CASE AUTH/3679/8/22

COMPLAINANT v CSL VIFOR

Allegations about a promotional article in The British Journal of Cardiology

CASE SUMMARY

This case was in relation to claims within a Ferinject (ferric carboxymaltose) promotional supplement by Vifor in the British Journal of Cardiology.

The Panel ruled a breach of the following Clause of the 2019 Code as whilst the article in question referred to certain side effects, in the Panel's view, this did not qualify the use of the word 'safe' in the key messages of the article:

Breach of Clause 7.9	**Use of the word 'safe' without qualification.**

The Panel ruled no breach of the following Clauses of the 2019 Code as:

- **whilst the Panel had some concerns about the completeness of the information, the article did state the primary endpoint for CONFIRM-HF;**
- **noting that the primary endpoint of the study had been achieved and the claim clearly stated it was a *post hoc* analysis, the Panel considered, in the context of the article, that the complainant had not established that there was inadequate evidence for the claim '*Post-hoc* analysis of the CONFIRM-HF study supported the hypothesis that treatment with IV iron was associated with reduced hospitalisation';**
- **whilst the Panel had concerns about the accuracy of data presented in a claim regarding a meta-analysis, the Panel, noting the very narrow allegation, considered that the complainant had not established that there was inadequate evidence;**
- **in relation to a table which only referred to study design, with no study results presented, the Panel considered that the complainant had not established that this table made a misleading comparison between ferric carboxymaltose and ferric derisomaltose:**

No Breach of Clause 7.2	**Requirement that claims must not be misleading**
No Breach of Clause 7.3	**Requirement that a comparison must not be misleading**
No Breach of Clause 7.4	**Requirement that claims must be capable of substantiation**

The Panel, noting section 5.1 of the Ferinject SPC, ruled no breach of the following Clause of the 2019 Code as the complainant had not established that the claim 'Heart failure with reduced ejection fraction is associated with iron insufficiency. Intravenous iron is a safe and effective treatment', in the context of the article in question, promoted Ferinject off-licence:

No Breach of Clause 3.2	Requirement that the promotion of a medicine must be in accordance with the terms of its marketing authorisation and must not be inconsistent with the particulars listed in its summary of product characteristics

The Panel ruled no breach of the following Clause of the 2019 Code as, despite its ruling in relation to Clause 7.9, the article provided some information on side effects and therefore, in its view, a health professional was unlikely to be left with the impression that Ferinject had no side effects and therefore the Panel considered that the complainant had not established, on balance, that CSL Vifor had failed to maintain high standards;

No Breach of Clause 9.1	Requirement that high standards must be maintained at all times

This summary is not intended to be read in isolation.
For full details, please see the full case report below.

FULL CASE REPORT

A complaint was received from an anonymous, contactable complainant about a promotional supplement by Vifor Pharma UK in the British Journal of Cardiology (ref: UK-FCM-2100010).

COMPLAINT

The complainant provided a link to an article on the British Journal of Cardiology website titled 'Intravenous iron therapies and their differences', which they stated Vifor Pharma was responsible for.

The complainant referred to a section of the article which stated:

> 'Could IV iron effect hard outcomes? *Post-hoc* analysis of the CONFIRM-HF study supported the hypothesis that treatment with IV iron was associated with reduced hospitalisation. An individual patient data meta-analysis of 839 patients found IV iron treatment was associated with a significant reduction in the risk of HF hospitalisation and cardiovascular mortality (rate ratio 0.59, 95% confidence interval 0.4 to 0.88, p=0.009).'

The complainant alleged that the article did not state the primary endpoints of the study, and also used a meta-analysis of the data. Whilst, in the complainant's view, such approaches might well be suitable in a non-promotional piece, this was clearly promotional and thus allegedly had inadequate evidence for the claims being made.

The complainant also referred to a Table titled 'Ongoing clinical trials of intravenous iron in patients with heart failure examining morbidity and mortality' and alleged that this was actively inviting comparisons to be drawn between the data in different studies rather than clearly stating that different studies should not be directly compared.

The complainant stated that at the end of the article was the following:

‘Key messages

- Heart failure with reduced ejection fraction is associated with iron insufficiency. Intravenous iron is a safe and effective treatment.’

The complainant stated that the product had been described as ‘safe’ – which was explicitly not allowed.

The complainant further stated that the product had been described as an effective treatment for heart failure with reduced ejection fraction when Ferinject was indicated for the treatment of iron deficiency when:

– oral iron preparations are ineffective.

– oral iron preparations cannot be used.

– there is a clinical need to deliver iron rapidly.

The diagnosis of iron deficiency must be based on laboratory tests.

The complainant alleged that none of these were mentioned and thus what was mentioned in the key facts was much broader than the licenced indication – in essence this widened claim was promoting off licence.

The complainant stated that this article was prepared in January 2021 which meant it had both been up for a year and a half and was created whilst the company was being audited for its inability to maintain high standards.

When writing to CSL Vifor, the Authority asked it to consider the requirements of Clauses 5.1, 6.1, 6.2, 6.4, 11.2 and 14.1 of the 2021 Code.

RESPONSE

CSL Vifor stated that it took all complaints seriously and agreed to adhere to the Code. CSL Vifor had investigated the complaint and the article in question, regarding Clauses 5, 6, 11 and 14. CSL Vifor submitted that the article and supplement were certified in January 2021 and published in February 2021 prior to the 2021 Code being fully implemented and therefore should be considered against the 2019 Code of Practice.

CSL Vifor submitted the article in question was part of a sponsored supplement supported by Vifor Pharma and consisted of five articles focused on issues relating to iron deficiency in heart failure (HF) and not on specific iron deficiency therapies. The supplement stated Vifor Pharma’s involvement on the front page, with the same disclaimer included with the online article which, according to CSL Vifor, was as required by Clause 9.10 of the 2019 Code. CSL Vifor submitted that as was evidenced by the layout, the five articles were intended to be read together, with each article complementing the other and providing the reader with a broad understanding of the topic ranging from prevalence and the causes of the condition to treatment considerations and their impact on heart failure. The supplement was certified under the 2019 Code and being intended to be read as a single piece, certified as a single job bag. Vifor Pharma considered it inappropriate for the complainant to highlight the content from a single article in the supplement without placing the article within the context of the remaining four.

With respect to points raised in the complaint, CSL Vifor's response was below:

1) **The *post hoc* analysis of the CONFIRM-HF trial:** the complainant inaccurately suggested that the only mention of the CONFIRM-HF trial in the article was with reference to the *post-hoc* analysis. The details of the study including the trial population, duration, and the primary endpoint were described earlier in the article . Achievement of the primary endpoint for the CONFIRM HF and those of other studies was discussed in an earlier article under the heading 'Efficacy and tolerability of iron'. The details of the CONFIRM-HF study and other related trials were included in other articles within the supplement and described their impact on Guidelines in this therapeutic area.

2) **Comparisons across studies**: The complainant alleged the article invited the reader to compare results across studies, which in the opinion of the complainant was not allowed. However, no results of any of the studies mentioned were referred to in the article or wider supplement. The article merely showed the similarity in study design across the trials. At no point in the piece were the results directly compared.

3) **Use of the word safe:** The complainant alleged that the supplement stated Ferinject (ferric carboxymaltose (FCM)) as being a 'safe product' which the complainant stated was explicitly not allowed as per the Code. CSL Vifor believed the complainant had inaccurately described the key messages as well as the wording from the Code. Firstly, the article in question and the key messages were referring to intravenous irons in general rather than a specific medication. As quoted from the article's key messages *'Heart failure with a reduced ejection fraction is associated with iron insufficiency. Intravenous iron is a safe and effective treatment'*. The word safe was used in reference to the class of intravenous irons rather than a specific product.

   CSL Vifor further stated that the code was very clear that the word 'safe' must not be used without qualification. As the article discussed in substantial detail the tolerability and safety of intravenous irons as a class of therapies, CSL Vifor believed the article did qualify the use of the word 'safe' in reference to the class of intravenous irons under discussion. Additionally, other articles in the supplement also discussed the use of intravenous irons and their activity further qualifying this statement.

4) **Promotion outside the licence:** The complainant alleged that in the article, Ferinject was promoted outside of its licence ie., the treatment of Iron deficiency when the diagnosis of Iron deficiency is based on a laboratory assessment. As previously stated, the article in question was part of a five-article supplement created, written, and certified as a single piece to be read sequentially. Consequently, the first article in the series discussed in detail the prevalence, causes and diagnosis of iron deficiency. A subsequent article in the series further discussed not only the diagnosis of iron deficiency in heart failure but also the tests required to determine if there was anaemia or iron deficiency without anaemia. A variety of UK and European Guidelines on the impact and use of iron therapy to treat iron deficiency in heart failure were also discussed. The article referred as previously stated to intravenous irons in general and not a specific intravenous iron medication as alleged. The discussion around the use of intravenous iron was consistently discussed for patients with heart failure with iron deficiency. At no point was intravenous iron discussed in patients who had heart failure

but who were not iron deficient. CSL Vifor therefore did not believe that there was any evidence to support the allegations of out of licence promotion.

All discussions of the potential impact of intravenous iron therapy were clearly focussed on patients who were iron deficient and had heart failure and this was covered within the indication of Ferinject as a treatment for iron deficiency in adults. The Ferinject indication doesn't differentiate as to cause or comorbidity of iron deficiency and strictly referred to the treatment of iron deficiency.

In summary, CSL Vifor did not believe that the allegations in the complainant's letter could be substantiated and it denied breaches of Clauses 5.1, 6.1, 6.2, 6.4, 11.2 and 14.1 of the 2021 Code.

CSL Vifor further submitted that the article in question was found in the online archives of the British Journal of Cardiology and not in the current edition of the journal. The online archive included editions going back for 10 years or more. CSL Vifor submitted that finding the article there would be no different to reading an old paper issue of the journal and therefore CSL Vifor requested that the Panel look at this case in respect of the 2019 Code.

PANEL RULING

The Panel noted CSL Vifor's submission that the article in question was part of a Vifor Pharma sponsored supplement in The British Journal of Cardiology (BJC Volume 28 Supplement 1. January-March 2021), titled 'Iron deficiency in heart failure' which consisted of five articles. The supplement included prescribing information for Ferinject (ferric carboxymaltose).

The Panel noted CSL Vifor's submission that the supplement was published on the BJC website in February 2021 and was, at the time of the complaint in August 2022, accessible within the 'archive' section of the journal website. The Panel therefore considered that the relevant Code was the 2019 Code. CSL Vifor had been asked to respond to Clauses 5.1, 6.1, 6.2, 6.4, 11.2 and 14.1 of the 2021 Code. The equivalent clauses in the 2019 Code were Clauses 9.1, 7.2, 7.4, 7.9, 3.2 and 7.3, respectively; there were no material differences in the wording of the relevant clauses between the two Code years.

The complainant's allegations related to one article in the supplement accessed online and they provided a direct link to that article, titled 'Intravenous iron therapies and their differences'. The Panel disagreed with CSL Vifor's submission that it was inappropriate for the complainant to highlight the content from a single article in the supplement without placing the article within the context of the remaining four. The Panel noted that each of the five articles in the promotional supplement had its own webpage on the BJC website and therefore the Panel considered each article needed to stand alone with regard to the requirements of the Code.

The Panel noted the complainant highlighted the following excerpt, alleging that the promotional article in question did not state the primary endpoints of the study and used a meta-analysis of the data which was alleged to be inadequate evidence for the claims being made:

'Could IV iron effect hard outcomes? *Post-hoc* analysis of the CONFIRM-HF study supported the hypothesis that treatment with IV iron was associated with reduced hospitalisation. An individual patient data meta-analysis of 839 patients found IV iron

treatment was associated with a significant reduction in the risk of HF hospitalisation and cardiovascular mortality (rate ratio 0.59, 95% confidence interval 0.4 to 0.88, p=0.009)'.

In this regard, the Panel noted CSL Vifor's submission that details of the CONFIRM-HF study was described earlier in the article in question. The Panel noted that Table 2 in the article in question was headed 'Clinical trials of heart failure with reduced ejection fraction (HFrEF) patients treated with intravenous iron' and referred to three IV ferric carboxymaltose studies (CONFIRM-HF, EFFECT-HF, FAIR-HF). For each of these studies, the table presented study details including patient population, number of participants, duration and primary end point. For CONFIRM-HF the primary endpoint was stated in Table 2 as the six minute walk test (6MWT) change.

The Panel noted that Ponikowski *et al* (2015), which had not been provided by either party but was accessible from a link in the references section in the online article in question, stated that the primary end point of CONFIRM-HF was the change in 6-min-walk-test (6MWT) distance from baseline to Week 24. Whilst the Panel had some concerns about the completeness of the information in Table 2 in the promotional article in question, based on the complainant's very narrow allegation that the article did not state the primary endpoint of the study, the Panel ruled **no breach of Clause 7.2 of the 2019 Code**.

Turning to the allegation that there was inadequate evidence for the claims, the Panel noted that the Code did not prohibit the use of data from *post hoc* analyses or meta-analyses in promotional material as long as the requirements of the Code were met which included that the claims must be accurate, not misleading and the material must be sufficiently complete to enable the reader to form their own opinion of the therapeutic value of the medicine.

With regard to the first claim that '*Post-hoc* analysis of the CONFIRM-HF study supported the hypothesis that treatment with IV iron was associated with reduced hospitalisation', the Panel noted that Ponikowski *et al* studied the effect of ferric carboxymaltose on the rate of hospitalisation for worsening heart failure as a secondary endpoint and found that treatment was associated with a significant reduction in the risk of hospitalisations for worsening heart failure [hazard ratio (95% confidence interval): 0.39 (0.19–0.82), P = 0.009]. In the *post hoc* sensitivity analysis, the combined risk of first hospitalisation due to worsening heart failure or all-cause death was significantly lower in the ferric carboxymaltose group [HR (95% CI): 0.53 (0.30–0.95), P = 0.03]. The *post hoc* sensitivity analysis of recurrent events on the number of hospitalisations due to worsening heart failure using the negative binomial regression models confirmed positive treatment effect of ferric carboxymaltose. The study author concluded that treatment of symptomatic, iron-deficient heart failure patients with ferric carboxymaltose may be associated with risk reduction of hospitalisation for worsening heart failure.

The Panel noted that the claim in the promotional article in question referred to a *post-hoc* analysis of the CONFIRM-HF study. Earlier in the promotional article it stated the primary endpoint measure in CONFIRM-HF (6MWT change). Whilst the article in question did not state the primary endpoint result, the Panel noted CSL Vifor's submission that the achievement of the primary endpoint for CONFIRM-HF was discussed in an earlier article in the supplement. Whilst noting that each article needed to standalone with regard to the requirements of the Code, the Panel considered that it was not necessarily unacceptable for the article in question not to detail the primary endpoint results; acceptability depended on a number of factors including that the reader must have sufficient information to put the claim into context to form his/her own opinion of the therapeutic value of the medicine.

Noting that the primary endpoint of the study had been achieved and the claim clearly stated it was a *post hoc* analysis, the Panel considered, in the context of the article in question, that the complainant, who bore the burden of proof, had not established that there was inadequate evidence for the claim '*Post-hoc* analysis of the CONFIRM-HF study supported the hypothesis that treatment with IV iron was associated with reduced hospitalisation' and the Panel ruled **no breach of Clauses 7.2 and 7.4 of the 2019 Code.**

With regard to the second sentence, 'An individual patient data meta-analysis of 839 patients found IV iron treatment was associated with a significant reduction in the risk of HF hospitalisation and cardiovascular mortality (rate ratio 0.59, 95% confidence interval 0.4 to 0.88, p=0.009)' referenced to Anker *et al* (2018), the Panel noted that neither CSL Vifor nor the complainant provided a copy of the clinical paper, however, it was accessible to the Panel from a link in the references section in the online article in question.

The Panel noted that Anker *et al* stated:

> 'Individual patient data were extracted from four RCTs comparing FCM [ferric carboxymaltose] with placebo in patients with systolic HF [heart failure] and ID [iron deficiency]. The main outcome measures were recurrent cardiovascular (CV) hospitalisations and CV mortality. Other outcomes included cause-specific hospitalisations and death. The main analyses of recurrent events were backed up by time-to-first-event analyses. In total, 839 patients, of whom 504 were randomised to FCM, were included. Compared with those taking placebo, patients on FCM had lower rates of recurrent CV hospitalisations and CV mortality [rate ratio 0.59, 95% confidence interval (CI) 0.40–0.88; P = 0.009]. Treatment with FCM also reduced recurrent HF hospitalisations and CV mortality (rate ratio 0.53, 95% CI 0.33–0.86; P = 0.011).'

The Panel noted that CONFIRM-HF was one of the studies included in this meta-analysis. The Panel further noted that the claim clearly stated it was a meta-analysis and gave the n number, rate ratio, confidence interval and p-value. The Code did not prohibit reference to meta-analyses in promotional material provided the requirements of the Code were met. The Panel considered the claim within the context of the article at issue. Whilst the Panel had concerns about the accuracy of the data presented, noting the complainant's very narrow allegation that the meta-analysis was not adequate evidence on which to base the promotional claim in question, and noting the complainant bore the burden of proof, the Panel considered that the complainant had not established that there was inadequate evidence for the claim in the context of the article at issue and thus the Panel ruled **no breach of Clauses 7.2 and 7.4 of the 2019 Code** in that regard.

With regard to the allegation that Table 3 in the article was inviting comparisons to be drawn between the data in different studies rather than clearly stating that different studies should not be directly compared, the Panel noted that the table was headed, 'Ongoing clinical trials of intravenous iron in patients with heart failure examining morbidity and mortality'. Immediately above the table, it was stated:

> 'Uncertainty remains about the long-term benefits of IV iron on cardiovascular outcomes, its safety and efficacy. Fortunately, ongoing clinical trials in symptomatic acute and chronic HFrEF patients with iron deficiency (table 3) powered to determine the effect on mortality and hospitalisation should provide an answer. The studies consist of three with

> ferric carboxymaltose and one with ferric derisomaltose allowing some comparison between the products.'

The Panel noted that Table 3 named the four studies, gave their clinicaltrials.gov registration numbers and details about each study's patient population, planned number of enrolment, duration, estimated completion date and primary endpoints; some studies appeared to be ongoing at the time the article was published.

Whilst the Panel considered Table 3 was inviting a comparison between the ferric carboxymaltose and ferric derisomaltose studies, and acknowledged the complaint's concern that different studies should not be directly compared, the content appeared to be limited to comparing the study designs; no results were presented.

The Panel noted that Clause 7.3 of the 2019 Code stated a comparison was only permitted in promotional material if, amongst other things, it was not misleading. In the Panel's view, given the table in question only referred to study design, with no study results presented, the Panel considered that the complainant had not established that this table made a misleading comparison between ferric carboxymaltose and ferric derisomaltose; differences in the study designs and populations were clear. The Panel therefore ruled **no breach of Clause 7.3 of the 2019 Code**.

The Panel noted that under 'Key messages' it stated:

> 'Heart failure with reduced ejection fraction is associated with iron insufficiency. Intravenous iron is a safe and effective treatment'.

The Panel considered that whilst Ferinject (ferric carboxymaltose) was not the only intravenous iron referred to in the article, the article and claim at issue could not be seen as anything other than promotion of Ferinject, particularly given the numerous references to ferric carboxymaltose in the article. The article was Ferinject promotional material and included prescribing information. In the Panel's view, reference to intravenous iron being safe in an article that promoted Ferinject could not be considered as anything other than as a claim that Ferinject was safe. The Code prohibited the use of the word safe without qualification. Whilst the article in question referred to certain side effects of IV iron in general, such as serious allergic reactions, and discussed the incidence of hypophosphataemia with Ferinject, in the Panel's view, this was not qualification of the use of the word 'safe' in the 'key messages' of the article and **a breach of Clause 7.9 of the 2019 Code** was ruled.

The Panel further noted the complainant's allegation, within the same extract cited above, that Ferinject had been described in the 'key messages' as an effective treatment for heart failure with reduced ejection fraction, which was promotion outside of licence.

The Panel noted that the Ferinject SPC stated:

> 'Ferinject is indicated for the treatment of iron deficiency when (see section 5.1):
> – oral iron preparations are ineffective.
> – oral iron preparations cannot be used.
> – there is a clinical need to deliver iron rapidly.
>
> The diagnosis of iron deficiency must be based on laboratory tests.'

The Panel noted that Section 5.1 of the Ferinject SPC referred to studies in patients with chronic heart failure and iron deficiency, including CONFIRM-HF which was also referred to in the article in question.

The Panel noted CSL Vifor's submission that the discussion of use of intravenous iron in the article in question was for heart failure patients with iron deficiency. In this regard, the Panel noted that the studies referred to by the complainant in their complaint about the article were in relation to patients with heart failure and iron deficiency.

Noting the above, the Panel considered that the complainant had not established that the claim 'Heart failure with reduced ejection fraction is associated with iron insufficiency. Intravenous iron is a safe and effective treatment' in the context of the article in question promoted Ferinject off-licence as alleged and **no breach of Clause 3.2 of the 2019 Code** was ruled.

The Panel noted its rulings above, which included one breach of Clause 7.9 of the 2019 Code in relation to use of the word 'safe' in the article. Considering the article in question provided some information on the side effects of IV irons in general and Ferinject specifically, in the Panel's view, a health professional was, on balance, unlikely to be left with the impression that Ferinject had no side effects. In this regard, the Panel considered that the complainant had not established, on balance, that CSL Vifor had failed to maintain high standards as alleged and **no breach of Clause 9.1 of the 2019 Code was ruled.**

Complaint received **4 August 2022**

Case completed **4 September 2023**