Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2500

ferric maltol 30mg hard capsules (Feraccru®)

Norgine Pharmaceuticals Ltd

09 December 2022

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a Resubmission

ferric maltol (Feraccru®) is not recommended for use within NHSScotland.

Indication under review: in adults for the treatment of iron deficiency.

Ferric maltol failed to demonstrate non-inferiority to an intravenous (IV) iron preparation, but was superior to placebo for correction of iron deficiency anaemia (IDA) in patients with inflammatory bowel disease (IBD).

The submitting company did not present a sufficiently robust clinical and economic analysis to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

Chair
Scottish Medicines Consortium

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Indication

In adults for the treatment of iron deficiency.[1]

Dosing Information

One capsule swallowed whole twice daily, morning and evening, on an empty stomach (with half a glass of water), as the absorption of iron is reduced when it is taken with food. Treatment duration will depend on the severity of iron deficiency but generally at least 12 weeks treatment is required. It is recommended that treatment is continued as long as necessary to replenish the body iron stores according to blood tests.[1]

Product availability date

23 March 2018

Summary of evidence on comparative efficacy

Ferric maltol is a complex of iron in the ferric state with a trimaltol ligand. It dissociates on uptake from the gastro-intestinal tract to provide iron that crosses the intestinal wall to correct IDA.[1]

The company has requested that SMC consider ferric maltol when positioned for use in the treatment of IDA in adult patients with IBD (excluding patients with IBD flare or haemoglobin [Hb] <95 g/L, as per summary of product characteristics [SPC[1]]) who are suitable for IV iron following treatment with conventional oral iron therapy.

An open-label phase IIIb study (AEGIS-H2H) recruited adults (>18 years) with quiescent or mild to moderate IBD and IDA, defined by Hb 80 to 110 g/L for women and 80 to 120 g/L for men plus either ferritin <30 ng/mL or ferritin <100 ng/mL with transferrin saturation (TSAT) <20%. Patients had a Simple Clinical Colitis Activity Index (SCCAI) score ≤5 or a Crohn Disease Activity Index (CDAI) score ≤300. In the investigators' opinion (without defined criteria), patients were suitable to receive IV iron. Randomisation was stratified by Hb (<100 or ≥100 g/L for women and <110 or ≥110 g/L for men) and IBD subtype (ulcerative colitis or Crohn's disease). Patients were equally assigned to ferric maltol 30mg orally twice daily for at least 12 weeks or ferric carboxymaltose IV administered within 5 days of randomisation according to local prescribing information, with additional doses after week 12 if the patient became anaemic. Patients were withdrawn from the study if their Hb was <75 g/L. Duration of treatment was reduced from 52 weeks to 12 weeks (or next study visit for those already in the study) by protocol amendment (when 80% of patients were randomised). The primary outcome was Hb response rate at week 12, where response was defined as an increase in Hb ≥20 g/L or normalisation of Hb (Hb ≥120 g/L in women or ≥130 g/L in men). This was primarily assessed in the intention to treat (ITT) population, which comprised all randomised patients, and in the per protocol (PP) population, which excluded from the ITT population patients with major protocol violations before week 12 and those with no visit or Hb measurement at week 12. The primary analysis assessed non-inferiority versus ferric carboxymaltose at a margin of 20%.[2]

Ferric maltol failed to demonstrate non-inferiority compared with ferric carboxymaltose for the primary outcome, Hb response at week 12: 67% versus 84% with a difference of -17% (95% confidence interval [CI]: -28% to -6%) in the ITT population; and 68% versus 85% with a difference of -17% (95% CI: -30% to -5%) in the PP population. As the lower bounds of the 95% CIs were outside the pre-specified non-inferiority margin of -20%, non-inferiority was not demonstrated. The secondary outcomes, mean changes from baseline in Hb and ferritin and proportion of patients with normalisation of ferritin, were lower with ferric maltol at week 12. The differences between the groups were smaller at later time points as detailed in Table 1 below.[2]

Table 1: Outcomes of AEGIS-H2H in the Intention-to-Treat (ITT) Population.[2,3]

		Ferric Maltol	Ferric carboxymaltose	Difference (95% CI)
Hb response*, % (n/N)	Week 12	67% (84/125)	84% (105/125)	17% (-28% to -6%)
	Week 24	80%	76%	
	Week 52	69%	73%	
LSM change Hb, g/L	Week 12	25	31	-6 (-10 to -2)
	Week 24	27	29	
	Week 52	28	29	
LSM change ferritin, ng/mL	Week 12	13.7	126.7	-113.1 (-145.9 to -80.2)
Normalisation of ferritin, %	Week 12	60%	76%	
	Week 24	73%	70%	
	Week 52	67%	70%	

CI = confidence interval; Hb = haemoglobin; LSM = least square mean; * Hb response defined as an increase in Hb ≥20 g/L or normalisation of Hb (Hb ≥120 g/L in women or ≥130 g/L in men).

Health-related quality-of-life was assessed using the short-form 36 (SF-36) questionnaire. Within the ferric maltol and ferric carboxymaltose groups, there were small mean changes (on 100-point scales) from baseline to week 12 in physical component summary (PCS) scores, 3.9 and 2.5, and mental component summary (MCS) scores, 4.3 and 2.8, respectively, with non-significant differences between the groups of 1.3 and 1.5 for the respective outcomes.[2]

AEGIS-1/2 comprised two identical double-blind phase III studies in patients with IDA (Hb 95 to 120 g/L in women and 95 to 130 g/L in men) associated with ulcerative colitis in AEGIS-1 and Crohn's disease in AEGIS-2. All patients were in remission or had mild-to-moderate IBD, defined by SCCAI score <4 for those with ulcerative colitis and by CDAI score <220 for those with Crohn's disease. Patients had previously failed on oral ferrous products for one of the following reasons: adverse effects (nausea, diarrhoea, constipation, abdominal pain, flatulence) causing withdrawal of therapy; deterioration of primary disease due to oral ferrous product; lack of efficacy; other signs of failure of therapy; or contra-indication. Patients were randomised equally to receive ferric maltol 30mg orally twice daily for at least 12 weeks or placebo. The primary efficacy endpoint was mean change in Hb from baseline to week 12 in the ITT population which comprised all randomised patients in both studies who had at least one dose of study drug. It was significantly greater with ferric maltol compared with placebo in a pooled analysis of AEGIS-1 and -2 as detailed in Table 2 below, which also describes effects on ferritin. There were no clinically meaningful differences from baseline to week 12 or between groups in the quality-of-life assessed using the

Inflammatory Bowel Disease Questionnaire (IBDQ). The 10 subscales scores of the SF-36 questionnaire remained stable or improved by 0.3% to 18% in the ferric maltol group and changed by -3.4% to 6.8% in the placebo group.[4,5]

Table 2: Results of AEGIS-1/2 study at week 12 in intention-to-treat (ITT) population.[4,5]

Mean change from baseline	Ferric maltol (N=64)	Placebo (N=64)	Difference (one-sided lower 97% CI)
Hb, g/L	22.5	-0.2	22.5 (1.81), p<0.001
Ferritin, ng/mL	17.3	1.2	

CI = confidence interval; Hb = haemoglobin.

After completing 12 weeks of randomised therapy in AEGIS-1/2, 97 patients received open-label ferric maltol 30mg orally twice daily in a 52-week extension study. Baseline was considered to be start of randomised treatment in the preceding studies. Over the initial 12 weeks of the extension study, mean change from baseline in Hb within the group switching from placebo to ferric maltol was similar to that with ferric maltol in the randomised studies. In both groups (continued and switched) mean Hb was generally maintained in the 35 and 36 patients who had observations at the end of the study: 139.5 and 133.3 g/L, respectively, with mean change in Hb from baseline of 30.7 g/L and 21.9 g/L in the respective groups. Hb normalisation was achieved by 89% and 83% of patients who continued treatment to the end of the extension study.[6]

Summary of evidence on comparative safety

In common with other oral iron preparations, ferric maltol is associated with gastrointestinal adverse events.[1]

In the open-label AEGIS-H2H study, mean duration of treatment was 30.2 weeks and 15.5 weeks in the ferric maltol and ferric carboxymaltose groups, respectively, reflecting the different dosing schedules (daily oral versus intermittent IV). More patients within the ferric maltol group compared with the ferric carboxymaltose groups had adverse events, 59% (75/127) versus 36% (43/120), treatment-related adverse events, 20% versus 5.8%, serious adverse events, 9.4% versus 3.3% (none were treatment-related), and adverse events leading to treatment discontinuation, 10% versus 2.5%, respectively. Gastrointestinal adverse events were more common within the ferric maltol group compared with the ferric carboxymaltose groups, including abdominal pain (9.4% versus 2.5%), upper abdominal pain (5.5% versus 1.7%), nausea (4.8% versus 1.7%), diarrhoea (4.8% versus 0.8%), constipation (3.9% versus 0.8%), flatulence (3.2% versus 0) and faecal discolouration (3.2% versus 0).[2,3]

In the double-blind study, AEGIS-1/2, patients received study treatment for a median of 85 days in both groups. Within the ferric maltol and placebo groups, adverse events were reported by 58% (35/60) and 72% (43/60) of patients and were treatment-related in 25% and 12%, respectively. The most common adverse events were gastrointestinal, 38% and 40%, including abdominal pain, 13% and 12%, diarrhoea, 8.3% and 10%, and constipation, 8.3% and 1.7%, respectively.[4]

*Other data were also assessed but remain confidential.**

Summary of clinical effectiveness issues

Iron deficiency anaemia occurs when iron levels are insufficient to support red blood cell production and is defined by the World Health Organisation (WHO) as Hb levels below 130 g/L in men over 15 years, below 120 g/L in non-pregnant women over 15 years, and below 110 g/L in pregnant women.[7] Many patients with IBD have IDA as the inflammation interferes with iron absorption and this condition may be associated with chronic intestinal bleeding. Patients may have decreased iron intake from avoidance of foods that may exacerbate symptoms of IBD. Symptoms commonly include chronic fatigue, weakness, lethargy, headaches, dizziness, vertigo and tinnitus.[5,8] The 2021 British Society of Gastroenterology (BSG) guidelines for the management of iron deficiency anaemia in adults recommend oral ferrous sulphate, fumarate or gluconate as initial treatment of IDA, with dose reductions, alternative oral preparations or parenteral iron to manage tolerability issues. They note that intolerance and malabsorption of oral iron can be particular problems in the treatment of IBD-associated IDA, and parenteral iron replacement therapy may be required.[9]

Ferric maltol is the first oral formulation of a ferric salt licensed in the UK.[1] In patients with IDA and IBD, ferric maltol failed to demonstrate non-inferiority to IV ferric carboxymaltose for Hb response at week 12 (although differences between treatments were smaller at weeks 24 and 52) and it was superior to placebo for mean change in Hb from baseline to week 12.[2,4,6]

Long-term efficacy and safety data up to one year's treatment are limited by sample size. In AEGIS-1/2, data at the end of the 52 week open-label extension were available for 35 and 36 patients in the groups who continued or switched to ferric maltol after the randomised phase.[6] A protocol amendment during AEGIS-H2H (after 80% of patients had been randomised) shortened study duration from 52 to 12 weeks for new patients and those already in the study had their final visit at the next scheduled visit if this was after week 12. This limited the sample size at week 52/end of treatment within the ferric maltol and ferric carboxymaltose groups to 51% (64/125) and 50% (63/125) of patients, respectively.[2]

Compared with IV ferric carboxymaltose, ferric maltol was associated with more gastrointestinal adverse events in AEGIS-H2H.[2] However, the open-label design of this study limits subjective data such as adverse events and quality of life. In contrast to IV iron, ferric maltol is not administered in a setting where resuscitation facilities are available.[1,10-13] IV iron therapy is invasive and associated with the risk of rare but serious hypersensitivity-reactions.[5]

The submitting company has requested that SMC consider ferric maltol when positioned for use in the treatment of IDA in adult patients with IBD (excluding patients with IBD flare or Hb <95 g/L, as per the ferric maltol SPC) who are suitable for IV iron following treatment with conventional oral iron therapy. In practice, these patients would have failed on first-line oral iron preparations (ferrous sulphate, ferrous gluconate and ferrous fumarate) before ferric maltol was initiated. In AEGIS-H2H, some patients had no record of previous iron therapy and in those patients who had a record of previous iron therapy, there is no evidence that they had failed on oral ferrous products.[3] Although AEGIS-1/2 recruited patients who had failed previous oral ferrous treatment,

a regulatory review noted that there was no information on dose (which can impact adverse events) and it was not clear that the study population was intolerant to previous oral ferrous therapy; mean time since last pre-study oral iron treatment was over 2 years. Despite a post-hoc survey of 13 study sites to address these concerns, it was concluded that data were insufficient to clarify the issue and could not support an indication for use in patients who had failed previous oral ferrous preparations.[5] Therefore, there appears to be a lack of robust data with ferric maltol in patients who are representative of a second-line positioning after failure of first-line oral ferrous therapies.

Ferric maltol has been compared with oral ferrous products (including unlicensed formulations) in small pharmacokinetic studies.[5,8] In the submission, there was no comparison of ferric maltol with oral ferrous products in their licensed regimens and in strategies (such as dose reduction) to manage adverse events.

The BSG guideline recommends that iron replacement therapy should be continued for around three months after normalisation of Hb to ensure adequate repletion of the marrow iron stores. After this, blood count should be monitored periodically to detect recurrent IDA.[9] Within the submission, there was no information on re-treatment in patients who had achieved restoration of Hb and iron stores with ferric maltol or ferric carboxymaltose.

There are no direct comparative data for ferric maltol versus IV iron preparations other than ferric carboxymaltose (in AEGIS-H2H). However, it was noted that an indirect comparison of IV iron preparations, which included five studies, suggested there were no significant differences in Hb response (normalisation or increase ≥20g/L) with ferric carboxymaltose versus iron sucrose and iron isomaltoside (also known as ferric derisomaltose), with odd ratios (95% credible intervals) of 0.7 (0.48 to 1.0) and 0.69 (0.34 to 1.4) for the respective comparisons.[14] The BSG guideline notes that the various IV iron formulations appear generally equivalent in terms of ultimate haematological response, but the total dose preparations provide more rapid replenishment of body iron stores (than the multiple dose preparations), usually in just one or two infusions.[9]

Clinical experts consulted by SMC noted ferric maltol may be used in place of IV iron preparations in patients who are intolerant of other oral iron preparations. They highlight potential decreases in use of day unit resource associated with a reduction in IV iron administration.

*Other data were also assessed but remain confidential.**

Summary of comparative health economic evidence

The company presented a simple cohort model aligned with the proposed positioning for ferric maltol. Over the period of 12 months, ferric maltol was compared against IV iron. Within the model, data from the AEGIS-H2H study were used to group patients based on Hb levels.[2,3] Normalisation was classified as Hb ≥ 130g/L in males and Hb ≥ 120g/L in females which is in line with the WHO definitions.[7] A patient's status was reviewed at 4, 12, 24 and 36 weeks. Those receiving ferric maltol were assumed able to receive IV iron should their anaemia be insufficiently

controlled. Those patients receiving IV iron were assumed to have exhausted all alternative treatment options. Patients in receipt of IV iron could receive multiple administrations, if Hb levels decreased again into the anaemic range.

Participants of the AEGIS-H2H study reported health related quality of life through the SF-36 instrument. This was converted to the EQ-5D-3L equivalent utility estimates using the algorithm developed by Rowen et al. (2009).[15] There was no disutility included for the infusion of IV iron and adverse events were assumed to have been captured in the health state values.

Costs included the acquisition of both ferric maltol and IV iron as well as adverse event costs. IV iron was also associated with an administration cost. Wider resource use included in the model was minimal, with only a consultation included at the point where treatment was initiated, and again in the case of treatment switching.

Within the base case modelling, ferric maltol was associated with a cost saving and a gain in quality adjusted life years over IV iron and was thus the dominant treatment (cheaper, more effective). This generated an incremental cost-effectiveness ratio of -46,952 £/QALY. The company estimated a net monetary benefit (NMB) of £288 with a 20k £/QALY threshold of willingness to pay. The SMC does not have fixed willingness to pay thresholds.

In addition to the base case, the company presented a number of scenarios intended to explore uncertainty within the economic case. These are presented below.

Table 3: Scenario analysis

#	Scenario	Base case	ICER (£/QALY)	NMB
1	Time horizon = 12 weeks	Time horizon = 52 weeks	103,235*	£128
2	Ferric maltol responder = normalised or 10g/L change from baseline	Ferric maltol responder = normalised or 20g/L change from baseline	-72,849 (Dominant)	£318
3	QoL measured via SF-36 instrument	QoL measured via SF-36 before conversion to EQ-5D values	-70,429 (Dominant)	£260
4	Equal utility across all responders (normalised and non-normalised)	Non-normalised responders have equal utility to non-responders	-38,313 (Dominant)	£308
5	No discontinuation beyond lack of efficacy	Discontinuation due to lack of efficacy and AEs etc.	-60,710 (Dominant)	£281
6	IV iron dose built from 10ml and 20ml vials (2ml assumed unavailable)	IV iron dose built from 2ml, 10ml and 20ml vials	-66,488 (Dominant)	£373
7	Band 5 nurse used for IV administration	Band 6 nurse used for IV administration	-41,735 (Dominant)	£266
8	No treatment effect of IV iron after ferric maltol	Equal treatment efficacy of IV iron used instead of or after ferric maltol	31,036*	£72

South West quadrant.* ***Abbreviations:* *ICER, incremental cost effectiveness ratio; NMB, net monetary benefit; QoL, quality of life; IV, intravenous*

Strengths of the economic case were identified as being:

- The comparator included within the model appears to be appropriate. However, it was noted by SMC that there was no analysis provided against other oral iron preparations, which may be used in this patient population in practice.
- The economic case was informed by direct comparative evidence between ferric maltol and IV iron. However, there were potentially significant generalisability issues, as noted in the clinical effectiveness section above.

Weaknesses of the economic case were identified as being:

- The clinical evidence used in the economic model was derived from the AEGIS-H2H study. Within that study, patients could receive ferric maltol for the full observation period up to 52 weeks. Within the model, patients are assumed to use ferric maltol for shorter durations, meaning a lack of evidence on how Hb levels may respond once ferric maltol treatment ends. The company had assumed that those patients who normalize through ferric maltol treatment would remain normalized up to 52 weeks while patients receiving IV iron could have repeated doses. Following the New Drugs Committee, the company provided some additional information to show the impact of making alternative assumptions. In this analysis it was assumed that all patients who normalized with ferric maltol following their initial 24 week treatment will receive retreatment costs with IV iron for the remaining duration of the model, and that there are QALY losses from slipping out of a normalized state. This resulted in ferric maltol having reduced cost savings compared to the base case and a small QALY loss (30,735 £/QALY SW quadrant result, NMB £31).
- Utility values were missing several elements – adverse event disutilities and IV infusion disutilities. These would typically be expected to have very minor impacts upon the overall results. However, the base case results show that the anticipated health gains from ferric maltol were very small, and utility values were shown to be highly impactful upon the economic results through sensitivity analysis. Additional analysis was provided by the company to show the impact of assuming adverse event disutilities in the model. As expected, this reduced the QALY gains with ferric maltol and reduced the NMB result to £210.
- Relative to the time horizon (52 weeks) the cycle length (12 weeks) was long. While the company provided additional analysis showing that a half cycle correction had minimal impact upon the results (e.g. base case NMB changed from £288 to £293), the economic case would have been improved if more granular data had been collected within the AEGIS-H2H study. This would have allowed the differing speeds of treatment effect to have been captured more accurately and reduces the scale of the jumps in state occupancy seen in the model.

As a result of the weaknesses, the economic case was not demonstrated.

*Other data were also assessed but remain confidential.**

Summary of patient and carer involvement

The following information reflects the views of the specified Patient Group.

- We received a patient group submission from Crohn's and Colitis UK, which is a registered charity.

- Crohn's and Colitis UK has received 5.23% pharmaceutical company funding in the past two years, including from the submitting company.

- The symptoms of Crohn's and Colitis, the two main forms of Inflammatory Bowel Disease (IBD), and their unpredictable nature, can have a profound and devastating impact on all aspects of a person's life. Whilst fatigue can be caused by a number of factors associated with IBD, around 1 in 4 people with Crohn's or Colitis have anaemia, with a higher rate reported amongst those admitted to hospital with active Crohn's or Colitis. Iron deficiency anaemia is the most common type of anaemia for people with IBD. Fatigue has a wide-ranging impact on the lives of those with Crohn's and Colitis, affecting physical activity, social activities, mood, relationships, memory and concentration, work and education.

- Currently those living with Crohn's or Colitis and iron deficiency anaemia are treated by oral iron capsules or iron infusions. Overall, patients express dissatisfaction with many of the current options.

- This new medicine would offer improved patient choice by providing an alternative treatment for anaemia, taken orally at home thus reducing the need for hospital visits with the associated costs to personal finances, time and fatigue levels. It may improve some of the more distressing symptoms described by patients and allow more control over daily life.

Additional information: guidelines and protocols

In 2021, the British Society of Gastroenterology (BSG) published guidelines for the management of iron deficiency anaemia in adults. These recommend that the initial treatment of IDA should be with one tablet per day of ferrous sulphate, fumarate or gluconate. If not tolerated, a reduced dose of one tablet every other day, alternative oral preparations or parenteral iron should be considered. Parenteral iron should be considered when oral iron is contraindicated, ineffective or not tolerated. This consideration should be at any early stage if oral iron is judged unlikely to be effective and/or the correction of IDA is particularly urgent. IDA is a common manifestation of IBD, particularly when the disease is active. Intolerance and malabsorption of oral iron replacement therapy can be particular problems in the treatment of IBD-associated IDA, and parenteral iron replacement therapy may be required. The guidelines also note that the best option for patients with significant intolerance to oral iron replacement therapy (usually gastrointestinal disturbance)

is unclear. Depending on the individual, oral ferric maltol, alternate day oral iron and parenteral iron are all options.[8]

Additional information: comparators

When positioned for use after first-line oral iron preparations (ferrous sulphate, ferrous gluconate and ferrous fumarate), the relevant comparators would be IV iron preparations including ferric carboxymaltose (Ferinject®); iron isomaltoside, which is also known as ferric derisomaltose, (Monofer®); iron sucrose (Venofer®); and iron dextran (Cosmofer®).

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per 24-week course (£)
Ferric maltol	30mg orally twice daily	286

Costs from BNF online on 14 September 2022. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 4,781 patients eligible for treatment with ferric maltol in year 1 and 5,558 in year 5 to which confidential estimates of treatment uptake were applied.

SMC is unable to publish the budget impact due to commercial in confidence issues.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 11 November 2022.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.