EPSOM AND ST HELIER UNIVERSITY HOSPITALS NHS TRUST
MEDICINES MANAGEMENT COMMITTEE

EVALUATION FOR NEW DRUGS

Drug Name Ferric Maltol

Preparations needed: Feraccru® 30mg Capsules

Licensed Indication: …For the treatment of iron deficiency anaemia (IDA) in patients with inflammatory bowel disease (IBD)

Indication sought (same as licensed indication or unlicensed/off-label?): … same as licensed indication

Licensed drug: Yes

- How strong is the evidence for claimed efficacy?
  (Grade A = > 1 RCT or meta-analysis; Grade B = 1 RCT or descriptive study;
  Grade C = expert committee report/opinion)

- Potential advantages in terms of: efficacy, compliance, pharmacokinetics, drug interactions and adverse effects?

- Does the requesting clinician have a clear idea of place in therapy?
  (E.g. patient type / characteristics, and relationship to other therapies)

- Is monitoring for efficacy required?

- Is monitoring for toxicity required?

- Is dose titration required?

- What is the role of the specialist?

- What is the role of the GP and if/when they would be asked to prescribe?

- Who will prescribe the drug?

- Restrictions within the Trust?

- Financial implications?

- Other issues

YOUR DECISION: Accept / Reject / 6 month Review
(If 6 month Review, what data should be collated)

EPSOM AND ST. HELIER UNIVERSITY HOSPITALS NHS TRUST

INDEPENDENT REVIEW FOR DRUG & THERAPEUTICS COMMITTEE

FERRIC MALTOL

Trade name (Company): (Licensing status in UK)	Feraccru® 30mg Capsules (Shield Therapeutics) Licensed February 2016
Requested by:	Dr Simon Moodie (Consultant Gastroenterologists)
Declaration of interest:	None declared
Pharmacology & pharmacokinetics:	Ferric maltol is a complex of a single ferric ion (Fe3+) chelated with high affinity to three maltol (3-hydroxy-2-methyl-4-pyrone) molecules. The maltol prevents the formation of iron hydroxide polymers and renders the iron available for absorption while stabilized in the ferric form (which, in turn, minimizes the potential for mucosal toxicity compared with ferrous iron). It is hypothesized that oral ferric maltol behaves as a carrier within the lumen of the gastrointestinal tract, making iron available in a biologically labile form for efficient uptake by mucosal enterocytes. The exact location of the dissolution of ferric maltol has not been definitively identified.[8] **Pharmacokinetics** In contrast to iron, maltol diffuses across the mucosa where it is rapidly conjugated and subsequently excreted in the urine [33]. Data from a cohort of 15 patients with IBD given 30 mg iron twice daily as ferric maltol showed that maltol is predominantly metabolized to maltol glucuronide with maximum plasma levels of maltol glucuronide ~70-fold greater than those of maltol (4677 ng/mL vs 67 ng/mL, respectively). Up to 82% of maltol is eliminated in the urine, the vast majority of this (95%) as maltol glucuronide. No iron or ferric maltol has been detected in urine, and unabsorbed ferric maltol is excreted in the faeces.[8]
Licensed indication(s):	Feraccru is indicated in adults for the treatment of iron deficiency anaemia (IDA) in patients with inflammatory bowel disease (IBD). Treatment duration will depend on the severity of iron deficiency but generally at least 12 weeks treatment required. The treatment should be continued as long as necessary to replenish the body iron stores according to blood tests.[1]
Indication(s) for which drug is being requested:	The specific place in therapy intended is for iron deficiency in IBD where oral ferrous iron salts are not tolerated before step up to IV iron administration.
Estimated no. of patients (1 year period):	Epsom: 20 St Helier: 30
Existing formulary drugs for same indication(s):	**9.1 ANAEMIAS AND SOME OTHER BLOOD DISORDERS**

9.1.1 Iron deficiency anaemias	
9.1.1.1 Oral iron	
Ferrous fumarate syrup 140mg (45mg iron/5ml)	
Ferrous gluconate 300mg (35mg iron)	
Ferrous sulfate 200mg (65mg iron)	
Sodium feredetate elixir 190mg (27.5mg iron/5ml) 'Sytron'®	
Iron and folic acid	
Ferrous fumarate and folic acid 'Pregaday'®	
9.1.1.2 Parenteral iron (*Hospital only)*	
MHRA Drug safety update Intravenous iron and serious hypersensitivity reactions: new strengthened recommendations to manage and minimise risk (Aug 2013)	
Ferric carboxymaltose 'Ferinject'®	*Nephrologists, Haematologists, Gastroenterologists and Obstetricians and Gynaecologists only* *Outpatient use only*
Iron (III)-hydroxide dextran complex 'Cosmofer'® (IV and IM)	
Iron isomaltoside 1000 'Monofer®,	*Haematologists, Gastroenterologists, Nephrologists and Obstetricians and Gynaecologists only 2nd line only when doses of 1gram are required in a single infusion* *Outpatient use only*
Iron sucrose injection 'Venofer'®	

<table>
<tr><td>Presentation(s):</td><td>A red capsule (19 mm long x 7 mm diameter) in a 56 pack container.[1]</td></tr>
<tr><td>Dosage & administration summary:</td><td>The recommended dose of Feraccru® is one capsule twice daily, morning and evening, swallowed whole on an empty stomach, as absorption of iron is reduced when Feraccru is taken with food.

Treatment duration will be determined by the 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.

Feraccru® has a shelf- life of 18 months. Shelf-life after first opening containers is 45 days.

The safety and effectiveness of Feraccru® in children (17 years and under) has not yet been established. No dose adjustment is needed for elderly patients. No clinical data on the need to adjust the dosage in patients with impaired hepatic or renal function are available.

(refer to SPC for more information)[1]

No current evidence or information regarding opening capsules for administration. (Personal communication with Shield Therapeutics Medicines Information Department).</td></tr>
<tr><td colspan="2">Side effects, precautions and contraindications summary:</td></tr>
<tr><td>Side effects:</td><td>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%].

<u>Tabulated list of adverse reactions</u>
Table 1: Adverse reactions observed during the 12 week controlled phase of study AEGIS 1/2 and the 52 week extension phase
<table>
<tr><th>SYSTEM ORGAN CLASS</th><th>COMMON (≥ 1/100 to < 1/10)</th><th>UNCOMMON (≥ 1/1000 to < 1/100)</th></tr>
<tr><td>Nervous system disorders</td><td></td><td>Headache</td></tr>
<tr><td>Gastrointestinal disorders</td><td>Abdominal pain (including upper abdomen)
Flatulence
Constipation
Abdominal discomfort/ distension
Diarrhoea
Nausea</td><td>Small intestinal bacterial overgrowth
Vomiting</td></tr>
<tr><td>Skin and subcutaneous tissue disorders</td><td></td><td>Acne
Erythema</td></tr>
<tr><td>Musculoskeletal and connective tissue disorders</td><td></td><td>Joint stiffness
Pain in extremity</td></tr>
<tr><td>General disorders and administration site conditions</td><td></td><td>Thirst</td></tr>
<tr><td>Investigations</td><td></td><td>Blood alkaline phosphatase increased
Blood thyroid stimulating hormone increase
Gamma-glutamyltransferase increased</td></tr>
</table>
(refer to SPC for more information)[1]</td></tr>
<tr><td>Precautions:</td><td>Ferric maltol should not be used in patients with inflammatory bowel disease (IBD) flare or in IBD-patients with haemoglobin (Hb) <9.5 g/dl.</td></tr>
</table>

	Iron preparations in excess may cause toxicity especially among children. Must not be administrated to children Special care should be taken if other dietary and/or iron salt supplementations are used concurrently. Before starting treatment, iron deficiency anaemia (IDA) diagnosis should be made based on blood tests; it is important to exclude underlying causes of anaemia other than iron deficiency (e.g. gastric erosion, colonic carcinoma). Ferric Maltol has not been studied in patients with impaired renal and/or hepatic function. This medicinal product contains lactose: patients with rare hereditary problems of galactose intolerance or glucose-galactose malabsorption should not take this medicine. This medicinal product also contains Allura Red AC (E129) and Sunset Yellow FCF (E110): these may cause allergic reactions. (refer to SPC for more information)[1]
Contraindications:	Hypersensitivity to the active substances or to any of the excipients listed in SPC.[1] Haemochromatosis and other iron overload syndromes. Patients receiving repeated blood transfusions. Should not be used in IBD patients with haemoglobin (Hb) <9.5g/dl or patients with IBD flare.[1]
Pregnancy & Lactation	<u>Pregnancy</u> There are no data from the use of Feraccru® in pregnant women. Ferric maltol is not systemically available. Definitive animal studies are not available for maltol with respect to reproductive toxicity. As a precautionary measure**,** it is preferable to avoid use during pregnancy. <u>Breastfeeding</u> Ferric maltol is not available systemically and is therefore unlikely to pass into the mother's milk. No clinical studies are available to date. As a precautionary measure, it is preferable to avoid the use during breast-feeding. <u>Fertility</u> There are no data on the effect of ferric maltol on human fertility. Ferric maltol is not systemically available. Fertility was unaffected following maltol treatment in animal studies. However, the conducted reproductive toxicity studies are insufficient to discard any risk in humans. (refer to SPC for more information)[1]
Interactions	No drug interaction studies have been performed with Feraccru®. Based on an in vitro study maltol is glucuronised through UGT1A6. Food has been shown to inhibit uptake of ferric maltol so should be taken on an empty stomach. Concomitant administration of ferric maltol and intravenous iron should be avoided as the combination may induce hypotension or even collapse due to the fast release of iron resulting from saturation of transferrin caused by intravenous iron.

Claimed advantage(s) over existing formulary drug(s) for same indication(s):

- Limits the need for the use of parenteral iron and the potential for hypersensitivity reactions. Also cheaper and does not require hospital resources.
- Convenient for patients and better quality of life measures.

Evidence for claimed benefits (including rating of quality of evidence):

Feraccru® has been previously reviewed by London Medicines Evaluation Network (LMEN), Northern Treatment Advisory Group (NTAG) and Greater Manchester Medicines Management Group (GMMMG). Reviews were also conducted by Gasche et al (2015), Schmidt et al (2016) and Stallmach & Buning (2015). The LMEN review is the most comprehensive and hence attached below for the evidence base.

LMEN_Ferric_Maltol_
IDA_IBD_FINAL_May

Summary of evidence

The Pivotal phase III trial programme of Feraccru® consisted of two identical prospective randomised, double blind, placebo-controlled, multicentre trials; AEGIS-1 and AEGIS-2 which involved 128 patients with mild to moderate IDA associated with (stable) IBD. After 12 weeks, Feraccru® led to a statistically significant improvement in Hb of 2.25g/dL from baseline to week 12 compared to placebo ($p<0.0001$) with the median time to normalisation of Hb levels being 57 days. Ferritin and transferrin saturation also improved over 12 weeks compared to placebo. Hb levels continued to increase to an average maximum of 14g/dL at 48 weeks in the open label extension study with continued use of Feraccru®.[6]

The most commonly reported adverse effects were arthralgia and mild to moderate gastrointestinal effects – abdominal pain, reflux, flatulence, rectal haemorrhage, abdominal distension and constipation. The iron in ferric maltol is highly bioavailable, which could allow lower doses of elemental iron to be used and so minimize the potential for adverse effects.[8]

Data from the AEGIS studies suggest that Feraccru® may be well tolerated in many patients with previous intolerance of oral ferrous salts. The EMA notes in the EPAR for Feraccru® that it did not exacerbate IBD during the AEGIS studies or during the open label extension study.[6,7]

Guidelines

The NICE Clinical Guidelines for IDA precedes the availability of Feraccru® and NICE has not produced any TA's for any of the oral iron salts. NICE recommends treating with oral ferrous sulphate 200 mg tablets two or three times a day.

- If ferrous sulphate is not tolerated, consider oral ferrous fumarate tablets or ferrous gluconate tablets.
- Do not wait for investigations to be carried out before prescribing iron supplements.

If dietary deficiency of iron is thought to be a contributory cause of iron deficiency anaemia, advise the person to maintain an adequate balanced intake of iron-rich foods (for example dark green vegetables, iron-fortified bread, meat, apricots, prunes, and raisins) and consider referral to a dietitian.[4]

Pharmacoeconomic implications:

	Cost per 12 weeks Treatment (At twice daily dosing)	
Drug/Dose	**Primary Care** (from drug tariff online)	**Secondary Care** All Secondary Care Prices are confidential and inclusive of VAT at 20%
Oral Iron		
Ferrous fumarate 140mg/5ml syrup	£15.99	£10.62
Ferrous gluconate 300mg capsules	£11.70	£2.58
Ferrous sulfate 200mg tablets	£7.26	£2.24
Ferrous fumuarate and folic acid	£7.50	£7.86
	Cost per dose	
Parental iron (Hospital only)		
Ferric carboxymaltose (Ferinject®) (100mg/2ml) (500mg/10ml)	N/A	 500mg: £87.67 1g: £175.34
Iron (III)-hydroxide dextran complex (Cosmofer®) (IV and IM) (500mg/10ml)	N/A	 500mg: £47.82

(100mg/2ml)		1g: £95.64
Iron isomaltoside 1000 (Monofer®) * (1g/10ml) (500mg/5ml)	N/A	1g: £168 1.5g: £252
Iron sucrose injection (Venofer®) (20mg/ml)	N/A	500mg: £261.10 1g: £522.20

***** Monofer® indicated for patients specifically requiring more than 1g of iron in a single infusion. Costs based on 1g dose as a minimum.

Place in therapy (including advantages and disadvantages):

Introduction

Inflammatory bowel disease (IBD) describes a set of chronic gastrointestinal illnesses, including Crohn's disease (CD) and ulcerative colitis (UC), of multifactorial etiology, which proceed with periods of relapse and remission. Anaemia is one of the most common manifestations of IBD; of which one-third of patients have haemoglobin levels below 12 g/dL. The anaemic state is strongly correlated with quality of life, and is an important problem in the therapeutic management of patients with chronic disease.[2]

Patients with IBD are increasingly likely to have iron deficiency anaemia (IDA), with an estimated prevalence of 36%–76%. Detection of iron deficiency is problematic as outward signs and symptoms are not always present.[3]

For IDA the usual recommendations for treatment involve the use of ferrous sulphate as the first-line option, as it is the most commonly used iron salt, is cost-effective, and has a high bioavailability. If in the case that ferrous sulphate is not tolerated, other oral options such as ferrous gluconate existed to be used as an alternative[4]. Oral iron supplementation remains the mainstay of treatment with intravenous iron being reserved only for secondary care settings, in exceptional circumstances.

Despite the convenience and the low cost of current oral ferrous salts, side effects are quite common and prove to be a barrier to efficacious outcomes. Some of the common side effects of ferrous iron salts include gastro-intestinal effects such as dark stools, constipation and nausea.

Feraccru® is a twice daily preparation that is licensed for the treatment of IDA in patients with IBD. Currently, it is indicated for adult patients with haemoglobin (Hb) 9.5 - 12g/dl for women and 9.5 – 13g/dl for men only. It is an option to be considered for patients as a second line alternative to oral ferrous salts, before consideration of parenteral iron products.

Evidence for efficacy and safety is from a 12 week placebo controlled study where patients had failed treatment with other oral iron salts and a 12 month extension study. This evidence shows a statistically significant ($p<0.0001$) mean increase of 2.3g/dL in 12 weeks, and more than 65% of treated subjects experienced normalised haemoglobin levels by week 12. Hb levels continued to increase to an average maximum of 14g/dL at 48 weeks in the open label extension study with continued use of Feraccru®.[6]

With respect to safety, the most common adverse effects were mild to moderate gastrointestinal effects reported by 38% of patients taking Feraccru® and by 40% of patients taking matched placebo. Specifically, the gastrointestinal adverse effects with greater incidence in the Feraccru® group vs. placebo groups were; abdominal pain (13% vs. 12%), gastrointestinal reflux (3% vs. 0%), flatulence (7% vs. 0%), rectal haemorrhage (5% vs. 2%), abdominal distension (3% vs. 0%) and constipation (8% vs. 2%). Nausea was not reported significantly in both groups, and diarrhoea (8% vs. 10%) and vomiting (2% vs. 3%) were more common in the placebo group. The only non-gastrointestinal adverse effect which was more common in the Feraccru® group was arthralgia (5% vs. 2%).[1]

Reviews conducted by NTAG and LMEN indicate the need to try Feraccru® once there is documented failure with previous oral ferrous treatment, which can be defined as one or more of the following: withdrawal from oral ferrous treatment because of adverse drug effects; deterioration of the primary IBD caused by oral ferrous treatment; lack of oral ferrous efficacy; and other signs of treatment failure.[7]

For consideration

Feraccru® drug costs are more expensive at £47.60 for a pack of 56 for a 28 day supply compared to £2.75 - £8.34 for 28 days of oral ferrous iron salts. It is estimated that there will be less financial implications by using Feraccru®, as it will reduce the need for patients to attend hospital for parenteral iron treatment and the associated costs needed for monitoring and trained practitioners. The Northern (NHS) Treatment Advisory Group (NTAG) supports the evidence of cost savings by using Feraccru® based on patients requiring fewer attendances in secondary care for parenteral iron products. The Greater Manchester Medicines Management Group (GMMMG) have recommended the use of Feraccru® as an alternative option in patients with mild to moderate IDA with IBD who have tried at **least three** oral ferrous salts and have a reported intolerance to oral ferrous salts due to adverse effects after an adequate trial. This criterion is not reflected by the LMEN reviewers as they did not specify how many ferrous iron salts to try before initiating a patient on Feraccru®. Despite this, it is agreed that Feraccru® should be initiated on advice of a gastroenterologist.[6] The duration considered adequate for trialling oral ferrous salts before initiation of Feraccru® is also not specified and will need consideration prior to approval/prescribing.

If approved on clinical grounds, the cost of treatment with Feraccru® vs. step up to IV iron will have to be reviewed by the medical division, in order to determine whether or not to approve funding for addition to formulary.

Advantages

- Higher bioavailability and less free iron circulating hence less side effects and / or worsening of IBD symptoms compared to oral ferrous iron salts even though taken on an empty stomach which potentially results in better quality of life measures.
- May reduce the need for parenteral iron and the potential for hypersensitivity reactions.

Disadvantages

- Drug acquisition cost compared to oral ferrous salts (see above).
- Short shelf life after opening which may lead to waste if patient is not compliant initially then resumes treatment at a later date.
- No information on opening capsules for patients with swallowing difficulties or enteral tubes.

National and local formulary status

NHS Scotland –Feraccru® is not recommended for use within NHS Scotland. The SMC felt that the manufacturer did not present sufficiently robust clinical and economic analyses. Resubmission to SMC is planned for 2018.

NHS Wales - Feraccru® is not recommended for use within NHS Wales for the treatment of iron deficiency anaemia in adults with inflammatory bowel disease. The cost-effectiveness data presented in the submission were insufficient for AWMSG to recommend its use.

Surrey CCG's – Not yet reviewed (Surrey PAD)

St Georges Hospital – Not on the formulary (online formulary accessed 14/09/17)

Croydon University Hospital – Not on the formulary (online formulary accessed 14/09/17).
Kingston Hospital -– Not on the formulary (online formulary accessed 14/09/17).

Royal Surrey County Hospital – Not on the formulary (online formulary accessed 14/09/17).

	It is not on formulary locally, however it is used in the UK in the following hospitals: London North West Healthcare NHS Trust The Pennine Acute Hospitals NHS Trust The Newcastle upon Tyne Hospitals NHSFT Barts Health NHS Trust Hull and East Yorkshire Hospitals NHS Trust University Hospital Southampton NHSFT North Bristol NHS Trust County Durham & Darlington NHS Foundation Trust Portsmouth Hospitals NHS Trust Northumbria Healthcare NHS Foundation Trust Hampshire Hospitals NHS Foundation Trust North Cumbria University Hospitals NHS Trust University Hospitals of Bristol NHSFT
Suggested protocol for use:	If approved for addition to formulary for the treatment IDA in adults with IBD, suggested restrictions are: • Gastroenterologists Initiation Only • 2nd Line Therapy
Key references:	1. Summary of Product Characteristics. (2017). Feraccru 30mg hard capsules. Retrieved 5th October 2017, from https://www.medicines.org.uk/emc/medicine/31722 2. Ali, T., Bashir, M. & Kaitha, S. (2015). Iron deficiency in inflammatory bowel disease. *World Journal of Gastrointestinal Pathophysiology, 6(3),* 62-72. 3. Gold, N. (2013). Iron deficiency anaemia in patients with inflammatory bowel disease. *Clinical and Experimental Gastroenterology, 6, 61-70.* 4. National Health Service Clinical Knowledge Summaries (2013). Anaemia: Iron Deficiency. Retrieved 5th October 2017 from https://cks.nice.org.uk/anaemia-iron-deficiency#!scenario 5. Northern Treatment Advisory Group. (2016). NTAG Decision Summary Feeric Maltol. Retrieved, 5th October 2017 from http://ntag.nhs.uk/docs/rec/NTAG%20Decision%20Summary%20Ferric%20Maltol.pdf #search=%22Ferric maltol%22 6. Greater Manchester Medicines Management Group. (2016). Ferric Maltol (Feraccru®) for the treatment of iron deficiency anaemia (IDA) in adults with inflammatory bowel disease (IBD). 7. London Medicines Evaluation Network. (2016). Ferric Maltol (oral Feraccru®) for the treatment of iron deficiency anaemia in adults with inflammatory bowel disease. 8. Buning, C. & Stallmach, A. (2015). Ferric maltol (ST10): a novel oral iron supplement for the treatment of iron deficiency anemia in inflammatory bowel disease. Expert Opin. Pharmacother.16(18).
Review date:	September 2017
Review by:	Sumbo Adeyemo (Senior Pharmacist, Medicines Management) David Babatunde (Senior Pharmacist, Medicines Management) Kuljit Gata-Aura (Principle Technician, Medicines Management)
Decision:	**APPROVED…./….NOT APPROVED..../....** **6 MONTH EVALUATION** **Any other recommendations?**

INFORMATION CORRECT AT TIME OF REVIEW. COPIES OF REFERENCES AVAILABLE FROM PHARMACY