Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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ferric maltol 30mg hard capsules (Feraccru®) SMC No. (1202/16)
**Shield TX UK Limited**

04 November 2016

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 Scotland. The advice is summarised as follows:

**ADVICE**: following a full submission

**ferric maltol (Feraccru®)** is not recommended for use within NHS Scotland.

**Indication under review:** in adults for the treatment of iron deficiency anaemia (IDA) in patients with inflammatory bowel disease (IBD).

In a pooled analysis of two phase III studies in IBD patients with IDA who had failed previous treatment with oral ferrous products, there was a significantly greater increase in haemoglobin concentrations after 12 weeks of ferric maltol treatment compared with placebo.

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

Overleaf is the detailed advice on this product.

**Chairman,**
**Scottish Medicines Consortium**

## Indication

In adults for the treatment of iron deficiency anaemia (IDA) in patients with inflammatory bowel disease (IBD).

## Dosing Information

One capsule twice daily, morning and evening, on an empty stomach. Treatment duration will depend on severity of iron deficiency but generally at least 12 weeks treatment is required. The treatment should be continued as long as necessary to replenish the body iron stores according to blood tests.

Ferric maltol capsules should be taken whole on an empty stomach (with half a glass of water) as the absorption of iron is reduced when it is taken with food.

## Product availability date

14 June 2016

## Summary of evidence on comparative efficacy

Anaemia is the most common extra-intestinal complication of inflammatory bowel disease (IBD) and may comprise both iron deficiency anaemia (IDA) and anaemia of chronic disease. Ferric maltol is a new oral iron complex rendering the iron stable (in the ferric form) and available for absorption. Maltol is a sugar derivative that strongly chelates iron in the ferric form ($Fe^{3+}$). The iron is absorbed via the endogenous dietary iron uptake system.[2] Ferric maltol has received marketing authorisation for the treatment of IDA in adult patients with IBD; however, the submitting company has requested that SMC considers ferric maltol when positioned for use in adult patients with IBD who have mild to moderate anaemia and have failed on therapy with oral ferrous products.

The key evidence comes from two identical, double-blind, randomised, phase III studies, one in patients with ulcerative colitis (UC) (AEGIS 1) and one in patients with Crohn's disease (AEGIS 2). Eligible patients were patients aged ≥18 years with a confirmed diagnosis of UC or Crohn's disease which was in remission or of mild to moderate disease activity. Patients had mild to moderate IDA at screening (defined as haemoglobin [Hb] ≥9.5g/dL to <12.0g/dL for females, Hb ≥9.5g/dL to <13.0g/dL for males, and serum ferritin <30 microgram/L). They had previously failed on oral ferrous products for at least one of the following reasons: adverse events that led to discontinuation (due to at least one of nausea, diarrhoea, constipation, abdominal pain, flatulence); resulted in deterioration of primary disease; lack of efficacy or other signs of treatment failure or documented reasons why oral ferrous products could not be used.

Eligible patients were randomised equally to receive oral ferric maltol 30mg (n=64) or placebo (n=64) twice daily for 12 weeks. Study medication was taken on an empty stomach with water, first thing in the morning before breakfast and last thing at night. Patients taking stable doses of immunosuppressive and immunomodulatory medicines permitted by the protocol (thiopurines and tumour necrosis factor inhibitors) for at least four weeks before randomisation were allowed to continue.

The primary outcome was the change in Hb concentration from baseline to week 12. Results have been published as a pooled analysis of both studies and are presented here. In the ferric maltol group, the mean (standard deviation [SD]) Hb concentration increased from a baseline of 11.00 (1.03) g/dL to 13.20 (1.04) g/dL at week 12, and in the placebo group from 11.10 (0.85) g/dL to 11.20 (0.98) g/dL. There was a significantly greater improvement in mean (standard error [SE]) Hb with ferric maltol versus placebo: 2.25 (0.12) g/dL, p<0.0001.

Secondary outcomes included change in Hb concentration from baseline to weeks 4 and 8, and responder analyses. There were significantly greater improvements in mean (SE) Hb with ferric maltol versus placebo at week 4 of 1.04 (0.11) g/dL and at week 8 of 1.73 (0.15) g/dL (both p<0.0001). Responder analyses assessed the proportion of patients in the ferric maltol and placebo group respectively achieving:

- ≥1g/dL increase in Hb concentration: 78% versus 11%: odds ratio 41.8 (95% confidence interval [CI]: 13.5 to 129.9)
- ≥2g/dL increase in Hb concentration: 56% versus 0% (odds ratio reported as not applicable)
- normalisation of Hb (defined as ≥12g/dL for females and ≥13g/dL for males): 66% versus 13%: odds ratio 15.3 (95% CI: 5.9 to 39.3)

There were also greater improvements in serum ferritin concentration and percentage transferrin saturation (TSAT) in ferric maltol compared with placebo patients.

Quality of life was assessed using the specific Inflammatory Bowel Disease Questionnaire (IBDQ) and the general 36-item Short-Form (SF-36) questionnaire. There were no clinically significant changes from baseline to week 12 in the IBDQ score: from 175.6 to 179.7 in ferric maltol patients and from 171.0 to 176.0 in placebo patients. The 10 subscales scores of the SF-36 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.[2,3]

The long-term efficacy and safety of ferric maltol was assessed in 97 patients who completed AEGIS 1 and 2 and entered an open-label, extension study.[4] All patients received up to 52 weeks of open-label ferric maltol 30mg twice daily and the study was completed by 73 patients. At week 52, the mean (SD) change in Hb concentration from baseline was 3.07 (1.46) g/dL in patients originally randomised to ferric maltol (n=50) and 2.19 (1.61) g/dL in patients originally randomised to placebo who then switched to open-label ferric maltol (n=47). Hb normalisation was achieved by 89% and 83% of patients respectively at the end of the extension.

## Summary of evidence on comparative safety

No comparative safety data are available other than versus placebo. Pooled analysis of the 12-week double-blind AEGIS 1 and 2 studies found adverse events in 58% (35/60) of ferric maltol patients and 72% (43/60) of placebo patients, most of which were of mild to moderate severity. Adverse events were considered to be treatment-related in 25% (15/60) and 12% (7/60) of patients respectively, and led to treatment discontinuation in 13% (8/60) and 8.3% (5/60) of patients respectively.

The most frequently reported adverse events were gastrointestinal, occurring in 38% (23/60) of ferric maltol and 40% (24/60) of placebo patients. These included abdominal pain (13% and 12%), diarrhoea (8.3% and 10%), constipation (8.3% and 1.7%) and nausea (0% and 1.7%). A

worsening of Crohn's disease was reported by 1.7% (1/60) of ferric maltol patients and 8.3% (5/60) of placebo patients. A worsening of UC was reported by 1.7% (1/60) and 3.3% (2/60) of patients respectively.[3]

The most frequently reported treatment-related adverse events were abdominal pain (6.7% and 5.0%), constipation (6.7% and 1.7%) and flatulence (6.7% and 0%).[3]

By the end of the 52-week extension study, 80% of patients reported at least one adverse event and these were considered to be treatment-related in 24% of patients. Discontinuation due to adverse events occurred in a total of 20% of patients. One patient with UC withdrew from the study due to increased UC activity.[4]

## Summary of clinical effectiveness issues

IDA due to chronic intestinal bleeding and decreased iron intake (from inflammation interfering with iron absorption and from avoidance of foods that may exacerbate symptoms of IBD) is an important contributor to anaemia in patients with IBD. The prevalence of IDA in various populations with IBD ranges from 36%-76%.[2] Guidelines recommend that patients with IBD should be regularly screened for IDA. Effective treatment of IBD may reduce intestinal bleeding and increase iron absorption, thereby helping to resolve IDA. However, iron supplementation, oral or IV, is also important in IDA management. Oral iron is often poorly tolerated and results in a significant proportion of IBD patients discontinuing treatment.

The submitting company has requested that SMC considers ferric maltol when positioned for use in adult patients with IBD who have mild to moderate anaemia and have failed on therapy with oral ferrous products.

The pivotal studies used a direct health outcome of change in Hb concentration from baseline to week 12 and showed a statistically significantly greater improvement in Hb concentration in the ferric maltol compared to the placebo group. The difference of 2.25g/dL was considered clinically relevant by the European Medicines Agency (EMA) and the treatment effect was seen from week 4 onwards.

The studies enrolled patients who were in remission or had mild to moderately active UC or Crohn's disease. There is no experience in patients with severely active disease and the summary of product characteristics (SPC) notes that ferric maltol should not be used in patients with IBD flare.[1] The study population was heterogeneous in terms of IBD severity as illustrated by mean time since last disease flare (34 months; range 0 to 45 months) and use of concomitant TNF inhibitors in 38% of patients and azathioprine in 31% of patients. However, post-hoc subgroup analysis found a consistent treatment effect by disease severity.[2,3] Study patients had mild to moderate IDA (baseline Hb ≥ 9.5g/dL).[3] The treatment effect of ferric maltol in patients with severe IDA is unknown and the SPC states that ferric maltol should not be used in IBD patients with Hb <9.5g/dL.[1] Study patients were required to have failed on previous oral ferrous products but the EMA notes that it is not well documented in the study that patients were intolerant to oral ferrous products.[2] Adverse events due to oral iron are generally considered to be dose-related but doses of previous oral ferrous products were not reported . Therefore, it is unclear if treatment intolerance could have been avoided by using a lower dose of oral ferrous products. The studies excluded patients who had received oral iron treatment within the

previous four weeks.[2,3] This may affect the generalisability of study results for patients unable to tolerate oral ferrous products being switched directly to ferric maltol.

There were no significant safety concerns and, in the AEGIS 1 and 2 studies, the adverse event profile of ferric maltol was similar to placebo. However, the studies generally recorded a low number of adverse events which did not allow statistical comparison between the treatment groups. Ferric maltol did not appear to be associated with a worsening of Crohn's disease or UC, or to have a detrimental effect on quality of life; however, controlled data are limited to 12 weeks.[3]

The submitting company did not consider oral or IV iron to be relevant clinical comparators as ferric maltol is expected to provide an additional treatment option before considering IV iron in patients who have failed oral ferrous products, avoiding the need for IV iron in 80% of patients. The submitting company considered that iron carboxymaltose is the most frequently used IV iron preparation in these patients and this was used as the comparator in the economic analysis. The submitting company did not perform an indirect comparison of oral ferric maltol and IV ferric carboxymaltose but assumed that they would have the same clinical benefits. No evidence is provided to support this assumption.

Ferric maltol provides a new oral iron preparation which increased Hb concentrations in patients intolerant to oral ferrous products. It offers a more convenient oral alternative for patients and the service to IV iron which is associated with rare but serious hypersensitivity reactions, including life-threatening and fatal anaphylactic reactions. These reactions require that IV iron should only be administered when appropriately trained staff and resuscitation facilities are immediately available, and patients need close monitoring during and for at least 30 minutes after every administration. [5] However, due to a lack of comparative data, the efficacy and tolerability of ferric maltol versus other oral or IV iron preparations remains unclear. A randomised, double-blind, phase III study is underway to compare 52 weeks of treatment with ferric maltol and IV iron carboxymaltose in IBD patients with IDA (n=240), using the change in Hb concentration from baseline to week 12 as the primary outcome.[6]

## Summary of comparative health economic evidence

The company submitted a cost-minimisation analysis comparing ferric maltol with IV ferric carboxymaltose in patients with IBD who have mild to moderate anaemia and have failed on therapy with oral ferrous products. SMC clinical experts confirmed that IV iron is currently used to treat these patients, and that ferric carboxymaltose and iron isomaltoside are the treatments most commonly used in practice.

The time horizon of the analysis was one course of treatment, which was assumed to be 12 weeks for both treatments. No clinical evidence was presented to support the assumption of comparable efficacy between ferric maltol and ferric carboxymaltose which is the basis of the cost-minimisation analysis. No direct study data are available and an indirect comparison was not conducted so comparable efficacy of the treatments was based on assumption only and is not supported by clinical evidence or SMC clinical expert opinion.

The analysis included medicine acquisition costs, administration costs, and GP/gastroenterologist follow-up visits. The cost of ferric maltol was based on 60mg per day for 12 weeks and the cost of ferric carboxymaltose was based on patients requiring a dose of

1500mg assuming a patient weight of >70kg. Administration costs were included for ferric carboxymaltose and it was assumed that patients would require two doses to be administered on two separate days. In the base case analysis, a band 6 nurse was assumed to administer the treatment in two appointments lasting 45 minutes each. Other resource use was assumed to be equal in both arms, except for an additional GP visit included in the ferric maltol arm to account for patients not receiving the full 12 week course of treatment at initiation. The company noted that the inclusion of this cost was a conservative assumption.

In the base case analysis, the submitting company estimated a total cost of £485 for ferric maltol versus £608 for ferric carboxymaltose, resulting in a saving with ferric maltol of £123. Based on medicine acquisition costs alone, ferric maltol was estimated to result in savings of £93.

The company provided sensitivity analysis which tested the resource use assumptions in the analysis, specifically the band of nurse administering ferric carboxymaltose treatment and the setting of the follow-up visit for ferric maltol patients. The results showed ferric maltol remained cost-saving, with savings reduced to £110 when a band 5 nurse was assumed to administer treatment and patients were followed-up in a secondary care setting. In the one-way sensitivity analysis, ferric maltol again remained cost-saving except in conservative scenarios when it was assumed patients in the ferric maltol arm would require two additional gastroenterology visits compared to the ferric carboxymaltose arm, or when no follow-up visits were required in the ferric carboxymaltose arm.

The following limitations were noted:

- No data were provided to support the assumption of comparable efficacy and safety which underpins the cost-minimisation analysis. In addition to the lack of any evidence, the assumption of comparable efficacy is not appropriate as the company indicates a proportion of patients will still require treatment with IV iron after ferric maltol treatment, which implies that ferric maltol may be less effective than ferric carboxymaltose and therefore a cost-minimisation analysis may not be appropriate. SMC clinical experts were asked to comment on the assumption of comparable efficacy and their responses indicated that this assumption may not be reasonable as it would be likely that IV iron would increase iron availability quicker and more effectively than oral iron.
- The cost of subsequent treatment was not included in the base case analysis despite the company stating that 20%-30% of patients will still require IV iron treatment following treatment with ferric maltol. Including the costs associated with 20% of patients requiring subsequent IV iron treatment reduced the savings to £37. Sensitivity analysis was also provided which assumed 29% (based on proportion of patients who had not achieved Hb normalisation by week 12 in the AEGIS studies) and 40% of patients require subsequent treatment with ferric carboxymaltose following a course of ferric maltol treatment, and this resulted in incremental costs with ferric maltol of £2 and £50 respectively.
- The time horizon of the analysis may not be sufficient to fully capture the costs of treatment. As noted above, some patients may require subsequent IV iron treatment and in addition some patients may continue on oral ferric maltol beyond 12 weeks.

Due to these limitations, and in particular the lack of evidence to support the assumption of comparable efficacy required for the cost-minimisation analysis, the economic case has not been demonstrated.

## Summary of patient and public involvement

The following information reflects the views of the specified patient group.

- We received a patient group submission from Crohn's and Colitis UK.
- Crohn's and Colitis UK has received 4.6% pharmaceutical company funding in the past two years, but none from the submitting company.
- Inflammatory Bowel Disease (IBD) is an unpredictable and relapsing condition with no known cure. The frequent and urgent need for the toilet, together with loss of sleep, pain and continual or profound fatigue can severely affect self esteem and social functioning. This can impact on ability to work leaving many patients feeling isolated.
- Current treatments for iron deficiency are iron tablets, capsules and intravenous iron infusions. Iron tablets and capsules are reported to cause problems with nausea and diarrhoea. While iron infusions appear to be a better option to increase iron levels in the body, they are not always offered and this treatment requires time away from work or education.
- Ferric maltol is taken orally and may result in a lower level of side effects compared to iron tablets or capsules, thus improving distressing symptoms and allowing patients more control over their daily lives.

## Additional information: guidelines and protocols

The European Crohn's and Colitis Organisation (ECCO) published a consensus on the diagnosis and management of iron deficiency in 2015.[7] This recommends iron supplementation in all IBD patients when IDA is present with a goal of normalising Hb and iron stores. This recommends that IV iron should be considered as first line treatment in patients with clinically active IBD with previous intolerance to oral iron, with Hb <10g/dL and in patients who need erythropoiesis-stimulating agents. It notes that the usual treatment of IDA with oral iron has relevant limitations in IBD patients. IV iron is more effective, shows a faster response, and is better tolerated than oral iron. Oral iron is effective in patients with IBD and may be used in patients with mild anaemia (Hb 11.0-12.9g/dL in men and 11.0-11.9g/dL in non-pregnant women) whose disease is clinically inactive and who have not been previously intolerant to oral iron. Side effects from oral iron are dose dependent and no more than 100mg of elemental iron per day is recommended in IBD patients.

The British Society of Gastroenterology published guidelines on the management of IDA in 2011.[8] The guideline makes general recommendations which are not specific to IBD patients. Iron therapy is recommended, most simply and cheaply with oral ferrous sulphate 200mg twice daily, but lower doses may be as effective and better tolerated and may be considered for patients not tolerating traditional doses. Other iron compounds and formulations may also be better tolerated. Although ascorbic acid may enhance iron absorption, there are no data for its effectiveness in the treatment of IDA. Patients not tolerating or responding to oral iron may be treated with parenteral iron.

## Additional information: comparators

Comparators relevant to the licensed indication under review are oral and IV iron.

## Cost of relevant comparators

| Drug | Dose Regimen | Cost for 12 weeks (£) | |
|---|---|---|---|
| **Ferric maltol 30mg capsules (Feraccru®)** | **30mg orally twice daily** | **143** | |
| **Oral iron** | | | |
| Ferrous sulphate 200mg film coated tablets | 200mg orally twice to three times daily | 17 to 26 | |
| Ferrous gluconate 300mg tablets | 600mg orally twice to three times daily | 23 to 35 | |
| Ferrous fumarate 210mg tablets | 210mg orally twice to three times daily | 5 to 8 | |
| **IV iron** | **Total dose infusions** | **Cost per dose** | |
| | | **1000mg** | **1500mg** |
| iron isomaltoside 1000 (Monofer®) | dose based on bodyweight and haemoglobin concentration | 170 | 254 |
| Ferric carboxymaltose (Ferinject®) | dose based on bodyweight and haemoglobin concentration | 154 | 235 |
| Iron sucrose (Venofer®) | dose based on bodyweight and haemoglobin concentration | 102 | 131 |
| Iron dextran (Cosmofer®) | dose based on bodyweight and haemoglobin concentration | 80 | 120 |

Doses are for general comparison and do not imply therapeutic equivalence. Costs for ferric maltol, ferric carboxymaltose and iron isomaltoside 1000 are from MIMs 1 September 2016. Costs for ferrous sulphate, ferrous fumarate, ferrous gluconate iron sucrose and iron dextran are from eVadis on 3 August 2016. The doses of IV iron are calculated based on body weight and individual iron needs. The costs in the table above are based on administration as a total dose infusion of 1000mg and 1500mg for comparison. The maximum single dose for ferric carboxymaltose is 15mg iron/kg body weight (1,000mg).

## Additional information: budget impact

The submitting company estimated there would be 1,487 patients eligible for treatment with ferric maltol in year 1 and 1,787 patients in year 5. The estimated uptake rate was 12% with 177 patients assumed to be treated in year 1, and 80% with 1,440 patients treated in year 5.

The gross impact on the medicines budget was estimated to be £43k in year 1, rising to £352k in year 5. As medicines were assumed to be displaced, the net medicines budget impact was estimated to a saving of £16k in year 1 and a saving of £130k in year 5.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. Shield TX (UK) Ltd. Feraccru® 30mg hard capsules, summary of product characteristics, last updated 20 April 2016.

2. European Medicines Agency. European Public Assessment Report: Feraccru (ferric maltol), CHMP assessment report, EMA/ 14567/2016, 17 December 2015. www.ema.europa.eu

3. Gasche C, Ahmad T, Tulassay Z et al. Ferric maltol is effective in correcting iron deficiency anemia in patients with inflammatory bowel disease: results from a phase-3 clinical trial program. Inflamm Bowel Dis 2015;21:579-88.

4. Schmidt C, Ahmad T, Tulassay Z et al. Ferric maltol therapy for iron deficiency anaemia in patients with inflammatory bowel disease: long-term extension data from a Phase 3 study. Aliment Pharmacol Ther 2016;44:259-70

5. European Medicines Agency. New recommendations to manage risk of allergic reactions with intravenous iron-containing medicines, EMA/377372/2013. www.ema.europa.eu

6. NCT02680756. Safety and efficacy study of oral ferric maltol compared to intravenous iron to treat iron deficiency anaemia in IBD. www.clinicaltrials.gov [accessed 29 August 2016].

7. Dignass AU, Gasche C, Bettenworth D et al. European consensus on the diagnosis and management of iron deficiency and anaemia in inflammatory bowel diseases. J Crohns Colitis. 2015;9:211-22.

8. Goddard AF, James MW, McIntyre AS et al. Guidelines for the management of iron deficiency anaemia. Gut 2011;60:1309-16

This assessment is based on data submitted by the applicant company up to and including 14 October 2016.

Drug 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.*