CASE AUTH/2886/11/16

PHARMACOSMOS v VIFOR

Promotion of Ferinject

Pharmacosmos UK complained about a Ferinject (iron carboxymaltose) leavepiece entitled 'Their world awaits' issued by Vifor Pharma UK. Ferinject was an intravenous (IV) iron preparation for the treatment of iron deficiency where oral therapy had been ineffective or could not be used. Pharmacosmos marketed Monofer (iron isomaltoside) which was similarly indicated.

Pharmacosmos stated that many of its concerns might be reflected in other promotional material. There appeared to be a clear intention to indirectly compare Ferinject and Monofer. The manner of the implied comparison resulted in claims that were alleged to be misleading as outlined below.

Page 1 of the leavepiece featured a red highlighted box which contained the following claims:

> **'Ferinject is the only high dose rapid infusion IV iron that;**
>
> - **has simplified dosing for all patients**
> - **contains product specific safety data in the Summary of Product Characteristics**
> - **is licenced *[sic]* for ages 14 years and over**
> - **can be administered up to 1g as a bolus injection**
>
> **Ferinject is the UK and Europe's market leading IV iron.'**

Pharmacosmos alleged that the layout of the phrase within the red box implied that Ferinject was the only product that could offer any of the points in the bullets, which was not true. A breach of the Code was alleged. By stating that Ferinject was the 'only high dose rapid iron infusion', the unstated but only comparison being made was with Monofer.

With regard to the claim that Ferinject was the only high dose rapid infusion IV iron that had simplified dosing for all patients, Pharmacosmos stated that there were two ways to calculate iron need based on patient body weight and haemoglobin levels; the Ganzoni formula or a simplified dosing table. Ferinject dose was based on the simplified table exclusively while clinicians could determine the dose of Monofer using either method. The Monofer summary of product characteristics (SPC) recommended but did not mandate the use of the Ganzoni formula in certain patients. Therefore, the Monofer SPC also allowed simplified dosing in all patients, and subsequently the implied comparison was alleged to be inaccurate and misleading in breach of the Code.

Pharmacosmos further alleged that the claim that Ferinject 'can be administered up to 1g as a bolus injection' was not accurate. The Ferinject SPC stated that 'Ferinject may be administered by intravenous injection using undiluted solution up to 1,000 mg iron *(up to a maximum of 15 mg/kg body weight)*' (emphasis added). By failing to include the 15mg/kg limit Pharmacosmos alleged that an important safety consideration was omitted, in breach of the Code.

The detailed response from Vifor is given below.

The Panel agreed with Pharmacosmos that the claims in the red box on page 1 of the leavepiece were an implied comparison with Monofer. By referring to Ferinject as 'the only high dose rapid infusion IV iron' implied that there was at least one other with which to draw a comparison. The claims were not presented simply as 'Ferinject offers etc'. The Panel noted the allegation that the layout of the claims in the red box implied that only Ferinject, unlike Monofer, could offer any of the attributes stated. In that regard the Panel noted that only Ferinject had simplified dosing for all patients; Monofer did not as the Ganzoni formula was recommended in certain patient groups. Only Ferinject was licensed for ages 14 years and over; Monofer could only be given to patients aged 18 years and over. Only Ferinject could be administered (in some circumstances – see below) up to 1g as a bolus injection; bolus injections of Monofer should not exceed 500mg. In the Panel's view, however, Ferinject was not the only high dose rapid infusion IV iron that contained product specific safety data in its SPC as claimed. The statement in the Monofer SPC that due to limited clinical data the side effects stated were *primarily* (emphasis added) based on the safety data for other parenteral iron solutions, implied that at least some of the safety data in the Monofer SPC was product specific. The Panel thus did not consider that Ferinject was the only product which provided all of the attributes listed in the red box. In that regard the claim in the highlighted red box was not accurate as alleged. A breach of the Code was ruled.

The Panel noted the allegation that the claim that Ferinject was the only high dose rapid infusion iron that had simplified dosing for all patients was inaccurate and misleading. As referred to above, the Panel noted that Monofer did not have simplified dosing for all patients as the Ganzoni formula was recommended in certain patient groups. The Panel noted Pharmacosmos' comment that the Ganzoni formula was not mandated for particular patients; only recommended. In that regard, however, simplified dosing was not a given for Monofer, prescribers would have to make a clinical decision to ignore the recommendation to use the Ganzoni formula for certain patients. The Panel did not consider that the claim was inaccurate or misleading as alleged. No breach of the Code was ruled.

With regard to the allegations about the claim that Ferinject 'can be administered up to 1g as a

bolus injection', the Panel noted that Section 4.2 of the Ferinject SPC stated that a single Ferinject administration should not exceed 15mg iron/ kg body weight (for IV injection) or 20mg iron/kg body weight (for IV infusion), nor should a single administration exceed 1,000mg iron. In that regard, patients with a body weight of less than 66.6kg could not receive a bolus injection of 1,000mg Ferinject. The Panel noted Vifor's submission that page 5 of the leavepiece contained the necessary detail but also noted that the Code required claims to be able to stand alone. In the Panel's view, the unqualified claim at issue implied that every patient could receive 1,000mg Ferinject as a single bolus injection and that was not so. The Panel considered that the claim was not accurate as alleged and it ruled a breach of the Code. The Panel did not consider that the claim was misleading about the side effects of Ferinject and in that regard it ruled no breach of the Code.

Pharmacosmos noted that page 3 of the leavepiece was headed 'Ferinject vs. oral iron therapy' and featured two graphs adapted from Onken *et al* (2014).

According to the simplified dosing in the Ferinject SPC, patients could receive a total dose of 500, 1,000, 1,500 or 2,000mg based on their weight and haemoglobin values. Onken *et al*, however, had dosed all patients with 2 x 750mg (1,500mg) completely independent and irrespective of the patient's weight and haemoglobin. This was an arbitrary and incorrect method of dosing patients and was not in-line with the licensed Ferinject dosing regimen. Pharmacosmos alleged that the presentation of data from Onken *et al* was thus in breach of the Code.

The Panel noted that the Ferinject SPC clearly stated that the determination of dose was based upon the patient's weight (below 35kg, 35-<70kg and 70kg and over) and his/her haemoglobin levels (<10g/dL, 10-14g/dL and >14g/dL). A table in the SPC showed the doses which should be given according to which of nine categories a patient fell within. A single dose of Ferinject should not exceed 15mg/kg/body weight for an IV injection and 20mg/kg bodyweight for an IV infusion. The maximum cumulative dose should not exceed 1,000mg of iron (20ml Ferinject) per week).

The Panel noted, however, that Onken *et al* administered Ferinject 15mg/kg to a maximum of 750mg on days 0 and 7 regardless of the patient's haemoglobin level. This was not in accordance with the SPC and meant that if a patient in the study weighed 70kg and had a haemoglobin level of ≤9g/dL in Onken *et al* would administer a total dose of 1,500mg. The SPC stated that for a patient of that weight and haemoglobin level, a total dose of 2,000mg should be given. Similarly if a patient weighed 68kg and had a haemoglobin level of ≥10.1g/dL, Onken *et al* would still administer Ferinject in two doses of 750mg (1,500mg in total) whereas the SPC gave a dose of only 1,000mg.

The Panel noted that page 5 of the leavepiece stated that the Ferinject dose was calculated according to the patient's weight and current haemoglobin level. Nonetheless, the Panel considered that the use of Onken *et al* on page 3 promoted a dose of Ferinject which was not in accordance with the SPC. The Panel ruled a breach of the Code. The Panel considered that the leavepiece was misleading in that regard. A breach of the Code was ruled.

Pharmacosmos referred again to page 3 of the leavepiece and the depiction of the Onken *et al* data discussed above. Pharmacosmos alleged that the only safety data in the leavepiece was in the prescribing information on the final page which was insufficient on this occasion.

Given that there was clearly an efficacy difference between Ferinject and oral iron demonstrated, it was appropriate and important to highlight that approximately 1 in 4 of the Ferinject study population experienced side effects compared with a much lower proportion of patients experiencing side effects with oral iron. Whilst Pharmacosmos recognised the comments of the authors, which explained the impact of the study run-in period, it was clear that the authors did not believe the study protocol accounted for all of the differences between IV and oral treatment. Given that the front page of the leavepiece drew attention to safety considerations in the SPC, Pharmacosmos believed that the difference in the safety profiles between Ferinject and oral iron in Onken *et al* should accordingly be highlighted. Pharmacosmos alleged that the absence of the balancing of safety data was in breach of the Code.

The Panel noted the comments above regarding the trial design and how it might have contributed to the relatively low frequency of drug-related treatment-emergent adverse events in the oral iron treatment group (6.3%) vs the Ferinject treatment group (22.8%). The run-in part of the trial had already screened out those patients who could not tolerate oral iron. The Panel noted that the authors had stated that the safety profile of Ferinject was generally comparable to that of oral iron.

Overall, the Panel did not consider that the leavepiece was misleading as to the relative safety of Ferinject vs oral iron as alleged. No breach of the Code was ruled.

The Panel noted that there were no claims about the adverse reactions of Ferinject nor was it stated that the medicine had no side effects. Ferinject was not described as safe. No breach of the Code was ruled.

Pharmacosmos UK Limited complained about a Ferinject (iron carboxymaltose) leavepiece entitled 'Their world awaits' (ref UK/FER/16/0116) issued by Vifor Pharma UK Limited. Ferinject was an intravenous (IV) iron preparation for the treatment of iron deficiency where oral therapy had been ineffective or could not be used. Pharmacosmos marketed Monofer (iron isomaltoside) which was similarly indicated.

Pharmacosmos raised a number of concerns, stating that many might be reflected in other promotional material. There appeared to be a clear intention to

indirectly compare Ferinject and Monofer and raise doubts about the safety of the latter. Pharmacosmos alleged that the manner of the implied comparison resulted in misleading claims. Pharmacosmos was also concerned about the fair representation of Ferinject in relation to a number of specific claims.

Vifor stated that it was extremely disappointed to again be required to answer a complaint made by Pharmacosmos. The company stated that its views on the continued abuse by Pharmacosmos of both the letter and the spirit of the UK pharmaceutical industry self-regulatory system were in the public domain.

Vifor again stated that the case preparation manager should not have accepted this complaint as Pharmacosmos did not have standing with the PMCPA. As stated in the Memorandum of Understanding between the ABPI, the PMCPA and the Medicines and Healthcare products Regulatory Agency (MHRA):

> 'Compliance with the Code is a condition of membership of the ABPI and, in addition, about 60 pharmaceutical companies that are not members of the Code have agreed to comply with the Code and submit to the jurisdiction of the PMCPA. **Members of the ABPI and non-members of the ABPI who have agreed to comply with the Code should send their complaints to the PMCPA'** (emphasis added).

Vifor submitted that this clearly implied that non-member companies which had not agreed to comply with the Code should refer their complaints to the MHRA.

The basis of Pharmacosmos's complaint was that Vifor had indirectly compared Ferinject and Monofer. There were only two high dose, short infusion time IV irons with marketing authorizations in the UK. Pharmacosmos seemed to assert that any and all Ferinject claims made in the leavepiece were by definition automatically also a comparison with Monofer. Vifor disputed this stance as such an assertion, if upheld, would *de facto* deprive the company of its right to promote its product on its own merits, as was the case with this leavepiece. Vifor noted that the Pharmacosmos 'ONE Visit' promotional campaign claimed, misleadingly, that all patients could be treated fully for their iron deficiency with Monofer in only one hospital visit. Vifor did not claim this for Ferinject. Vifor queried whether Pharmacosmos had therefore made indirect comparisons to Ferinject in its promotional materials.

Vifor was concerned that Pharmacosmos selected specific complaints to refer to the PMCPA without acknowledging Vifor's comments during inter-company dialogue some of the alleged breaches of the Code considered in inter-company dialogue had not been included in the complaint to PMCPA; Vifor had not received any confirmation from Pharmacosmos that its response to these components of the complaint had been accepted.

Vifor stated that this and other discrepancies between the substance and content of the Pharmacosmos complaint during inter-company dialogue and that submitted to the PMCPA, illustrated Pharmacosmos's clear manipulation of the self-regulatory system of medicines promotion in the UK. Vifor was not able to complain to the PMCPA about this situation, nor was it able to raise issues against Pharmacosmos via the PMCPA.

In summary, Vifor did not consider that this complaint should have been accepted by the Authority because Pharmacosmos lacked standing and the inconsistencies inherent in the inter-company dialogue process followed by Pharmacosmos. Furthermore, Vifor submitted that the leavepiece was not in breach of the Code as alleged.

1 Page 1

Page 1 of the leavepiece featured a red highlighted box which contained the following claims:

> 'Ferinject is the only high dose rapid infusion IV iron that;
>
> - has simplified dosing for all patients
> - contains product specific safety data in the Summary of Product Characteristics
> - is licenced *[sic]* for ages 14 years and over
> - can be administered up to 1g as a bolus injection
>
> Ferinject is the UK and Europe's market leading IV iron.'

COMPLAINT

Pharmacosmos alleged that the layout of the phrase within the red box implied that Ferinject was the only product that could offer *any* of the points in the bullets, which was not true. A breach of Clause 7.2 was alleged. By stating that Ferinject was the 'only high dose rapid iron infusion', the unstated but only comparison being made was with Monofer.

With regard to the claim that Ferinject was the only high dose rapid infusion IV iron that had simplified dosing for all patients, Pharmacosmos stated that iron need was estimated based on patient body weight and haemoglobin levels, and there were two primary ways to calculate this; the Ganzoni formula or a simplified dosing table. The summary of product characteristics (SPC) for Ferinject was based on the simplified table exclusively while Monofer's SPC allowed for both options and clinicians could select between the two at their discretion. The Monofer SPC recommended but did not mandate the use of the Ganzoni formula in certain patients. Therefore, the Monofer SPC also allowed simplified dosing in all patients, and subsequently the implied comparison was alleged to be inaccurate and misleading in breach of Clause 7.2.

Pharmacosmos further alleged that the claim that Ferinject 'can be administered up to 1g as a bolus injection' was not accurate and omitted important safety caveats. The Ferinject SPC stated that 'Ferinject may be administered by intravenous

injection using undiluted solution up to 1,000 mg iron (**up to a maximum of 15 mg/kg body weight**)' (emphasis added). By failing to include the 15mg/kg limit Pharmacosmos alleged that an important safety consideration was omitted, in breach of Clause 7.9.

RESPONSE

Vifor noted that Pharmacosmos had emphasised the word 'any' in its complaint. All of the attributes listed were taken directly from the Ferinject SPC and were indeed true only for Ferinject. Hence, Vifor did not see how this could be a breach of Clause 7.2 as all of these statements were fact, properly referenced and based on Ferinject's individual substantiable attributes. These statements highlighted Ferinject's properties and were not a comparison, direct or indirect, to Monofer.

Vifor fundamentally disagreed with Pharmacosmos's reasoning and stated that the Ferinject claims were based on its own attributes one of which was that it was the only high dose intravenous iron that had simplified dosing for all patients. Pharmacosmos stated that '… Monofer's **SPC allows for both options and clinicians can select** between the two at their discretion …' (*sic*). The Monofer SPC actually stated '… The cumulative iron need can be determined using either the Ganzoni formula (1) or the Table below (2). It is recommended to use the Ganzoni formula in patients who are likely to require individually adjusted dosing such as patients with anorexia nervosa, cachexia, obesity, pregnancy or anaemia due to bleeding …'. Vifor submitted there was a major difference in regulatory documents between 'recommended' and Pharmacosmos's interpretation of this, 'discretion'. There was no such recommendation (or discretion) in the Ferinject SPC. Vifor denied a breach of Clause 7.2.

With regard to the claim that Ferinject 'can be administered up to 1g as a bolus injection', Vifor noted that the leavepiece was a six page document, the final page of which was Ferinject prescribing information. The claim at issue was on the first page. The fifth page included the statement '… A maximum single dose of 15mg/kg body weight up to 1000mg of iron can be administered by intravenous injection'. This was factual, accurate and very clearly referenced, Vifor therefore submitted that no breach of Clause 7.9 had occurred as there was no omitted important safety consideration.

PANEL RULING

The Panel disagreed with Vifor's submission that as Pharmacosmos was neither a member of the ABPI nor a non member that had agreed to comply with the Code and accept the jurisdiction of the Authority, it was not able to complain under the Code. This point was previously raised by Vifor in its appeal in Case AUTH/2830/4/16. In that case the Appeal Board noted that the Memorandum of Understanding between the ABPI, the PMCPA and the MHRA did not exhaustively detail who could submit complaints under the Code, referring only to the position of ABPI member companies and non members that had agreed to comply with the Code. Paragraph 5.1 of the Constitution and Procedure was clear that the complaints procedure could commence once the Director had received information that certain companies might have contravened the Code. Paragraph 5.1 of the Constitution and Procedure only required the respondent company to be either an ABPI member or a non member company which had agreed to comply with the Code and accept the jurisdiction of the Authority. There was thus nothing in the Constitution and Procedure to preclude Pharmacosmos from submitting a complaint; indeed if there were, the Appeal Board considered that such provision might encourage some companies to submit complaints anonymously. In the Appeal Board's view, the Authority had been correct to allow the complaint in Case AUTH/2830/4/16 to proceed.

Turning to the present case, Case AUTH/2886/11/16, the Panel agreed with Pharmacosmos that the claims in the red box on page 1 of the leavepiece were an implied comparison with Monofer. By referring to Ferinject as 'the only high dose rapid infusion IV iron' implied that there was at least one other with which to draw a comparison. The claims were not presented simply as 'Ferinject offers etc'. The Panel noted the allegation that the layout of the claims in the red box implied that only Ferinject, unlike Monofer, could offer any of the attributes stated. In that regard the Panel noted that only Ferinject had simplified dosing for all patients. Monofer did not have simplified dosing for all patients as the Ganzoni formula was recommended in certain patient groups such as those with anorexia nervosa or with anaemia due to bleeding. Only Ferinject was licensed for ages 14 years and over; Monofer could only be given to patients aged 18 years and over. Only Ferinject could be administered (in some circumstances – see below) up to 1g as a bolus injection; bolus injections of Monofer should not exceed 500mg. In the Panel's view, however, Ferinject was not the only high dose rapid infusion IV iron that contained product specific safety data in its SPC as claimed. The statement in the Monofer SPC that due to limited clinical data the side effects stated were *primarily* (emphasis added) based on the safety data for other parenteral iron solutions, implied that at least some of the safety data in the Monofer SPC was product specific. The Panel thus did not consider that Ferinject was the only product which provided all of the attributes listed in the red box. In that regard the claim in the highlighted red box was not accurate as alleged. A breach of Clause 7.2 was ruled.

The Panel noted the specific allegation that the claim that Ferinject was the only high dose rapid infusion iron that had simplified dosing for all patients was inaccurate and misleading. As referred to above, the Panel noted that Monofer did not have simplified dosing for all patients as the Ganzoni formula was recommended in certain patient groups such as those with anorexia nervosa or with anaemia due to bleeding. The Panel noted Pharmacosmos' comment that the Ganzoni formula was not mandated for particular patients; only recommended. In that regard, however, simplified dosing was not a given for Monofer, prescribers would have to make a clinical decision to ignore the recommendation to use the Ganzoni formula for certain patients. The

Panel did not consider that the claim was inaccurate or misleading as alleged. No breach of Clause 7.2 was ruled.

With regard to the specific allegations about the claim that Ferinject 'can be administered up to 1g as a bolus injection', the Panel noted that Section 4.2 of the Ferinject SPC stated that a single Ferinject administration should not exceed 15mg iron/kg body weight (for IV injection) or 20mg iron/kg body weight (for IV infusion), nor should a single administration exceed 1,000mg iron. In that regard, patients with a body weight of less than 66.6kg could not receive a bolus injection of 1,000mg Ferinject. The Panel noted Vifor's submission that page 5 of the leavepiece contained the necessary detail. However the supplementary information to Clause 7 of the Code stated that claims in promotional material must be capable of standing alone as regards accuracy etc. In the Panel's view, the unqualified claim at issue implied that every patient could receive 1,000mg Ferinject as a single bolus injection and that was not so. The Panel considered that the claim was not accurate as alleged and it ruled a breach of Clause 7.2. The Panel did not consider that the claim was misleading about the side effects of Ferinject and in that regard it ruled no breach of Clause 7.9.

2 Alleged off-label patients

Page 3 was headed 'Ferinject vs. oral iron therapy' and featured two graphs comparing Ferinject and oral iron. The first graph compared median serum ferritin saturation (mcg/L) and the second compared median haemoglobin saturation (g/dL). The data was at baseline and the change to day 35. Each graph was adapted from Onken *et al* (2014).

COMPLAINT

Pharmacosmos stated that the two graphs were intended to demonstrate that Ferinject was effective in treating iron deficiency. The company was concerned about the use of Onken *et al*.

As the leavepiece correctly stated, the simplified dosing table had to be used with all patients receiving Ferinject and this was the only option for estimating patient's iron need identified in the Ferinject SPC. According to this table, patients could receive a total dose of 500, 1,000, 1,500 or 2,000mg based on their weight and haemoglobin values. Onken *et al*, however, had dosed all patients with 2 x 750mg (1,500mg) completely independent and irrespective of the patient's weight and haemoglobin. This was an arbitrary and incorrect method of dosing patients that did not take into account their weight or haemoglobin values. This was not in-line with the licensed Ferinject dosing regimen. Pharmacosmos alleged that the presentation of data from Onken *et al* was thus in breach of Clause 3.2 and was also misleading in breach of Clause 7.2.

RESPONSE

Vifor noted that Onken *et al* was a multicenter, randomised, active-controlled study to investigate the efficacy and safety of Ferinject in patients with iron deficiency anemia; it was one of the registration studies conducted in order to gain licence approval for Ferinject in the US. The average weights of the groups who received Ferinject were 82.8kg for Group A and 79.5kg for Group C. This was consistent with the Ferinject SPC and there was nothing in the SPC that prevented the administration of two doses of 750mg to make a total cumulative dose of 1,500mg being given to appropriate patients according to the dosing table in Section 4.2 of the SPC. The leavepiece clearly provided the dosing table from the SPC which described dose based on haemoglobin level and body weight.

Vifor submitted that Pharmacosmos's allegation that Ferinject had been promoted in an unlicensed manner was not correct and therefore there was no breach of Clauses 3.2 and 7.2.

PANEL RULING

The Panel noted that the Ferinject SPC clearly stated that the determination of dose was based upon the patient's weight (below 35kg, 35-<70kg and 70kg and over) and his/her haemoglobin levels (<10g/dL, 10-14g/dL and >14g/dL). A table in the SPC showed the doses which should be given according to which of nine categories a patient fell within. A single dose of Ferinject should not exceed 15mg/kg/body weight for an IV injection and 20mg/kg bodyweight for an IV infusion. The maximum cumulative dose should not exceed 1,000mg of iron (20ml Ferinject) per week).

The Panel noted, however, that Onken *et al* administered Ferinject 15mg/kg to a maximum of 750mg on days 0 and 7 regardless of the patient's haemoglobin level. This was not in accordance with the SPC. The mean weight of patients in Group A was 82.8kg (± 22.5) and in Group C it was 79.5kg (± 20.4). The Panel noted that if a patient in the study weighed 70kg and had a haemoglobin level of ≤9g/dL (there were 23/246 patients in Group A and 122/253 in Group C with that baseline haemoglobin level), Onken *et al* would administer a dose of 750mg on days 0 and 7 giving 1,500mg in total. The SPC stated that for a patient of that weight and haemoglobin level, a total dose of 2,000mg should be given. Similarly if a patient weighed 68kg and had a haemoglobin level of ≥10.1g/dL (there were 175/246 patients in Group A and 71/253 patients in Group C with that haemoglobin level), Onken *et al* would still administer Ferinject in two doses of 750mg (1,500mg in total) whereas the SPC gave a dose of only 1,000mg.

The Panel noted that page 5 of the leavepiece stated that the Ferinject dose was calculated according to the patient's weight and current haemoglobin level. Nonetheless, the Panel considered that the use of Onken *et al* on page 3 promoted a dose of Ferinject which was not in accordance with the SPC in that doses had not been calculated according to bodyweight and haemoglobin level. The Panel ruled a breach of Clause 3.2. The Panel considered that the leavepiece was misleading in that regard. A breach of Clause 7.2 was ruled.

3 Balancing safety data

Pharmacosmos referred again to page 3 and the depiction of the Onken *et al* data discussed above.

COMPLAINT

Pharmacosmos alleged that the only safety data in the leavepiece was in the prescribing information on the final page which was insufficient on this occasion.

Given that there was clearly an efficacy difference between Ferinject and oral iron demonstrated, it was appropriate and important to highlight that approximately 1 in 4 of the Ferinject study population experienced side effects compared with a much lower proportion of patients experiencing side effects with oral iron. Whilst Pharmacosmos recognised the comments of the authors, which explained the impact of the study run-in period, it was clear that the authors did not believe the study protocol accounted for all of the differences between IV and oral treatment. Given that the front page of the leavepiece drew attention to safety considerations in the SPC, Pharmacosmos believed that the difference in the safety profiles between Ferinject and oral iron in Onken *et al* should accordingly be highlighted.

Pharmacosmos alleged that the absence of the balancing of safety data was in breach of Clauses 7.2 and 7.9.

RESPONSE

Vifor submitted that it managed all compliance with the utmost of seriousness, especially any complaint in relation to safety. That said, the argument used by Pharmacosmos to state that Vifor was not balanced in relation to safety data was fundamentally incorrect. During inter-company dialogue, Pharmacosmos stated '…it seems appropriate to highlight that 1 in 4 (28%) of the study population experienced side effects with Ferinject; we believe this is pertinent information, especially given the safety inference on the first page …'. This was a clear misrepresentation of the Onken *et al* study data.

In Onken *et al*, the actual number of treatment-emergent adverse events that were considered drug related were 22.8% of subjects in group A (Ferinject), 6.3% in group B (oral iron), 25.3% in group C (Ferinject) and 26.5% in group D (standard of care IV iron). The 28% figure stated by Pharmacosmos was the number of subjects reporting a treatment-emergent adverse event during the run-in period, which used oral iron only and included all adverse events, not just drug-related ones.

In addition, the study included a primary composite safety end point which was generally comparable for Ferinject and oral iron. Furthermore, the authors stated that the relatively low frequency of drug-related treatment-emergent adverse events in group B could be explained by the trial design. Cohort 1 subjects, who formed groups A and B were pre-selected for lack of severe reaction to oral iron. In addition, events related to oral iron for subjects in group B (oral iron) that began during run-in would not have been counted as adverse events during treatment phase because the study medicine was the same, whereas all drug-related treatment-emergent adverse events in group A (Ferinject) after randomization to Ferinject were considered new events. Therefore, Vifor submitted that the only reliable measure of safety was the primary composite safety end point, which was generally comparable for Ferinject and oral iron. Vifor did not consider that there was an absence of balancing of safety data and there was no breach of Clauses 7.2 and 7.9.

PANEL RULING

The Panel noted the comments above regarding the trial design and how it might have contributed to the relatively low frequency of drug-related treatment-emergent adverse events in the oral iron treatment group (6.3%) vs the Ferinject treatment group (22.8%). The run-in part of the trial had already screened out those patients who could not tolerate oral iron. The Panel noted that the authors had stated that the safety profile of Ferinject was generally comparable to that of oral iron.

Overall, the Panel did not consider that the leavepiece was misleading as to the relative safety of Ferinject vs oral iron as alleged. No breach of Clause 7.2 was ruled.

Clause 7.9 stated that information and claims about adverse reactions must reflect available evidence or be capable of substantiation by clinical experience. It must not be stated that a product had no adverse reactions, toxic hazards or risks of addiction or dependency. The word 'safe' must not be used without qualification. The Panel noted that there were no claims about the adverse reactions of Ferinject nor was it stated that the medicine had no side effects. Ferinject was not described as safe. No breach of Clause 7.9 was ruled.

Complaint received **7 November 2016**

Case completed **22 February 2017**