of the product was lost through renal elimination, unlike other small iron complexes.

Once in the body, iron was released gradually, which avoided the acute toxicity of many other iron compounds and allowed large amounts of iron to be delivered which resulted in a much wider therapeutic window and reduced the likelihood of adverse events.

The cited reference clearly illustrated that the molecular weight of Ferinject was less than iron dextran and for iron complexes Ferinject had a low molecular weight, both of which were facts. Vifor therefore did not consider this was misleading and denied a breach of Clause 7.2.

In response to a request for more information, Vifor confirmed that the audience for the leavepiece was secondary care health professionals as the company's sales force was entirely hospital focused.

Vifor confirmed that the sales force was provided with extensive verbal briefing on a number of items, including the leavepiece at issue, during a sales meeting in March. Slides relevant to the leavepiece were provided.

PANEL RULING

The Panel noted that the reference cited in support of the claim was an editorial by Geisser entitled 'The

pharmacology and safety profile of ferric carboxymaltose (Ferinject): structure/reactivity relationships of iron preparations'. The author stated that the tolerability of iron compounds depended not only on the reactivity of the iron and how easily it was released from the carbohydrate but also on the size of the iron-carbohydrate complex and the nature of the carbohydrate moiety. The release of iron from the polynuclear iron hydroxide-carbohydrate complexes was stated to be inversely related to the molecular weight of the complex. The author also stated that once Ferinject was in the body, iron was gradually released, avoiding the acute toxicity of many other iron compounds. The Panel considered that the claim 'Ferinject has a low molecular weight thus limiting adverse events' implied a simple correlation between molecular weight and side effects. In the Panel's view the situation was more complex than that. The author had noted a relationship between release rate and acute toxicity.

The Panel noted that one slide of the training presentation given to the sales force in March was entitled 'New dosing leavepiece', with the subtitle 'Answers to common questions'. One of these answers was 'Low adverse events'.

The Panel considered that the claim sought to minimise a prescriber's concerns about all side effects 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.

During its consideration of the case, The Panel noted that both of the claims at issue had been ruled to be misleading with regard to the safety profile of Ferinject. The Panel considered that each would minimise a prescriber's concerns in that regard. The Panel further noted that activities which were prejudicial to patient safety were regarded as serious matters and so it decided to report Vifor to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

COMMENTS FROM VIFOR ON THE REPORT

Vifor understood the Panel's decision to refer the case to the Appeal Board. However, Vifor considered it important to clarify its activities with regard to the initial inter-company dialogue which preceded the referral of the case to the PMCPA. Due to a number of significant omissions in its communication, Vifor considered that it might have failed to represent its position fully and clearly.

Vifor submitted that it was committed to resolving issues as frequently as possible through inter-company dialogue and to abiding to the letter and spirit of the Code. In this case, the initial letter to Vifor from Pharmacosmos was sent in late May 2011. Vifor reviewed the material at issue in light of Pharmacosmos's comments and responded accordingly. Additionally, no further copies of the leavepiece were printed or distributed to its sales force after this date; new material without the two claims in question was issued on 10 June 2011. Unfortunately, due to an administrative error, Vifor failed to notify Pharmacosmos of these actions and had only recently rectified this matter. Vifor submitted that this omission in communication was an oversight on its part and might have been the reason inter-company dialogue was passed to the PMCPA for review and ruling.

Nonetheless, Vifor accepted the Panel's decision to report the company to the Appeal Board as patient safety was an extremely important matter. Vifor noted that all of its staff were regularly trained (most recently in March and May 2011) on the potential for hypersensitivity with iron products as part of the company's risk management plan. Unfortunately due to the holiday period this information was not provided to the Panel when further information on the claims in question was requested at short notice in August.

Vifor was reviewing its internal processes and materials to ensure the referencing of claims was accurate. It reassured the Appeal Board that it took its commitment towards this process and safety issues very seriously; safety was always its priority in producing new promotional materials.

At the consideration of the report Vifor apologised and accepted that the company had made significant errors. Vifor noted that it had not advised Pharmacosmos that it had discontinued use of the material at issue because its standard operating procedure (SOP) for inter-company dialogue had not included an instruction to notify the complainant about actions undertaken. The SOP had now been amended to deal with this serious oversight. Vifor submitted that as part of its internal review of processes it had increased support for medical sign-off. Vifor noted that it had recently been inspected by the Medicines and Healthcare products Regulatory Agency (MHRA). Vifor was confident that it had robust procedures in place to ensure that previous errors were not repeated.

APPEAL BOARD CONSIDERATION

The Appeal Board was extremely concerned about the material at issue; that it had the potential to compromise patient safety was a serious worry. It had been certified as required by Clause 14.1. The Appeal Board was concerned that, as in Case AUTH/2422/6/11, this case raised very serious concerns regarding the expertise of Vifor signatories and the role of senior management in compliance matters.

The Appeal Board noted that Vifor had accepted that it had made serious errors and in that regard it had already started to review its policies and procedures. Nonetheless, the Appeal Board decided, in accordance with Paragraph 11.3 of the Constitution and Procedure, to require an audit of Vifor's procedures in relation to the Code to be carried out by the Authority. The audit should be conducted as soon as possible. The audit would take place at the same time as that required in Case AUTH/2411/6/11. On receipt of the audit report the Appeal Board would consider whether further sanctions were necessary.

FURTHER CONSIDERATION BY THE APPEAL BOARD

Vifor was first audited in November 2011 and upon receipt of that audit report the Appeal Board was concerned that the report indicated that Vifor had much work to do. It noted from Vifor's response that a preliminary corrective and preventative actions programme had been drawn up. It requested that Vifor be asked to provide timescales for the actions. It also decided that Vifor should be asked to provide copies of the correspondence between the company and its head office about the audit report and details about the role of an external consultant.

The Appeal Board was concerned to note that since deciding that Vifor should be audited, another case, which involved a breach of undertaking (Case AUTH/2442/10/11), had been considered by the Panel. On the day of the audit that case was still ongoing and so was not discussed. The Appeal Board noted, however, that the case had now completed.

The Appeal Board decided that Vifor should be re-audited in March 2012. On receipt of the report for that audit, the Appeal Board would consider if further sanctions were necessary.

Upon receipt of the March 2012 audit report the Appeal Board was disappointed at the lack of progress since the November 2011 audit particularly with regard to the revision of standard operating procedures (SOPs). The Appeal Board noted that new staff were due to be appointed. The Appeal Board considered that Vifor should be re-audited in six months time at which point it expected there to be significant improvement. In the meantime Vifor should provide a detailed interim response to the recommendations of the March 2012 audit to include an update on recruitment and SOPs. This interim response should be provided by the end of June 2012 and Vifor advised that if the Appeal Board was not satisfied then the re-audit would be brought forward.

Upon receipt of the next audit report, the Appeal Board would decide whether further sanctions were necessary.

On consideration of the interim response from Vifor the Appeal Board decided that there was no need to re-audit sooner than the currently arranged date, in October 2012.

Upon receipt of the October 2012 audit report, the Appeal Board noted that good progress had been made since the last audit. New staff had been appointed who would have key roles in compliance. New standard operating procedures had been written and resources had been committed to Code compliance. The Appeal Board considered that on the basis that Vifor's current commitment to compliance was maintained, no further action was required.

Complaint received	**27 July 2011**
Undertaking received	**31 August 2011**
Appeal Board consideration	**12 October 2011** **7 December 2011** **19 April 2012** **26 July 2012** **15 November 2012**
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