## Summary

### Background
Between 20-76% of patients with inflammatory bowel diseases (IBD) experience Iron Deficiency Anaemia (IDA) which impairs quality of life causing symptoms such as headache and fatigue. Feraccru® (oral ferric maltol), which will launch during 2016, is a new iron complex consisting of a single ferric iron (Fe³⁺) chelated, with high affinity, to three maltol molecules. Maltol is a natural sugar derivative used in foods and it binds with high affinity to the iron until it is released directly into the area of the gastrointestinal system where it is best absorbed. This is suggested to confer high bioavailability and better tolerability compared with ferrous iron salt complexes, due to reduced exposure of free iron throughout the gastrointestinal tract.

### Dosing
One hard capsule of oral Feraccru®, containing 30mg of elemental iron, given twice daily on an empty stomach.

### Alternatives
IDA in patients with IBD is treated with oral or IV iron products. Some guidelines suggest that IV iron is better tolerated and more effective than oral iron and others suggest that IV iron be considered as second-line in patients who are intolerant of oral iron. Feraccru® is intended for use in patients who have not tolerated other oral iron products (e.g. ferrous sulphate, ferrous gluconate or ferrous fumarate) and for whom IV iron products are being considered – as long as they do not have an urgent need for correction of IDA.

### NICE
No relevant NICE guidance or technology approvals published or in-progress at time of writing.

### Clinical studies
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®. The AEGIS studies were relatively small, of short duration and only compared Feraccru with placebo. They included only patients with mild to moderate IDA at baseline so it is not clear how these results would apply to patients with more severe IDA. A direct comparison study of Feraccru® vs. Ferinject® (n=240) is currently in progress and aims to report data in 2017.

### Safety and tolerability
Data from the AEGIS studies suggest that Feraccru® may be well tolerated in many patients with previous intolerance of oral ferrous salts. 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 European Medical Agency (EMA) notes in the EPAR for Feraccru that it did not exacerbate IBD during the AEGIS studies or during the open label extension study.

### Conveniency
Compared with IV iron, administration of Feraccru is more convenient for patients. It would also reduce healthcare resource utilisation in hospital outpatient departments.

### Risk assessment
Identified risks or potential risks which require cautionary measures or mitigation steps are gastrointestinal adverse effects and drug-drug interactions and, rarely, hypersensitivity to excipients such as the colourants E110 and E129.

### Budget impact
Feraccru® will have an acquisition cost of £47.60 per month (more compared with other oral iron products which all cost < £5 per month). However, Feraccru® is intended as an alternative to IV iron in patients who do not require urgent treatment, and up to 10 patients per 100,000 of the population could be eligible to receive Feraccru® or Ferinject® (or other brands of IV iron) after not tolerating ferrous iron products. Six months of treatment with Feraccru® (using licensed doses) could offer a saving of around £219 when compared with 2 injections of Ferinject 1000mg (£528 vs. £747) assuming that administration is in a hospital outpatients department and is carried out by a band 6 nurse.

### Funding
It is expected that Feraccru® would be initiated by gastroenterologists with the possibility of transfer to primary care, potentially facilitated by shared care agreements. It is expected that funding would be via CCG’s.

### Suggested place in therapy
Oral Feraccru® may be useful as an alternative to IV iron (if there is no urgent need to raise Hb levels) in patients with IBD and mild to moderate IDA and who cannot tolerate oral ferrous salts. Feraccru® would be used for 12 weeks to raise Hb levels to target, after which it should be continued for 1-3 months according to clinical judgement. Using Feraccru® for longer periods is unlikely to confer further benefit but safety data to 12 months is available to support use of Feraccru® for longer in some patients who may require it. Feraccru® is currently only licensed for patients with underlying IBD and off-label prescribing for other indications associated with IDA should be challenged.
1. **Background and introduction**

Ulcerative Colitis (UC) and Crohn’s Disease (CD) are chronic inflammatory diseases of the gastrointestinal tract which follow a course of relapse, remission and exacerbations. UC and CD both have an estimated incidence in the UK of approximately 10 per 100,000 people annually and is most common in late adolescence/early adulthood. There are important differences between UC and CD but they can both cause diarrhoea, constipation, abdominal pain, urgency and malaise, fever as well as extra-intestinal manifestations (e.g. in the joint, skin and eye) and complications such as toxic megacolon. A poorly functioning gut can cause weight loss and nutritional deficiencies such as Iron Deficiency Anaemia (IDA) due to malabsorption. (1,2)

IDA occurs commonly in patients with inflammatory bowel diseases (IBD); between 20-76% of patients with IBD may have IDA. IDA is defined by the World Health Organisation (WHO) as having serum haemoglobin (Hb) level below 13 g/dL in men, below 12 g/dL in women and below 11 g/dL in pregnant women. (3) IDA may result from chronic blood loss, reduced iron intake or malabsorption or it may be of mixed origin (AMO). The reason for this relatively high prevalence in patients with IBD is likely to be multifactorial. Inflamed and ulcerated gastric mucosa may lead to blood loss and malnutrition and inflammation itself may play a role in the pathogenesis of IDA; (4,5) IDA can significantly impair quality of life; causing fatigue and affecting physical and emotional function and possibly even cognitive ability. IDA can also cause headaches, sleep disorders, decreased libido, restless leg syndrome and it can affect growth of nails and hair.

**Guidelines on management of IDA in patients with IBD**

Guidelines recommend that IDA in patients with IBD is corrected with the aim of restoring Hb concentrations and replenishing iron stores. A rate of increase of 2g/dL over 4 weeks is considered acceptable. Guidelines generally suggest that oral iron is tried first but advocate use of IV iron in patients with clinically active IBD with previous intolerance to oral iron. The ECCO guidelines suggest that intravenous (IV) iron is better tolerated and more effective than oral iron. (3;5; 6) However, these recommendations are based on studies of IV iron compared with oral ferrous sulphate; there are no completed studies comparing IV iron with oral ferric maltol. Oral ferrous iron products are cautioned (or even contra-indicated) in patients with history of IBD due to theoretical concern about them worsening the condition. It has been hypothesised that free iron can complex with oxygen to form an iron oxide product that, when exposed to an inflamed gastric mucosa, could lead to exacerbations, carcinogenesis and alteration of microbiota. However, this is mainly based on animal studies and use of oral ferrous sulphate in patients with IBD has only rarely been associated with exacerbations of IBD in clinical practice. (4,6-9)

The British National Formulary (BNF) recommends that iron salts be given by mouth unless there are good reasons for using anot

Furthermore, use of IV iron is not without risk and adverse effects such as hypersensitivity reactions means doses need to be given in hospitals or clinics where resuscitation facilities are available. (4) For some patients with IBD, oral iron products may be a suitable first line choice and the currently available oral iron products are ferrous fumarate, ferrous gluconate and ferrous sulphate. However absorption of oral ferrous salts (Fe²⁺) can be limited and they are not always well tolerated with frequent reports of dose related adverse effects - constipation, diarrhoea, epigastric pain, gastro‐intestinal irritation and nausea. (10,11)

**Ferric Maltol**

Ferric maltol is a novel trivalent iron complex consisting of a single ferric iron ion (Fe³⁺) chelated with high affinity to three maltol (3-hydroxy-2-methyl-4-pyrene) molecules. Maltol is a naturally occurring sugar derivative which is formed during when sugar caramelises and it is often used as a flavour enhancer in food products. The maltol moiety ensures that the ferric iron remains tightly bound to maltol at the higher pH of the gut where most iron absorption occurs. This purported high comparative bioavailability means that greater amounts of elemental iron can be delivered more easily. Also, the gastrointestinal mucosa is not exposed to high levels of free iron so it is hypothesised that the potential for tolerability problems is minimised. (4;12)

2. **Proposed place in therapy**

There is an unmet need for effective and well tolerated treatments for IDA in IBD that are easy and safe to administer. This can affect compliance and reduce the likelihood of desired treatment outcomes (raised serum iron levels) being achieved. Reducing the dose of elemental iron or taking with food can reduce the intensity of these adverse effects but it would also reduce the amount of elemental iron delivered. The incidence of side-effects due to ferrous sulfate is no greater than with other ferrous iron salts when compared on the basis of equivalent amounts of elemental iron. (10) IV iron must be administered carefully due to the risk of serious hypersensitivity reactions. (4)

It is hypothesised that oral ferric maltol will be better tolerated than other iron salts such as ferrous sulphate and unlike IV iron; it can be safely self-administered by the patient at home. It is also hypothesised that the elemental iron from Feraccru® (ferric maltol) will be absorbed better than other oral iron salts. The manufacturer intends Feraccru® to be second-line to currently available oral iron products and an alternative option in patients with mild to moderate IBD with either CD or UC who have reported intolerance to oral ferrous salts due to adverse effects. In these patients, it should be considered as an alternative to IV iron if there is no urgent need to raise Hb levels (e.g. prior to surgery).

3. **Evidence selected for inclusion**

Pharmacokinetic data suggest that absorption of ferric maltol is comparable to, or possibly faster than, that of equivalent (with respect to elemental iron content) doses of ferrous sulphate in iron-deficient patients with and without IBD. (4;13) Ferric maltol was especially well absorbed when taken in the fasted state compared to ferrous sulphate after a meal (which is how it must be given to reduce gastrointestinal adverse effects). (4) Clinical data selected for evaluation were a small phase II study (n=23) (11) and the pivotal AEGIS 1 and AEGIS 2 studies (n=128) of Feraccru® in patients with IDA and UC/CD who did not tolerate other forms of iron. (14) Results are also presented from a 12 month open label extension study of continued use of Feraccru® for 12 months involving patients recruited from the AEGIS 1 and 2 studies. (12)
Phase III data

The pivotal phase III trial programme of Feraccru® for treatment of IDA associated with UC and CD consisted of two identical prospective randomised, double-blind, placebo-controlled, multicentre trials; AEGIS-1 [NCT01340872] and AEGIS-2 [NCT01352221]. The AEGIS trials enrolled 128 patients in Austria, Germany, Hungary and the UK. Patients included in the AEGIS trials had all ‘failed’ treatment with oral ferrous iron supplements at baseline due to adverse effects leading to withdrawal (65%) and/or deterioration of the primary disease (2%) and/or lack of efficacy (37%) and/or other reasons (14%). (14)

For inclusion, patients had to be adults with mild to moderate IDA (defined as having a Hb concentration of ≥ 9.5g/dL and < 12g/dL for women and ≥ 9.5g/dL and < 13g/dL for men and serum ferritin levels of < 30 micrograms/L at screening) and either UC (45% of patients) or CD (55% of patients) which was either in remission or with mild to moderate disease activity at the time of randomisation. Mild to moderate disease activity was defined as having a SCCAI score of < 4 at screening and randomisation for UC and as having a CDAI score of < 220 at randomisation for CD (scores are explained in the Appendix). Patients who had recently received IV iron infusions, erythropoietin or blood transfusions within a year before randomisation were excluded. Patients who had used certain immunosuppressive treatments (e.g. thiopurines, anti-TNF agents) 4 weeks before randomisation were required to be on a stable dose prior to randomisation. Patients who had used certain immunosuppressant’s (e.g. methotrexate, tacrolimus, ciclosporin A), which are known to have potential to induce IDA, were excluded if they had used these within 4 weeks of randomisation. Other exclusion criteria were; folate deficiency, uncorrected vitamin B12 deficiency, renal impairment (serum creatinine > 176 micromol/L), abnormal liver function tests and pregnancy. (14)

Patients were screened over a 7-14 day period before being randomised (1:1 ratio) to one of two groups to receive either Feraccru® hard capsules (containing 30mg elemental iron) or matched placebo capsules twice daily (morning and night on an empty stomach with water) for 12 weeks. Compliance was assessed monthly using a capsule-counting method with patients considered non-compliant if they took less than 80% of their assigned medication. (14)

The primary efficacy endpoint was change in Hb concentration from baseline to week 12. As Table 1 shows, Feraccru® led to a statistically significant improvement in Hb of 2.15g/dL from baseline to week 12 compared to placebo (p<0.0001). The median time to normalisation of Hb (amongst evaluable patients taking Feraccru® at 12 weeks) was 57 days, with normalisation defined as having Hb values of ≥ 12 g/dL in women and ≥ 13g/dL in men. Decreased haemoglobin was reported as an ‘adverse effect’ and was reported in 0% of patients taking Feraccru® and in 5% of those taking placebo. (14)

### Table 1: Results for primary efficacy endpoint (change in Hb levels over 12 weeks) for ITT population

<table>
<thead>
<tr>
<th>Randomisation group</th>
<th>Mean baseline Hb level (g/dL)</th>
<th>Mean Hb level at 12 weeks (g/dL)</th>
<th>Mean change in Hb level (g/dL)</th>
<th>Statistical analysis (absolute difference between groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral ferric maltol capsules (n=64)</td>
<td>11.0</td>
<td>13.25</td>
<td>2.25</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Oral matched placebo capsules (n=64)</td>
<td>11.1</td>
<td>11.2</td>
<td>0.10</td>
<td></td>
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</tbody>
</table>

Subgroup analyses which looked at disease severity of UC and of CD against changes in Hb levels over the 12 weeks showed significant increases in Hb in each disease severity subgroup of similar magnitudes. This suggests that response to Feraccru® in the IBD population is not influenced by their disease severity at baseline. IBD aetiology (i.e. whether patients had UC or CD) did not impact the response to Feraccru®. As expected, patients with lower Hb levels at baseline responded better to Feraccru®. Disease severity of UC and CD was assessed monthly using the SCCAI and CDAI scales to evaluate changes in disease severity from baseline (see appendix) in the AEGIS studies as well as in the open label extension study. (12;14)

Secondary outcome measures included evaluation of serum ferritin and percentage transferrin saturation (TSAT). As Table 2 shows, there were clinically relevant increases in serum ferritin levels and transferrin saturation levels in the Feraccru® group to within the normal ranges. (15;16)

The open-label extension study was conducted for an additional year following the randomised treatment period of the AEGIS studies. Of the 128 patients included in AEGIS 1 and 2, 97 (n=50 from the ferric maltol arm and n=47 from the placebo arm) were enrolled in the extension study to receive Feraccru® 30 mg twice daily for an additional 52 weeks. Seventy-three patients completed 12 months of the extension study, 37 from the Feraccru® arm and 36 from the placebo arm. During the open-label extension study, Hb levels of patients who had taken Feraccru® in the double-blind phase continued to increase to an average of 14g/dL by around 48 weeks after which levels levelled and remained stable. In comparison, patients who took Feraccru® after taking 12 weeks of placebo showed a rapid increase in Hb levels by 24 weeks, after which there appeared to be no difference compared to the group who had received Feraccru® throughout. In these patients, Hb rose to an average of around 13g/dL by 64 weeks. Serum ferritin levels continued to show an upward trend from 12 weeks to 64 weeks in both groups with serum ferritin concentrations of around 40-60 micrograms/L at 64 weeks. Ferric maltol did not exacerbate IBD (median SCCAI and CDAI scores did not worsen) during this open label extension study. (12)
Feraccru randomised to placebo or suffered with UC or CD worsened (in study has similar planned inclusion/exclusion criteria as for patients with IDA and IBD. The week comparison with IV iron will be available in the future. Tolerated orally administered ferrous sulphate is likely to be well tolerated, and is unlikely to make patients IBD worse, even in this population with prior intolerance to oral ferrous salts. However, the studies were relatively small in size and of short duration given the number of patients in practice to whom the results may potentially be applicable to. The relatively small size of the study precluded statistical analysis of safety data and of some efficacy data describing secondary outcome measures. The AEGIS studies found that Feraccru® led to a statistically and clinically significant improvement in Hb concentration in patients with mild to moderate IDA at baseline but it is not clear how these results would apply to patients with more severe IDA at baseline. Finally the AEGIS studies compared Feraccru® with placebo. (14) Data comparing Feraccru® with oral ferrous sulphate or IV iron complexes would be clinically useful to help define their relative places in therapy. At present, therefore, it is unknown how effective and tolerable Feraccru® is compared to other treatment options for IDA such as oral ferrous sulphate or IV iron dextran. Indirect comparisons are difficult due to important variances between study populations involved in pertinent placebo controlled studies.

The manufacturer of Feraccru® intends it to be used in a population of patients with IDA associated with IBD who had already tried and not tolerated orally administered ferrous salts; therefore they have not designed trials comparing Feraccru® with these. (17) However, direct comparison with IV iron will be available in the future since the manufacturer is supporting a phase III randomised, controlled, multicentre, 52-week safety and efficacy study (NCT02680756) which is currently in progress and is designed to compare Feraccru® with IV iron (Ferinject) in 240 patients with IDA and IBD. The primary outcome measure (change in Hb from baseline) will be evaluated after 12 weeks of treatment and the study has similar planned inclusion/exclusion criteria as for patients in the AEGIS studies. Data can be expected in 2017. (14,18)

4. Critical evaluation
4.1. Clinical application
The phase II study (n=23) was small, uncontrolled and of open-label design used a different formulation of ferric maltol to Feraccru® so it was not described in detail in this review. (11) The pivotal AEGIS studies were adequately powered to observe a difference in primary outcome between treatment and placebo groups, the randomisation method is reliable, the groups are reasonably well matched at baseline and double-blinding and masking methods were adequate. The studies suggest that Feraccru® is likely to be well tolerated, and is unlikely to make patients IBD worse, even in this population with prior intolerance to oral ferrous salts. However, the studies were relatively small in size and of short duration given the number of patients in practice to whom the results may potentially be applicable to. The relatively small size of the study precluded statistical analysis of safety data and of some efficacy data describing secondary outcome measures. The AEGIS studies found that Feraccru® led to a statistically and clinically significant improvement in Hb concentration in patients with mild to moderate IDA at baseline but it is not clear how these results would apply to patients with more severe IDA at baseline. Finally the AEGIS studies compared Feraccru® with placebo. (14) Data comparing Feraccru® with oral ferrous sulphate or IV iron complexes would be clinically useful to help define their relative places in therapy. At present, therefore, it is unknown how effective and tolerable Feraccru® is compared to other treatment options for IDA such as oral ferrous sulphate or IV iron dextran. Indirect comparisons are difficult due to important variances between study populations involved in pertinent placebo controlled studies.

4.2. Safety
4.2.1. Key adverse events
In the AEGIS studies, safety and tolerability of Feraccru® and of placebo were assessed based on adverse events, vital sign measurements and routine haematological and biochemical analysis of blood. Patients whose Hb levels fell to ≤ 8.5g/dL withdrew from the trial as did patients whose UC or CD worsened (worsening was defined as SCCAI score increasing to ≥ 5 or CDAI score increasing to ≥ 320) or patients who become pregnant or suffered with serious adverse effects related to study medication. Discontinuations due to adverse effects (mostly gastrointestinal adverse effects including abdominal pain, diarrhea, constipation and flatulence) occurred in 13% of all patients randomised to Feraccru® and in 8% of all randomised to placebo. In those who completed the study, treatment emergent adverse events (TEAE’s) were reported by 58% of patients taking Feraccru® and by 72% taking matched placebo. The most common adverse events were mild to moderate gastrointestinal effects reported by 38%

<table>
<thead>
<tr>
<th>Secondary outcome measures</th>
<th>Baseline value</th>
<th>Value after 12 weeks treatment with Feraccru®</th>
<th>Baseline value</th>
<th>Value after 12 weeks treatment with oral matched placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ferritin level</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(18-270mcg/L men &amp; 18-160mcg/L women)</td>
<td>8.6 mcg/L</td>
<td>26 mcg/L</td>
<td>8.2 mcg/L</td>
<td>9.8* mcg/L</td>
</tr>
<tr>
<td>Change from baseline in value</td>
<td>+ 17.3 mcg/L</td>
<td>+1.2* mcg/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline transferrin saturation levels (TSAT)</td>
<td>10.6 %</td>
<td>28.5 %</td>
<td>9.5 %</td>
<td>9.6 %</td>
</tr>
<tr>
<td>(20% to 50%)</td>
<td>Change from baseline in value</td>
<td>+18 %</td>
<td>+0.3 %</td>
<td></td>
</tr>
<tr>
<td>SCCAI score in patients with UC, n=58</td>
<td>2.0</td>
<td>2.5</td>
<td>2.0</td>
<td>1.5</td>
</tr>
<tr>
<td>(0–19, lower scores indicate more quiescent UC)</td>
<td>Change from baseline in value</td>
<td>+0.5</td>
<td>-0.5</td>
<td></td>
</tr>
<tr>
<td>CDAI score in patients with CD, n=70</td>
<td>75.0</td>
<td>51.7</td>
<td>108.0</td>
<td>109.0</td>
</tr>
<tr>
<td>(0 to over 600, lower scores indicate more quiescent CD)</td>
<td>Change from baseline in value</td>
<td>- 23.3</td>
<td>+ 1.0</td>
<td></td>
</tr>
<tr>
<td>IBDD score</td>
<td>175.6</td>
<td>179.7</td>
<td>171.0</td>
<td>176.0</td>
</tr>
<tr>
<td>(0-224, higher scores indicate better quality of life)</td>
<td>Change from baseline in value</td>
<td>+ 4.1</td>
<td>+ 5.0</td>
<td></td>
</tr>
<tr>
<td>SF-36 symptom score**</td>
<td>0.3%</td>
<td>18%</td>
<td>-3.4%</td>
<td>6.8%</td>
</tr>
<tr>
<td>(Mean population score 50%. Higher scores indicate better health).</td>
<td>Change from baseline in value</td>
<td>17.7%</td>
<td>10.2%</td>
<td></td>
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</tbody>
</table>

* High variability seen in placebo group for this secondary outcome measure.
** Greatest improvement in SF-36 score was in the vitality domain: m18% in the Feraccru® group and 7% in the placebo group. Statistical analysis was not carried out for secondary outcome measures.

This LMEN review is produced by the NHS for the NHS and is not to be used for commercial and marketing purposes.
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 either group and diarrhoea (8% vs. 10%) and vomiting (2% vs. 3%) were more common in the placebo group. Data from the open label extension study show that the rate of reported adverse effects possibly related to Feraccru® to week 64 rose from an average of 18% to 24%. Abdominal pain increased in incidence from 6% to 7% and discontinuations due to abdominal pain rose to 3% (from 1% in the 12 week study). Patients continued to discontinue because of flatulence, constipation and diarrhoea. One patient discontinued due to severe abdominal pain (flare-up of CD). The manufacturer reported that the adverse event profile in the open-label phase confirms the benign safety profile of Feraccru®. (12;14) These data suggest that Feraccru® may be tolerated in many patients who have reported previous intolerance of oral ferrous salts.

The only non-gastrointestinal adverse effect which was more common in the Feraccru® group was arthralgia (5% vs. 2%). All other non-gastrointestinal adverse effects did not occur more frequently in the Feraccru® group; nasopharyngitis (7% vs. 12%). Similarly fatigue (3% vs. 5%), headache (2% vs. 5%), upper respiratory tract infection (2% vs. 3%), oropharyngeal pain (0% vs. 5%), allergy (0% vs. 3%) and pruritus (0% vs. 3%) were all more often reported in the placebo group. (14)

**Disease severity of UC and CD with use of ferric maltol**

Concern that Feraccru® could potentially lead to exacerbation of IBD were not borne out in AEGIS studies. Although rectal haemorrhage was more common in the Feraccru® group, IBD flare-ups did not occur more frequently in the Feraccru® group compared with placebo and disease symptom scores did not worsen with use of Feraccru®. In fact, for patients with CD, use of Feraccru® led to improved CDAI scores compared to placebo, although it should be noted that they were in remission from baseline. For patients with UC, disease severity in patients using Feraccru®, based on the SCCAI score, seemed to worsen slightly but there was no statistical analysis of the marginal difference between treatment and placebo groups. The EPAR for Feraccru® states that Feraccru® did not exacerbate IBD during the AEGIS studies or the open label extension study. (19)

### 4.2.2. Risk assessment.

Identified risks or potential risks with the use of Feraccru® and steps to mitigate these risk the EPAR for Feraccru® were: (19)

- Gastrointestinal side effects; monitoring for early symptoms is advised to help prevent side effects and patients should be advised to talk to their doctor if these develop.
- Interactions with other medicines; It is advised that Feraccru® is taken 2 hours apart from other medicines.
- Worsening of disease symptoms; this is a theoretical risk of which there was no evidence from the AEGIS trials in patients treated with Feraccru® for 12 weeks compared with placebo. The EPAR notes that CD or UC disease activity scores did not get worse from start of treatment to 64 weeks of treatment. There is no risk mitigation advice in the EPAR but clinicians may wish to be aware of the hypothetical concern about this.
- Hypersensitivity and allergic reactions; the EPAR notes that some of the ingredients in Feraccru® may cause an allergic reaction, namely the colourants E110 and E129. They advise that patients with a known allergy to these colourants should not take Feraccru®.
- Currently, there are no data for use of Feraccru® in patients who are pregnant, breast-feeding or under 18 years of age and therefore it should not normally be used in these groups.

In comparison, all IV iron products have a small risk of causing allergic reactions which can be life-threatening if not treated promptly. The European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) that IV iron products should only be administered when staff trained to evaluate and manage anaphylactic and anaphylactoid reactions are immediately available as well as resuscitation facilities; and that all patients should be closely observed for signs and symptoms of hypersensitivity reactions during and for at least 30 minutes following each injection of an IV iron product. (20)

### 4.3. Potential advantages and disadvantages over existing technologies

#### 4.3.1. Convenience

Compared with IV iron products, oral Feraccru® is more convenient for patients. There is no need for outpatient hospital visits to take place (as is required for IV drug administration) and the time needed for monitoring for hypersensitivity reactions afterwards is saved. However, whereas with IV iron, a few (around 1-4) outpatient visits for treatment of IDA would suffice to raise Hb level to target, with Feraccru®, patients would need to take their medication for a longer period of time to achieve similar Hb target levels. In patients with IBD, who would have earlier resolution of symptoms, uptake of Feraccru® by some patients who would otherwise have been candidates for IV iron, may reduce waiting times for others (i.e. those needing urgent treatment).

Compared with other oral iron products, Feraccru® is just as convenient to take, and compliance and reported adverse effects data from the pivotal trials suggest that Feraccru® may be a useful and reasonably well tolerated option in many patients with prior intolerance to oral ferrous salts.

#### 4.3.2. Healthcare resource utilisation

Feraccru® offers an alternative to IV iron products and fewer patients needing to have IV iron may have the effect of freeing up time that medical and nursing staff currently dedicate to the administration and monitoring associated with IV iron administration. In areas where there are waiting lists for patients to receive IV iron infusions, uptake of Feraccru® by some patients who would otherwise have been candidates for IV iron, may reduce waiting times for others (i.e. those needing urgent treatment).

No additional monitoring or precautions are required (compared with the monitoring needed with use of other oral iron products such as ferrous sulphate). Monitoring for adverse effects and for change in Hb levels and other biochemistry could take place in primary care and potentially be guided by Shared Care Agreements (SCA’s).
4.3.3. Suitability for shared care

It is expected that Feraccru® would be initiated by gastroenterologists but could be continued by GP’s if local funding agreements are in place.

4.3.4. Drug cost and likely budgetary impact

Feraccru® compared to intravenous iron

Feraccru is priced at £1.70 per day which may offer a saving per patient compared to IV iron products. In the budget impact model provided by the manufacturer, a saving was demonstrated with use of Feraccru® over Ferinject. However the model does not compare against any other IV iron products nor does it compare with any other orally administered iron product. (17)

Table 3: Budget Impact Model for Feraccru from Shield Therapeutics per patient per treatment course: (17)

<table>
<thead>
<tr>
<th></th>
<th>Ferric maltol (Feraccru®)</th>
<th>Ferinject® - 1000mg weekly (≤70kg patient)</th>
<th>Incremental</th>
<th>Assumptions and limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug cost</td>
<td>£310.46</td>
<td>£382.00</td>
<td>-£53.28</td>
<td>This model assumes use of Ferinject 1000mg weekly (given by a band 6 nurse) for up to 2 weeks and use of Feraccru® 30mg used twice daily for 6 months. An NHS Outpatient clinic visit +transport cost of £190 and GP visit cost of £38 based on NHS reference costs from 2013/14.</td>
</tr>
<tr>
<td>Outpatient visits</td>
<td>£162.00</td>
<td>£324.00</td>
<td>-£324.00</td>
<td></td>
</tr>
<tr>
<td>Patient transport</td>
<td>-</td>
<td>£10.84</td>
<td>-£10.84</td>
<td></td>
</tr>
<tr>
<td>GP visits</td>
<td>£38.00</td>
<td>-</td>
<td>£33.00</td>
<td></td>
</tr>
<tr>
<td>Nurse time</td>
<td>-</td>
<td>£30.30</td>
<td>-£30.30</td>
<td></td>
</tr>
<tr>
<td>Total cost per patient</td>
<td>£528.73</td>
<td>£747.14</td>
<td>-£218.41</td>
<td></td>
</tr>
<tr>
<td>Total cost per 100,000 of population*</td>
<td>£5287.30</td>
<td>£7471.40</td>
<td>-£2184.10</td>
<td></td>
</tr>
<tr>
<td>Final Hb (assumed baseline 10.9g/dL)</td>
<td>13.40</td>
<td>13.19</td>
<td>0.21</td>
<td></td>
</tr>
</tbody>
</table>

*There are no population data available from the manufacturer estimating how many patients there are in a health economy of 100,000 patients who may be eligible for treatment with Feraccru®, However, assuming that both UC and CD each have an incidence of approximately 10 per 100,000 of the population, 20 patients per 100,000 of the population would have IBD. It is estimated that the prevalence of IDA in patients with IBD varies from 20-76%, so assuming that around half (50%) of all patients with IBD might require treatment for IDA, this means that 10 patients per 100,000 patients in a population may require iron supplementation and some of these patients, who did not tolerate ferrous iron who are being considered for IV iron, could be candidates for receiving Feraccru®.

Feraccru® compared to other oral iron products

The NHS Drug Tariff (Part VIIIA Category M) price for 28 standard release tablets of ferrous sulphate is £1.75 so the cost for a twelve daily dose would be £3.50 per month of treatment. The Drug Tariff (Part VIIIA Category C) price for 84 tablets of ferrous fumarate is £2.75 for a month of treatment at thrice daily dosing. Feraccru® will be priced at £1.70 per day so per month, it would cost £47.60, significantly more than currently available oral iron products. However, note that the manufacturer intends Feraccru® to be second-line to these currently available oral iron products and so it may be more pertinent to compare the price with IV iron products such as Ferinject (see Table 3).

Health Economics

Health economic data for Feraccru® in patients with IBD were not available at the time of writing.

Likely commissioning and funding pathway

The likely commissioning pathway for oral Feraccru® is via CCG’s.

Suggested place in therapy

Feraccru® may be a useful treatment option in patients with mild to moderate IDA with either CD or UC who have reported intolerance to oral ferrous salts. In these patients, it should be considered as an alternative to IV iron products if there is no urgent need to raise Hb levels (e.g. prior to surgery). I.e. second line to other oral ferrous iron products and an alternative to IV iron products. It is expected that at least 12 weeks of treatment with Feraccru® would be required to raise Hb levels to target, after which it should be used for 1-3 months afterwards as is the current practice with other orally administered iron products in IBD. Data for use of Feraccru® for up to 12 months is available to support safe use in patients who require continued use for a longer period of time. The decision to discontinue treatment with Feraccru®, as with other orally administered iron products, is a clinical one. However, the open-label extension study suggests that Feraccru® is unlikely to confer further benefit with respect to increase in Hb after 12 months of use. Feraccru® is only licensed currently for patients with underlying IBD and off-label prescribing for other indications associated with IDA should be challenged.

Reference List

(3) Goddard, AF, James, MW. McIntyre, AS. Management of iron deficiency anaemia. Gut 2011; 60:1309-1316.
CDAI score for patients with CD: Frequently used to assess disease severity. It gives a score ranging from 0 to over 600, based on a diary of symptoms kept by the patient for 7 days, and other measurements such as the patient’s weight and haematocrit. A CDAI score of less than 150 is considered to be remission, a score greater than 150 is considered to be moderate to severe disease, and a score greater than 300 is considered to be severe disease.

IBDQ scores: Quality of life (QoL) questionnaire for patients with inflammatory bowel diseases consisting of 32 questions grouped into 4 dimensions; bowel, systemic, social and emotional. The IBDQ scores are: 1 (poorest quality of life) to 7 (best quality of life).

Short Form Health Survey (SF-36): Covers 36 items grouped into 8 general domains: physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems and mental health. Mean population score is 50 and higher scores indicate better health.

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Appendix: Scoring systems

IBDQ score for patients with UC: A validated symptom based index score from 0–19 with lower scores indicating more quiescent UC. The index is based on scores for five clinical criteria which are bowel frequency day and night, urgency of defecation and blood in stool, general wellbeing and extra colonic features.

CDAI score for patients with UC: A validated clinical index score from 0–220. A score below 150 is considered to be quiescent UC, a score between 150 and 199 is considered to be active UC with lower scores indicating more quiescent UC. The index is based on scores for five clinical criteria which are bowel frequency day and night, urgency of defecation and blood in stool, general wellbeing and extra colonic features.

Quality of Life (QoL) project: Quality of Life Concepts University Health Network (Toronto, ON and the Centre for Interdisciplinary Research in Rehabilitation and Social Integration Canada.

Quality of life questionnaire for IBD with 36 items grouped into 8 domains. The questionnaire is completed by a single patient or caregiver.

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