NO BREACH OF THE CODE

CASE AUTH/3465/2/21

COMPLAINANT v VIFOR

Alleged off-licence promotion of Venofer

An anonymous, contactable complainant, who described him/herself as a concerned UK health professional, alleged that use of the PIVOTAL study by Vifor Pharma UK Limited to promote Venofer (iron sucrose for intravenous (IV) administration) promoted its off-licence use. The complainant referred to a sponsored symposium. Venofer was indicated for, *inter alia*, the treatment of iron deficiency in chronic kidney disease when oral therapy was less effective.

The complainant provided a link to a Vifor sponsored symposium entitled 'High dose proactive intravenous iron treatment in ESKD [end-stage kidney disease] – sub-analysis of the PIVOTAL study'. The 15-minute symposium took place in October 2020.

The complainant stated that the PIVOTAL trial used Venofer in patients proactively, rather than using its licensed indication.

The complainant noted that the Venofer licence stated:

> **'Venofer is indicated for the treatment of iron deficiency in the following indications:**
>
> **• Where there is a clinical need for a rapid iron supply,**
>
> **• In patients who cannot tolerate oral iron therapy or who are non-compliant,**
>
> **• In active inflammatory bowel disease where oral iron preparations are ineffective,**
>
> **• In chronic kidney disease when oral iron preparations are less effective.**
>
> **The diagnosis of iron deficiency must be based on appropriate laboratory tests (e.g. Hb, serum ferritin, TSAT, serum iron, etc.).**
> **(Hb haemoglobin, TSAT transferrin saturation).'**

The complainant stated that in the trial, patients did not have to have iron deficiency to receive treatment, they merely did not receive treatment if there was a raised ferritin level. The complainant alleged that to use the PIVOTAL trial was highly likely to promote Venofer off-licence since the entire design of the trial was off-licence.

The detailed response from Vifor is given below.

The Panel noted that according to the Venofer SPC, one of the licensed indications for the medicine was in the treatment of iron deficiency in chronic kidney disease when oral iron preparations were less effective, with the diagnosis of iron deficiency being based on appropriate laboratory tests (eg Hb, serum ferritin, TSAT, serum iron, etc.). The SPC did not specify what test values were required for the diagnosis of iron deficiency.

The Panel noted the complainant's concern that patients in the PIVOTAL study did not need to have iron deficiency, they merely did not receive treatment if there was a raised ferritin level. The Panel noted that patients in the high-dose, proactive treatment arm all received Venofer unless they had raised ferritin levels (>700µg per litre) or a TSAT score of ≥40%; for those in the low-dose arm, reactive treatment, Venofer therapy was appropriate for patients with ferritin levels of <200µg per litre and a TSAT score of <20%.

With regard to ferritin levels, the Panel noted that the Guidelines for the Laboratory Diagnosis of Functional Iron Deficiency stated that in CKD patients on haemodialysis, ferritin levels of up to 800µg per litre were consistent with a diagnosis of iron deficiency and that ferritin values up to 1200µg per litre did not exclude the possibility of functional iron deficiency and that some such patients might respond to IV iron therapy. An algorithm for the management of CKD patients stated that haemodialysis patients with ferritin levels of <200µg per litre had classical iron deficiency (ie those in the low dose arm of the PIVOTAL study) and that haemodialysis patients with ferritin levels >200µg per litre but <800µg per litre had functional iron deficiency (ie the patients in the high dose arm of the study).

With regard to TSAT levels, the Panel noted that the guidelines referred to above stated that values of <20% indicated the need for parenteral iron in the setting of anaemia treated with erythropoiesis stimulating agents but that used in isolation, TSAT had poor sensitivity and specificity in detecting those who would respond to IV iron.

Overall, the Panel did not consider that the complainant had shown that the use of Venofer in the PIVOTAL study was off-licence; it appeared to the Panel that the use of Venofer was in line with the indication as set out in the SPC and complied with the current, clinically accepted definition of iron deficiency in haemodialysis patients. No breaches of the Code were ruled including Clause 2.

An anonymous, contactable complainant, who described him/herself as a concerned UK health professional, alleged that use of the PIVOTAL study by Vifor Pharma UK Limited to promote Venofer (iron sucrose for intravenous (IV) administration) promoted its off-licence use. The complainant referred, in particular, to a sponsored symposium available on another party's website. Venofer was indicated for, *inter alia*, the treatment of iron deficiency in chronic kidney disease when oral therapy was less effective.

COMPLAINT

The complainant provided a link to a Vifor sponsored symposium entitled 'High dose proactive intravenous iron treatment in ESKD [end-stage kidney disease] – sub-analysis of the PIVOTAL study'. The 15-minute symposium took place in October 2020.

The complainant stated that the PIVOTAL trial used Venofer in patients proactively, rather than using its licensed indication. The complainant noted that in a report of the results of the PIVOTAL trial (Macdougall *et al* 2019, link provided) the authors stated that:

> 'In a multicenter, open-label trial with blinded end-point evaluation, we randomly assigned adults undergoing maintenance hemodialysis to receive either high-dose iron sucrose, administered intravenously in a proactive fashion (400mg monthly, unless the ferritin concentration was >700µg per liter or the transferrin saturation was ≥40%), or low-dose iron sucrose, administered intravenously in a reactive fashion (0 to 400mg monthly, with a ferritin concentration of <200µg per liter or a transferrin saturation of <20% being a trigger for iron administration).'

The complainant noted that the Venofer licence stated:

> 'Venofer is indicated for the treatment of iron deficiency in the following indications:
>
> - Where there is a clinical need for a rapid iron supply,
> - In patients who cannot tolerate oral iron therapy or who are non-compliant,
> - In active inflammatory bowel disease where oral iron preparations are ineffective,
> - In chronic kidney disease when oral iron preparations are less effective.
>
> The diagnosis of iron deficiency must be based on appropriate laboratory tests (e.g. Hb, serum ferritin, TSAT, serum iron, etc.).
>
> (Hb haemoglobin, TSAT transferrin saturation).'

The complainant stated that in the trial, patients did not have to have iron deficiency to receive treatment, they merely did not receive treatment if there was a raised ferritin level. The complainant alleged that to use the PIVOTAL trial was highly likely to promote Venofer off-licence since the entire design of the trial was off-licence.

When writing to Vifor, the Authority asked it to consider the requirements of Clauses 3.2, 9.1 and 2 of the Code.

RESPONSE

Vifor submitted that the allegations were unfounded because the use of Venofer in both arms of the PIVOTAL study was consistent with the summary of product characteristics (SPC). The symposium addressed the efficacy and safety of different treatment approaches to iron deficiency in a haemodialysis population in end-stage chronic kidney disease (CKD).

Vifor noted that the SPC stated that Venofer was indicated for the treatment of iron deficiency in chronic kidney disease when oral iron preparations were less effective. The diagnosis of iron deficiency must be based on appropriate laboratory tests (eg Hb, serum ferritin, TSAT, serum iron, etc.).

As in the SPCs for other IV iron formulations, the SPC for Venofer did not specify what test values were required for the diagnosis of iron deficiency in the different indicated populations. Given the lack of precise diagnostic criteria in the SPC, Vifor stated that it aimed to demonstrate that the symposium material described the use of Venofer in patients whose test values lay within the current, clinically accepted definition of iron deficiency for the haemodialysis population.

The inclusion criteria for the PIVOTAL study were adult patients on haemodialysis for 0-12 months, with ferritin <400mcg/l and transferrin saturation (TSAT) <30%, and on erythropoiesis stimulating agents (ESAs).

Vifor noted the complainant's allegation that the proactive treatment approach taken in the PIVOTAL study involved treatment at levels of ferritin and TSAT that were not consistent with a diagnosis of iron deficiency. Vifor submitted that the Guidelines for the Laboratory Diagnosis of Functional Iron Deficiency, published on behalf of the British Society for Standards in Haematology, demonstrated that that was not correct (Thomas *et al* 2013, copy provided). Those guidelines substantiated that in the CKD population on haemodialysis, ferritin levels of up to 800mcg/l were consistent with a diagnosis of iron deficiency. Vifor noted that the introductory summary of recommendations stated that ferritin values as high as of 1200mcg/l in CKD patients did not exclude the possibility of functional iron deficiency and that some such patients might respond to IV iron therapy.

Vifor referred to the algorithm below, taken from Thomas *et al*, in which the recommended management of iron restricted erythropoiesis (IRE) in patients with CKD on ESA was summarised. The ferritin range described included the range measured in patients treated with Venofer in the PIVOTAL trial, namely values of between <200mcg/l (reactive arm) and 700mcg/l (proactive arm).

The guideline algorithm subdivided the diagnosis of iron deficiency into classical (ferritin less than 200mcg/l) or functional (200-800mcg/l). Elsewhere the guideline explained that patients with end stage CKD would usually have mixed absolute (classical) and functional iron deficiency.

Vifor submitted that, in relation to the blood test TSAT which reflected iron circulating in plasma, Thomas *et al* clarified the limitations of reliance on that test in chronic disease such as CKD and thus it did not feature in the algorithm above. The guidelines did, however, support the PIVOTAL study level of <20% as indicating classical iron deficiency and also aligned with the PIVOTAL trial proactive arm in that they did not recommend IV iron at ferritin >800mcg/l and higher TSAT values to avoid the risk of iron overload.

Vifor submitted that prior to the PIVOTAL study, it was not known whether a high dose, proactive approach to manage the functional component (that was more difficult to ascertain by blood tests alone than absolute iron deficiency) would be limited by safety issues. These uncertainties were the rationale for the PIVOTAL study in terms of clinical equipoise, as highlighted on slide 3 of Professor Kalra's presentation which then went on to provide key safety analyses from the PIVOTAL study to examine these.

Vifor submitted that the reactive arm of the PIVOTAL study permitted intervention with Venofer only when ferritin and TSAT values dropped to levels so low that they clearly indicated absolute iron deficiency whereas the proactive arm ensured the treatment of any significant component

of functional iron deficiency by only withholding Venofer if patients had high ferritin (>700mcg/l) and TSAT (>40%) levels. The forthcoming CKD guidelines from the National Institute for health and Care Excellence (NICE), currently open for consultation, featured a recommendation for a high dose IV Venofer regimen in CKD patients on haemodialysis that was taken from the PIVOTAL study proactive arm, based on the evidence generated on its benefit:risk. Vifor noted that any recommendation for product use in those guidelines that was considered by NICE to have been outside the licensed indication was clearly highlighted and that that was not the case for the proactive, high dose Venofer regimen that was described.

Vifor referred to a table that was included in the draft NICE CKD guideline and referred specifically to the PIVOTAL trial data.

Vifor noted that its customer-facing employees were not currently asked to direct health professionals to the website on which the symposium was hosted.

In summary, Vifor stated that it considered that the PIVOTAL study was suitable educational content for a promotional symposium because the use of Venofer in both arms was consistent with its licensed indication for the treatment of iron deficiency. Vifor therefore refuted the allegation of a breach of Clause 3.2.

Vifor hoped that it had adequately clarified the most salient issues with reference to respected guideline publications. Those illustrated that the range of ferritin and TSAT values used to guide treatment with Venofer in the PIVOTAL study reflected current, evidence-based consensus on the management of iron deficiency in end stage CKD.

Vifor submitted that the symposium content was of high scientific quality and that all requirements of the Code were met in its organisation and approval. In conclusion, Vifor did not consider that there had been any failure to maintain high standards and it denied breaches of Clauses 9.1 and 2.

PANEL RULING

The Panel noted that the complainant was concerned that a Vifor sponsored symposium, 'High dose proactive intravenous iron treatment in ESKD patients Sub-analysis of the PIVOTAL study', promoted the off-licence use of Venofer since the entire design of the PIVOTAL study was off-licence. The Panel noted the narrow scope of the complaint which did not raise concerns about the symposium *per se.* The Panel noted that the PIVOTAL study recruited adults with end-stage kidney disease in whom maintenance haemodialysis had been initiated no more than 12 months before the initial screening visit, who had a ferritin concentration <400µg/l and a transferrin saturation (TSAT) of less than 30%, and who were receiving an erythropoiesis stimulating agent; any iron therapy that had been prescribed previously was discontinued at the screening visit.

The Panel noted that according to the Venofer SPC, one of the licensed indications for the medicine was in the treatment of iron deficiency in chronic kidney disease when oral iron preparations were less effective, with the diagnosis of iron deficiency being based on appropriate laboratory tests (eg Hb, serum ferritin, TSAT, serum iron, etc.). The SPC did not specify what test values were required for the diagnosis of iron deficiency.

The Panel noted the complainant's concern that patients in the PIVOTAL study did not need to have iron deficiency, they merely did not receive treatment if there was a raised ferritin level. The Panel noted that patients in the high-dose, proactive treatment arm all received Venofer unless they had raised ferritin levels (>700µg per litre) or a TSAT score of ≥40%; for those in the low-dose arm, reactive treatment, Venofer therapy was appropriate for patients with ferritin levels of <200µg per litre and a TSAT score of <20%.

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With regard to TSAT levels, the Panel noted that the guidelines referred to above stated that values of <20% indicated the need for parenteral iron in the setting of anaemia treated with erythropoiesis stimulating agents but that used in isolation, TSAT had poor sensitivity and specificity in detecting those who would respond to IV iron.

Overall, the Panel did not consider that the complainant had shown that the use of Venofer in the PIVOTAL study was off-licence; it appeared to the Panel that the use of Venofer was in line with the indication as set out in the SPC and complied with the current, clinically accepted definition of iron deficiency in haemodialysis patients. No breach of Clause 3.2 was ruled. The Panel thus also ruled no breach of Clauses 9.1 and 2.

Complaint received **1 February 2021**

Case completed **25 August 2021**