Case AUTH/3326/3/20

VOLUNTARY ADMISSION BY NORGINE

Feraccru claims based on inaccurate statistical analysis

Norgine voluntarily admitted a breach of the Code in that claims for Feraccru (oral ferric maltol) were based on inaccurate statistical reporting from a clinical trial. Feraccru was indicated in adults for the treatment of iron deficiency.

As Paragraph 5.6 of the Constitution and Procedure required the Director to treat a voluntary admission as a complaint, the matter was taken up with Norgine.

Norgine explained that the claims at issue, 'In the new head-to-head trial, Feraccru was found to be non-inferior to IV ferric carboxymaltose' and 'Feraccru may be an appropriate alternative to IV iron for treatment of [iron deficiency anaemia]', were based on inaccurate statistical reporting from the AEGIS-H2H study. The primary endpoint of the study, as set out in the protocol, stated that Feraccru could be considered non-inferior to IV iron if the difference in the proportion of responders in each arm at week 12 was less than 20% in *both* the ITT (Intention to Treat) *and* the PP (Per Protocol) analyses. However, in the ITT analysis Feraccru did not demonstrate non-inferiority compared with IV iron therapy, so did not meet the primary endpoint as specified in the protocol and statistical analysis plan. The abstract on which the Feraccru claims were based, (Howaldt *et al* 2019), had inaccurately defined the primary endpoint as being considered to be met in *either* the ITT *or* the PP population rather than requiring both populations.

Norgine submitted that, following identification of the inaccuracies, training, marketing and market access materials which contained the claims at issue were promptly withdrawn. The salesforce and other externally facing staff had been briefed accordingly.

Further details from Norgine are given below.

The Panel noted that the AEGIS-H2H study compared Feraccru vs IV ferric carboxymaltose for the treatment of iron deficiency anaemia in patients with inflammatory bowel disease. The Panel further noted Norgine's submissions that the study protocol required less than a 20% difference in the number of responders in each arm in both the ITT and PP populations at week 12 and that such a difference had not been shown in the ITT population. Howaldt *et al* had incorrectly stated that the primary endpoint would be met if the difference in the number of responders in each arm was less than 20% in *either* the ITT *or* the PP population and wrongly concluded non-inferiority of Feraccru vs IV ferric carboxymaltose based on the PP analysis alone. Given that the claims at issue were based on the flawed conclusion of Howaldt *et al* the claims were inaccurate and a breach of the Code was ruled as acknowledged by Norgine.

Norgine voluntarily admitted a breach of the Code in that claims for Feraccru (oral ferric maltol) were based on inaccurate statistical reporting from a clinical trial. Feraccru was indicated in adults for the treatment of iron deficiency.

As Paragraph 5.6 of the Constitution and Procedure required the Director to treat a voluntary admission as a complaint, the matter was taken up with Norgine.

VOLUNTARY ADMISSION

Norgine voluntarily admitted a breach of Clause 7.2 in that claims for Feraccru, an in-licensed medicine, were based on inaccurate statistical reporting from the AEGIS-H2H study which was not under Norgine's control. The claims at issue were: 'In the new head-to-head trial, Feraccru was found to be non-inferior to IV ferric carboxymaltose' and 'Feraccru may be an appropriate alternative to IV iron for treatment of [iron deficiency anaemia]'.

Norgine submitted that, following identification of the inaccuracies, it promptly withdrew materials containing the claims at issue (by close of business on 9 March) as a precautionary measure and whilst further investigation was undertaken. A list of the materials at issue was provided and included those used for training, marketing and market access. The salesforce and other externally facing staff had been briefed accordingly.

Norgine explained that the primary endpoint of the AEGIS-H2H study, as set out in the protocol, stated that Feraccru could be considered non-inferior to IV iron if the difference in the proportion of responders in each arm at week 12 was less than 20% in both the ITT (Intention to Treat) and the PP (Per Protocol) analyses, rather than in either the PP or ITT populations. However, in the ITT analysis Feraccru did not demonstrate non-inferiority compared with IV iron therapy, so did not meet the primary endpoint as specified in the protocol and statistical analysis plan.

The abstract on which the Feraccru claims were based had inaccurately defined the primary endpoint as being considered to be met in either the ITT or the PP population rather than requiring both populations. As soon as this inconsistency was confirmed, claims related to secondary and supportive endpoints and the statement that the primary endpoint could be met by either the ITT or the PP population were identified to be inaccurate. The materials containing these claims were promptly withdrawn.

Norgine stated that it was currently working as a matter of urgency to brief staff and communicate with third parties with whom this data was shared in collaboration with the partner company which conducted the study.

RESPONSE

Norgine submitted that it had no further comments to add with regard to the requirements of Clause 7.2.

PANEL RULING

The Panel noted that the AEGIS-H2H study was a multicentre phase 3b, open-label randomised control trial that compared Feraccru vs IV ferric carboxymaltose for the treatment of iron deficiency anaemia in patients with inflammatory bowel disease. The Panel further noted Norgine's submissions that the study protocol required less than a 20% difference in the number of responders in each arm in both the ITT and PP populations at week 12 and that such a difference had not been shown in the ITT population. The study abstract (Howaldt *et al* 2019) upon which the claims at issue were based incorrectly stated that the primary endpoint was Hb (haemoglobin) responder rate defined as the proportion of patients achieving either a 2g/dL increase in Hb or normalisation of Hb (women ≥12g/dL; men ≥13g/dL) at week 12, with a non-inferiority limit set to 20% in **either** the ITT **or** the PP population. Howaldt *et al* only detailed the PP population results and based on that analysis alone had, wrongly, concluded non-inferiority of Feraccru vs IV ferric carboxymaltose. Given

that they were based on the flawed conclusion of Howaldt *et al,* the claims at issue were inaccurate and a breach of Clause 7.2 was ruled as acknowledged by Norgine.

Voluntary admission made	**19 March 2020**
Case completed	**28 April 2020**