CASES AUTH/3231/7/19 AND AUTH/3255/7/19

COMPLAINANT v SHIELD AND NORGINE

Feraccru website

A complainant who described him/herself as a concerned UK health professional, complained about claims on the Feraccru (ferric maltol) website. Feraccru was used to treat adults with iron deficiency; it had been marketed by Shield Therapeutics PLC. Norgine Pharmaceuticals Limited became the marketing authorization holder in February 2019.

The complainant noted that the claim that Feraccru was well tolerated would reassure clinicians although the summary of product characteristics (SPC) did not give the same level of reassurance. The complainant stated that in total there were 6 adverse drug effects in the common category and so in his/her view, Feraccru was definitely not well tolerated without a caveat.

The complainant further noted that a web-page explaining how Feraccru worked stated that:

> **'Feraccru creates a stable complex for delivery by tightly binding ferric iron (Fe^{3+}) to three maltol molecules .Fe^{3+} in Feraccru remains tightly bound to maltol until the point of iron absorption [Barrand *et al* 1991 and Barrand and Callingham 1991], preventing damage by free radicals in the gastrointestinal mucosa that may cause inflammation [Erichsen *et al* 2003].**
>
> **Like other oral treatments, Feraccru is physiologically absorbed to avoid iron overload.'**

What was not evident was that two of the papers cited (Barrand *et al* and Barrand and Callingham) were on the rat model. Furthermore, a third paper (Erichsen *et al*) did not support how Feraccru prevented damage by free radicals; it merely showed how that happened in a different oral iron. The complainant queried whether there was evidence to support the text which he/she found very misleading.

Finally, the complainant alleged that the Feraccru website to the general public promoted Feraccru. The complainant provided a page headed 'What is iron deficiency and iron deficiency anaemia?'. The page then described the conditions and suggested that if readers were concerned they should speak to a health professional. It appeared that there was a link to the Feraccru product information.

The detailed response from Shield and Norgine is given below.

The Panel noted the incidence of the most frequently reported adverse reactions given in the Feraccru SPC which were described as mainly mild to moderate in severity. The European public assessment report (EPAR) described the safety profile of ferric maltol in

the pivotal trial as reassuring. It further stated that, in general, the product was well tolerated and the profile of adverse events was expected since adverse events were similar to those described for other iron containing compounds and their incidence was low. The EPAR conclusion on the clinical safety was described as '… an acceptable safety profile although 18% of patients discontinued treatment …'.

The Panel also noted the companies' submission regarding the differences between tolerability and adverse events and that the pivotal studies involved patients with inflammatory bowel disease. Further the Panel did not consider that the complainant had shown on the balance of probabilities that there was evidence to show the medicine was not well tolerated. Taking all the circumstances into consideration the Panel did not consider that the number of common adverse events necessarily meant that the product was not well tolerated. The Panel did not consider that the complainant had established that the claim was inconsistent with the SPC as alleged. Thus the Panel ruled no breaches of the Code.

The Panel noted that the information about the mechanism of action was based on two studies in rats. This was not mentioned in the description of how Feraccru worked on the website as provided by the complainant. The SPC stated that the complex dissociated on uptake from the gastro-intestinal tract and the complex itself did not enter the systemic circulation. The SPC did not mention that the damage by free radicals which might cause inflammation was prevented. The Panel noted that the information on the website in this regard was referenced to Erichsen *et al* and Feraccru was not used in Erichsen *et al*. The Panel considered that the claim at issue implied that there was direct data to show that Feraccru, due to its mechanism of action, prevented damage by free radicals in the gastrointestinal mucosa that might cause inflammation and that was not so. The Panel considered that the use of a reference showing activities of free radicals was not necessarily a breach of the Code. The question to be considered was whether the information misled as to the significance of the data or was extrapolated to the clinical situation.

The Panel considered it was not clear that the data related to two studies on animals or that the third study did not involve Feraccru and in this regard the material was misleading and not capable of substantiation. The Panel therefore ruled breaches of the Code.

The Panel considered that a page for the general public referring to a disease which linked to a product, advertised that medicine to the public. Feraccru was a prescription only medicine and the Panel ruled a breach of the Code as acknowledged by the companies.

A complainant who described him/herself as a concerned UK health professional, complained about claims on the Feraccru (ferric maltol) website. Feraccru was used to treat adults with iron deficiency; it had been marketed by Shield Therapeutics PLC.

Norgine Pharmaceuticals Limited became the marketing authorization holder in February 2019.

COMPLAINT

The complainant noted that the claim that Feraccru was well tolerated would reassure clinicians although the summary of product characteristics (SPC) did not give the same level of

reassurance. The SPC stated that 'The most frequently reported adverse reactions were gastrointestinal symptoms (abdominal pain [8%], flatulence [4%], constipation [4%], abdominal discomfort [2%]/distension [2%] and diarrhoea [3%]) and these were mainly mild to moderate in severity. Reported severe adverse reactions were abdominal pain [4%], constipation [0.9%] and diarrhoea [0.9%]'. The complainant stated that in total there were 6 adverse drug effects in the common category and so in his/her view, Feraccru was definitely not well tolerated without a caveat.

The complainant further noted that a web-page explaining how Feraccru worked stated that:

> 'Feraccru creates a stable complex for delivery by tightly binding ferric iron (Fe3+) to three maltol molecules .Fe3+ in Feraccru remains tightly bound to maltol until the point of iron absorption [Barrand *et al* 1991 and Barrand and Callingham 1991], preventing damage by free radicals in the gastrointestinal mucosa that may cause inflammation [Erichsen *et al* 2003].
>
> Like other oral treatments, Feraccru is physiologically absorbed to avoid iron overload.'

What was not evident in that text was that Barrand *et al* and Barrand and Callingham were on the rat model. Furthermore, Erichsen *et al* did not support how Feraccru prevented damage by free radicals; it merely showed how that happened in a different oral iron.

The complainant queried whether there was evidence to support the text; after reading it he/she found it very misleading.

Finally, the complainant alleged that the Feraccru website to the general public promoted Feraccru. The complainant provided a page headed 'What is iron deficiency and iron deficiency anaemia?'. The page then described the conditions and suggested that if readers were concerned they should speak to a health professional. It appeared that there was a link to the Feraccru product information.

When writing to Shield the Authority asked it to consider the requirements of Clauses 3.2, 7.2, 7.4 and 26.1 of the Code.

RESPONSE

Shield and Norgine submitted a joint response and explained that although the complaint had been forwarded to Shield, Feraccru was now licensed to Norgine; Norgine became the marketing authorization holder in February 2019 and as part of the transition process, management of the website at issue was moved over in April. The website was in the process of being updated when the complaint was received.

With regard to the claim 'Feraccru is well tolerated' referenced to Schmidt *et al* (2016), the companies noted that tolerability referred to the degree to which adverse effects of a medicine could be tolerated by a patient. Tolerability of a particular medicine could be discussed in a general sense, or it could be measured as part of a clinical study. Usually, it was measured by the rate of dropouts from the study or by the percentage of subjects who completed the study.

Although a medicine might have adverse events listed as occurring commonly in the SPC, this did not mean that it was not well tolerated. Furthermore, as the data in the SPC was derived from the pivotal studies in subjects with inflammatory bowel disease, the common adverse

events listed were all symptoms of the underlying disease state, and the incidence of these adverse events in subjects in the placebo arm were similar. This supported the claim that Feraccru was well tolerated.

Moreover, in Schmidt *et al*, of 128 subjects who had previously failed on oral irons (either due to lack of tolerability or failure to respond), 5 withdrew from the Feraccru arm and 6 from the placebo arm during the 12-week blinded phase. Seventy five percent of subjects completed the 52 week long term extension phase (77% of those initially on placebo and 74% of those who started on Feraccru). In a study of inflammatory bowel disease subjects, this was a very high percentage and supported the claim that Feraccru was well tolerated. Therefore, the claim was not inconsistent with the particulars listed in the SPC, was not misleading and was supported by Schmidt *et al*. As such it was not in breach of Clauses 7.2 or 3.2.

The companies noted that the complainant referred to the references used to support information regarding the ferric maltol molecule and its chemical activity in the gut ie Barrand *et al*, Barrand and Callingham and Erichsen *et al*. The complainant stated that it was not clear that the data in Barrand *et al* and Barrand and Callingham were from a rat model, and that Erichsen *et al* did not support how Feraccru prevented damage by free radicals, it merely showed how that happened in a different oral iron.

The companies submitted that the Code did not prohibit the use of data derived from animals. However, care must be taken with the use of such data so as not to mislead as to its significance. The extrapolation of such data to the clinical situation should only be made where there was data to show that it was of direct relevance and significance.

The companies stated that animal models were commonly used to determine the behaviour, absorption path and activity of medicines prior to human exposure. Mammalian models used needed to reflect human biology and physiology. In this instance, the Wistar rat model demonstrated the chemical activity of ferric maltol in the gut, whereby the molecule remained stable as ferric maltol until absorption of iron occurred, meaning that there was no ‘free iron’ in the gut. This was different from oral iron salts which must dissociate from the salt in order to be absorbed. This free iron chelated together in the gut and created free radicals that damaged the gastrointestinal mucosa. This was supported by Erichsen *et al*. It was a matter of logic that if no free radicals were formed by Feraccru, then that would prevent damage by free radicals in the gastrointestinal mucosa that might cause inflammation.

The companies submitted that the use of animal data to support the chemical behaviour of ferric maltol in the gastrointestinal tract was reasonable and not in breach of Clause 7.4. The use of Erichsen *et al* to support the fact that free radicals, formed with oral iron salts, caused gastrointestinal mucosa damage was not misleading as it was clear that when no free radicals were formed, such damage would not occur. There was no breach of Clause 7.2.

With regard to the allegation that Feraccru had been promoted to the public, the companies accepted that the page submitted by the complainant, as accessed, promoted Feraccru to the general public. Although the intention was for this page to be only for patients who had been prescribed Feraccru, its position on the website meant that any member of the public was taken to this page. Shield acknowledged a breach of Clause 26.1. As such, the website was taken down on receipt of the notification to resolve this issue. Given the pending complaint, the updated website had been reviewed with consideration of the complaint above.

PANEL RULING

The Panel noted the incidence of the most frequently reported adverse reactions given in the Feraccru SPC which were described as mainly mild to moderate in severity. The European Public Assessment Report (EPAR) described the safety profile of ferric maltol in the pivotal trial as reassuring. It further stated that in general the product was well tolerated and the profile of adverse events was expected since adverse events were similar to those described for other iron containing compounds and their incidence was low. The EPAR conclusion on the clinical safety was described as '… an acceptable safety profile although 18% of patients discontinued treatment …'.

The Panel also noted the companies' submission regarding the differences between tolerability and adverse events and that the pivotal studies involved patients with inflammatory bowel disease. Further the Panel did not consider that the complainant had shown on the balance of probabilities that there was evidence to show the medicine was not well tolerated. Taking all the circumstances into consideration the Panel did not consider that the number of common adverse events necessarily meant that the product was not well tolerated. The Panel therefore ruled no breach of Clause 7.2. The Panel did not consider that the complainant had established that the claim was inconsistent with the SPC as alleged and thus ruled no breach of Clause 3.2 of the Code.

The Panel noted that the information about the mechanism of action was based on two studies in rats. This was not mentioned in the description of how Feraccru worked on the website as provided by the complainant. The mechanism of action section of the SPC stated that the complex dissociated on uptake from the gastro-intestinal tract and the complex itself did not enter the systemic circulation. The SPC did not mention that the damage by free radicals which might cause inflammation was prevented. The Panel noted that the information on the website in this regard was referenced to Erichsen *et al* and Feraccru was not used in Erichsen *et al*. The Panel considered that the claim at issue implied that there was direct data to show that Feraccru, due to its mechanism of action, prevented damage by free radicals in the gastrointestinal mucosa that might cause inflammation and that was not so. The Panel considered that the use of a reference showing activities of free radicals was not necessarily a breach of the Code. The question to be considered was whether the information misled as to the significance of the data or was extrapolated to the clinical situation.

The Panel considered it was not clear that the data related to two studies on animals or that the third study did not involve Feraccru and in this regard the material was misleading. A breach of Clause 7.2 was ruled. The misleading impression was that the data related to humans and Feraccru was not capable of substantiation and the Panel therefore ruled a breach of Clause 7.4.

The Panel considered that a page for the general public referring to a disease which linked to a product advertised that medicine to the public. Feraccru was a prescription only medicine and Clause 26.1 prohibited such advertising. The Panel ruled a breach of Clause 26.1 as acknowledged by the companies.

Complaint received **26 July 2019**

Case completed **28 January 2020**