Formulary Support Document

Adverse events should be reported.
Reporting forms and information can be found at
https://yellowcard.mhra.gov.uk/
Adverse events should also be reported to Norgine Pharmaceuticals Ltd on:
Tel. +44 (0)1895 826 606
E-mail medinfo@norgine.com

This document contains FERACCRU® promotional messaging.

	UK - GB[1]; NI[2]
MA holder	Norgine Pharmaceuticals Limited (GB); Norgine B.V. (NI)
MA number	PLGB 20011/0063 (GB); EU/1/15/1075/001, EU/1/15/1075/002 (NI)
Trade name	FERACCRU®
Generic name	Ferric maltol
Indication	The treatment of iron deficiency in adults

Image not to scale – for illustrative purposes only

Document no: UK-HAE-FER-2100084
Date of preparation: September 2021

Prescribing Information and Adverse Event reporting is available at the end of this document

Table of contents

Introduction

This formulary support document has been produced by Norgine to act as a repository of information that could assist with formulary submissions. It is comprised of key information related to the licence for FERACCRU® along with clinical study data.

Summaries

Within the text, short summaries have been included which provide top line information, along with references. These are marked with the notepad symbol (see left) and are contained within the blue and grey boxes.

References:

Further information

Please contact Medical Information at Norgine Pharmaceuticals Ltd by email: **medinfo@norgine.com** or phone: +44 1895 826606 if you would like any further information.

Glossary

Therapy Area:

- ID – Iron Deficiency
- IDA – Iron Deficiency Anaemia
- IBD – Inflammatory Bowel Disease
- CD – Crohn's Disease
- UC – Ulcerative Colitis
- SCCAI – Simple Clinical Colitis Activity Index
- CDAI – Crohn's disease activity index
- OFP – Oral ferrous product
- IM – Intramuscular
- IV – Intravenous
- DMT1 – Divalent metal transporter 1
- CKD – Chronic Kidney Disease

Measures:

- Hb - Haemoglobin
- TSAT – Percentage transferrin saturation
- C_{MAX} – Maximum Concentration
- AUC – Area under the curve
- CHr – reticulocyte Hb content

Licence:

- SmPC – Summary of Product Characteristics
- PIL – Patient Information Leaflet

Study Design:

- FAS – Full analysis set
- ITT – Intention to treat
- PP – Per protocol
- BD – twice daily
- PE – Primary endpoint
- OLE – Open label extension
- ESA – Erythropoiesis stimulating agent
- TEAE – Treatment emergent adverse event
- AE – adverse event
- SAE – serious adverse event
- IBDQ – Inflammatory bowel disease questionnaire
- QoL – Quality of life
- SF-36 – 36-item Short-Form questionnaire
- EOS – End of study

Statistics:

- SD – Standard deviation
- SE – Standard error
- LSM – Least squares mean
- SE – Standard error
- ANCOVA – Analysis of covariance
- OR – Odds ratio
- CI – Confidence interval

Economics:

- HTA – Health Technology Assessment
- NICE – The National Institute for Health and Care Excellence
- SMC – Scottish Medicines Consortium
- AWMSG – All Wales Medicines Strategy Group

Prescribing Information and Adverse Event reporting is available at the end of this document

Key Points

- FERACCRU® is indicated for the treatment of iron deficiency in adults[1,2]
- FERACCRU® contains the ferric form of iron (Fe^{3+})[1,2]
- FERACCRU® is a stable complex: ferric iron is tightly bound to three maltol molecules (a naturally-occurring sugar derivative)[1–3]
- Unlike oral ferrous (Fe^{2+}) salts, the Fe^{3+} in FERACCRU® remains tightly bound to maltol until the point of iron absorption[1,2,4,5]
- In a phase III clinical trial programme investigating treatment of patients with IDA (Hb ≥ 9.5g/dL) with mild-to-moderate IBD (without flare) versus placebo[3]:
  - FERACCRU® increased Hb concentrations by 2.25g/dL from baseline (at 12 weeks)
  - 66% of patients in the FERACCRU® group had normal* Hb levels (percentage based on a responder analysis at 12 weeks)
  - Efficacy of FERACCRU® was not affected by IBD type, severity or time since flare
- Common undesirable effects include gastrointestinal symptoms such as abdominal pain, flatulence, constipation, abdominal discomfort/distension, diarrhoea, discoloured faeces and nausea[1,2]

* normal Hb; women ≥12g/dL; men ≥ 13g/dL[3]

Dosage and administration

The recommended dose is one capsule twice daily, morning and evening, on an empty stomach

References:
Feraccru 30mg hard capsules - Summary of Product Characteristics (SmPC). Available from:
https://www.medicines.org.uk/emc
https://www.emcmedicines.com/en-GB/northernireland

Each FERACCRU® capsule contains 30mg iron (as ferric maltol), excipients include[1,2]:

Capsule Contents:
- Lactose monohydrate
- Sodium laurilsulfate
- Magnesium stearate
- Colloidal anhydrous silica
- Crospovidone (Type A)

Capsule Shell:
- Hypromellose
- Brilliant Blue (E133)
- Allura Red AC (E129)
- Titanium dioxide (E171)
- Sunset Yellow FCF (E110)

The recommended dose is one capsule twice daily, morning and evening, on an empty stomach[1,2]. Patients should take FERACCRU® with half a glass of water (one hour before a meal, or at least 2 hours after a meal)[6,7].

Treatment duration will depend on 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 iron stores, according to blood tests[1,2].

No dose adjustment is needed in elderly patients. FERACCRU® has not been studied in patients with impaired renal (eGFR<15 ml/min/1.73 m^2) and/or impaired hepatic function[1,2]. Information about drug interactions is included in table 1 below.

Interaction with other medicines

Description	Advice
Concomitant administration of FERACCRU® and intravenous iron may induce hypotension/collapse	Avoid concomitant administration
Oral iron is known to reduce the absorption of penicillamine, bisphosphonates, ciprofloxacin, entacapone, levodopa, levofloxacin, levothyroxine (thyroxine) moxifloxacin, mycophenolate, norfloxacin and ofloxacin	These medicines should be given at least 2 hours apart from FERACCRU®
Absorption of both iron and antibiotic may be reduced if oral iron is given with tetracycline	Administration of iron preparations and tetracyclines should be separated by 2 to 3 hours
Absorption of oral iron may be reduced by calcium and magnesium salts (such as magnesium trisilicate)	Administration of iron preparations with such compounds should be separated by at least 2 hours

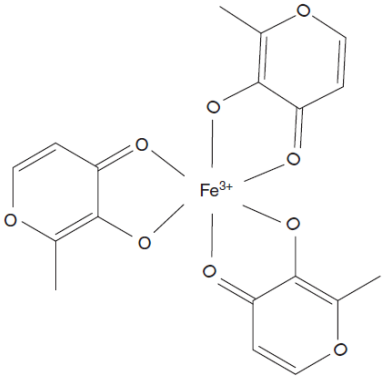
Table 1: Interaction with other medicinal products[1,2]

Mode of Action

FERACCRU® contains iron in a stable ferric state as a complex with a trimaltol ligand. The complex is designed to provide, in a controlled way, utilisable iron for uptake across the intestinal wall.

The complex dissociates on uptake from the gastro-intestinal tract.

References:
Feraccru 30mg hard capsules - Summary of Product Characteristics (SmPC). Available from: https://www.medicines.org.uk/emc



FERACCRU®, ferric maltol, contains a ferric (Fe^{3+}) iron that is chelated with 3 maltol molecules (3-hydroxy-2-methyl-4-pyrone) (see figure 1)[4].

The complex is designed to provide, in a controlled way, utilisable iron for uptake across the intestinal wall and transfer to the iron transport and storage proteins in the body (transferrin and ferritin, respectively). The complex dissociates on uptake from the gastro-intestinal tract and the complex itself does not enter the systemic circulation[1,2].

Figure 1: Image from: Stallmach & Buning 2015[4]

Iron absorption

Dietary iron (haem and non-haem iron) is absorbed in the duodenum and proximal jejunum[8]. The iron content of FERACCRU® is available for transport into the enterocytes via the route(s) available to non-haem iron.

DMT1 (divalent metal transporter 1) is key for the absorption of iron from the gut lumen into the enterocyte (figure 2), and the subsequent transport of iron into the systemic circulation is reliant on the another transmembrane domain protein, ferroportin[8].

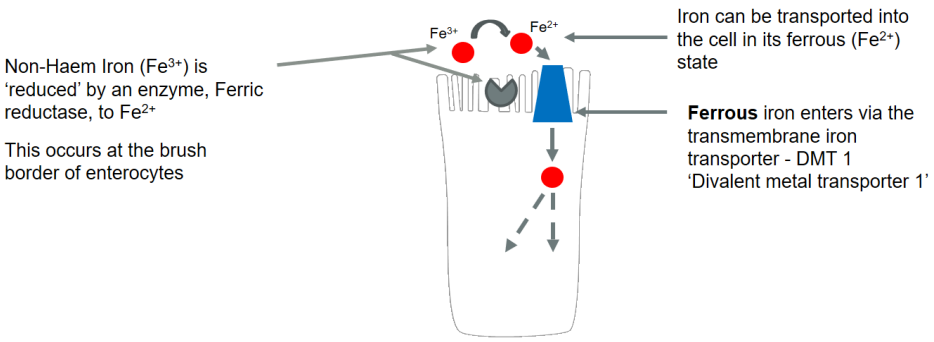


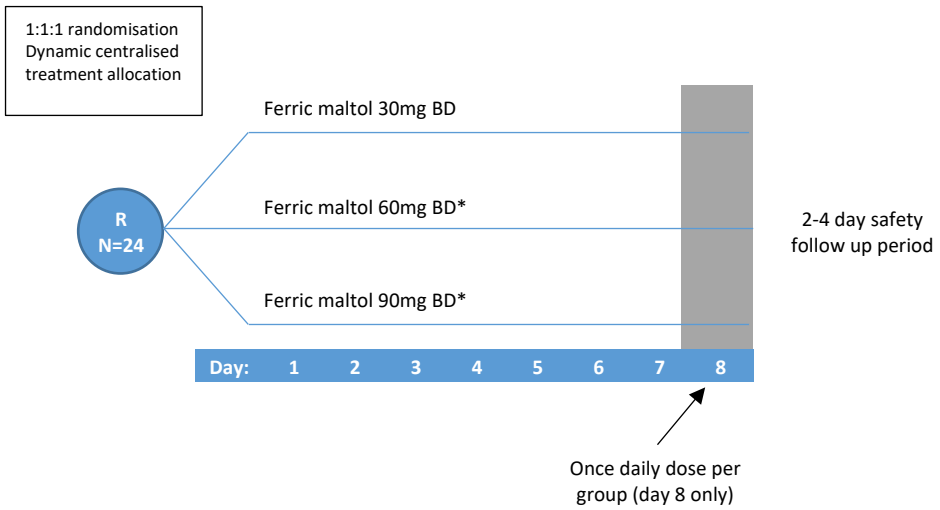
Figure 2: DMT1 transport of iron into the enterocyte from the gut lumen[9]

Another potential pathway for iron absorption is the β3 integrin pathway, where the uptake of ferric (Fe^{3+}) can occur by ligand exchange. The relative importance of this pathway compared with the DMT1 pathway is not known in humans[10].

Clinical Pharmacology: Phase I study

Randomized Open-Label Phase 1 Study of the Pharmacokinetics of Ferric Maltol in Inflammatory Bowel Disease Patients with Iron Deficiency[11]

Bokemeyer B, Krummenerl A, Maaser C et al. 2016

<table>
<tr><td>Study Design</td><td colspan="2">Phase I, prospective, open-label, randomised study</td></tr>
<tr><td>Aim</td><td colspan="2">To evaluate the pharmacokinetics of ferric maltol and its effect on iron indices in IBD patients with iron deficiency (with or without anaemia)</td></tr>
<tr><td>Patients</td><td>Key inclusion criteria</td><td>Key exclusion criteria</td></tr>
<tr><td></td><td>• Diagnosis of IBD (CD or UC)
• Aged ≥ 18 years
• Iron deficiency:
- Ferritin <30µg/L
OR
Ferritin <50µg/L with TSAT <20%
• With or without anaemia (Hb≥8.5g/dL)</td><td>• Untreated/untreatable severe malabsorption syndrome
• Previous major upper gastrointestinal surgery
• Known contraindication for treatment with iron preparations</td></tr>
<tr><td>Treatments, randomisation and follow-up</td><td colspan="2"> 

Patients were not permitted other oral or parenteral iron, blood transfusions, antibiotics or ESAs during relevant periods prior to, and during, the study

* Please note: licensed dose of FERACCRU® is 30mg BD, please review the summary of product characteristics for more information</td></tr>
<tr><td>Assessments</td><td colspan="2">• Baseline blood and urine pharmacokinetic samples
• Serum iron markers, plasma maltol, maltol glucuronide (0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0 and 6.0 hours post dose)
• Non-transferrin bound iron (5.0 min and 1.0, 2.0 and 4.0 hours post dose)
• Urine test for maltol glucuronide
• Safety assessments: TEAEs, blood/urine test abnormalities, changes in vital signs and concomitant medication use</td></tr>
</table>

Table 2: Phase I (Bokemeyer et al. 2016) study design[11]

Results

Of 28 patients randomised, 9, 8 and 7 patients were allocated to received 30mg, 60mg and 90mg BD of ferric maltol respectively. The mean age (range) across the 28 patients was 39 years (20-54), with 67% female. Within treatment arms the 90mg group had fewer female patients (42.9%) compared with the 30mg and 60mg dosing groups (77.8% and 75% respectively). The haematological characteristics were well matched between groups at baseline.

Pharmacokinetic results: Maltol

Plasma maltol, and the metabolite, maltol glucuronide increased at all doses, reaching C_{MAX} around 1.0–1.5 hours post-dose and returning to baseline after 3–6 hours. Maltol and maltol glucuronide measurements appeared dose proportional with BD dosing, with higher exposure to maltol glucuronide compared to maltol.

The mean day 1 $AUC^{0\text{-}t}$ was 26.6h·ng/ml (30mg BD group) and 105h·ng/ml (90mg BD group) for maltol, and 9.83h·µg/ml (30mg BD group) and 30.0h·µg/ml (90mg BD group) for maltol glucuronide. Mean day 8/day 1 ratios for C_{MAX} and $AUC_{0-\infty}$ indicated no accumulation after 7 days of BD dosing.

Pharmacokinetic results: Iron

Serum iron and TSAT increased with all doses, with C_{MAX} around 1.5–3.0 hours post-dose. Maximum serum iron concentrations were 32.3, 49.1 and 48.7 µmol/L for the 30mg BD, 60mg BD and 90mg BD groups. By 6 hours post-dose, the mean serum iron concentrations decreased to 11.8, 33.0 and 24.3 µmol/L respectively.

Pharmacokinetic results: Other

Serum ferritin and reticulocyte Hb content (CHr) increased by day 8, with greater improvements with 60 and 90 mg BD doses than with 30 mg BD doses.

Safety

In the safety analysis, 41.7% of patients experienced 14 TEAEs. Two were allocated to the 30mg dosing, 4 allocated to both the 60mg, and 90mg dosing groups. Gastrointestinal adverse events were the most commonly reported, occurring in 29 % of patients overall:

- Diarrhoea in 3/24 (12.5 %) patients
- Abdominal pain in 2/24 (8.3 %) patients

One serious adverse event (sacral abscess) was recorded but not thought to be related to study medication. No deaths during the study and no clinically relevant changes in clinical laboratory values or vital signs.

Evidence for use: IBD Phase III studies

In a phase III clinical trial investigating treatment of patients with IDA (Hb ≥ 9.5g/dL) with mild-to-moderate IBD (without flare) versus placebo:

- FERACCRU® increased Hb concentrations by 2.25g/dL from baseline (at 12 weeks)
- 66% of patients in the FERACCRU® group had normal* Hb levels (percentage based on a responder analysis at 12 weeks)
- Efficacy of FERACCRU® was not affected by IBD type, severity or time since flare
- In the extension study, 74% of patients completed 64 weeks of treatment
- The most common treatment-related AEs for FERACCRU® were abdominal pain, constipation and flatulence

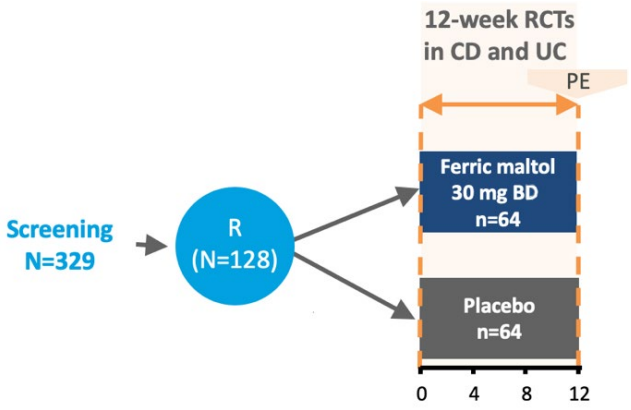
* normal Hb; women ≥12g/dL; men ≥ 13g/dL

References:
Phase III:
Gasche C, Ahmad T, Tulassay Z, Baumgart DC, Bokemeyer B, Büning C, 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. Inflammatory Bowel Diseases. 2015 Mar;21(3):579–88

Schmidt C, Ahmad T, Tulassay Z, Baumgart DC, Bokemeyer B, Howaldt S, 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 Aug;44(3):259–70.

Ferric Maltol Is Effective in Correcting Iron Deficiency Anemia in Patients with Inflammatory Bowel Disease: Results from a Phase-3 Clinical Trial Program (AEGIS 1 & 2)[3]

Gasche C, Ahmad T, Tulassay Z et al. 2015

<table>
<tr><td>Study design</td><td colspan="2">Two phase III, prospective, randomised, double-blind, placebo controlled, multicentre studies in patients with UC and CD, analysed as one data set</td></tr>
<tr><td>Aim</td><td colspan="2">Assess the efficacy and tolerability of FERACCRU® for the treatment of IDA in patients with IBD who were intolerant of, or unresponsive to, oral ferrous iron products</td></tr>
<tr><td>Patients</td><td>Key inclusion criteria</td><td>Key exclusion criteria</td></tr>
<tr><td></td><td>• Age ≥18 years
• Current diagnosis of quiescent UC as defined by SCCAI score of <4, or quiescent CD as defined by CDAI score of <220 (for more information on SCCAI and CDAI scores please see the appendix)
• Current diagnosis of IDA as defined by Hb ≥9.5 g/dl and <12.0g/dl for women and ≥9.5 g/dl and <13.0g/dl for men; ferritin < 30µg/l
• Prior OFP failure as defined per protocol
• If receiving protocol-allowed immunosuppressant must be on stable dose</td><td>• Anaemia due to any cause other than iron deficiency
• IM/IV/depot iron, blood infusions, or erythropoietin within 12 weeks of randomisation
• Oral iron supplementation use within 4 weeks of randomisation
• Use of immunosuppressant with known effect of anaemia induction within 4 weeks of randomisation
• Untreated Vitamin B-12 or Folic acid deficiency/treatment within 4 weeks
• Known hypersensitivity or allergy to FERACCRU®, or contraindication for treatment with iron preparations
• Other chronic or acute inflammatory or infectious diseases
• Creatinine > 2.0 mg/dl
• Abnormal liver function tests
• Pregnancy</td></tr>
<tr><td>Treatments</td><td colspan="2"> 

PE: Primary Endpoint</td></tr>
</table>

Assessments	**Primary endpoint:** • Change in Hb concentration from baseline to week 12 **Secondary endpoints:** • Changes in Hb concentration. Serum ferritin concentration, and TSAT from baseline to weeks 4 and 8 • Responder analysis; defined as patients with Hb increase of ≥1g/dL, ≥2g/dL, or Hb normalisation by week 12 (Normalisation defined as Hb ≥12g/dL for females or ≥13g/dL for males) • Clinical symptoms and disease-specific QoL assessments (SCCAI for patients with UC, CDAI for patients with CD) • General quality of life; SF-36 questionnaire • Safety/Adverse event monitoring

Table 3: AEGIS 1 & 2 Study design[3]

Study: Results

Patient population numbers

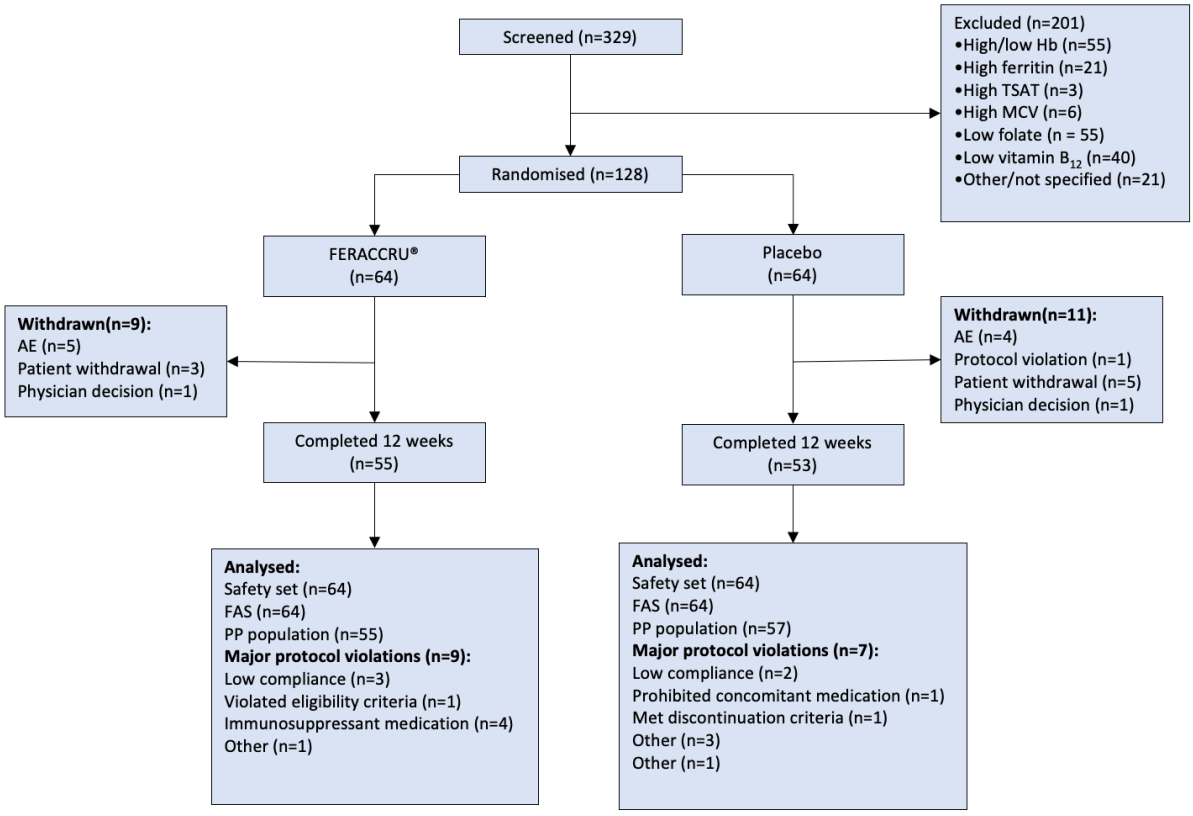


Figure 3: AEGIS 1 & 2 patient disposition[3]

Baseline characteristics were generally comparable between treatment groups. The mean age (SD) was similar in the FERACCRU® group (40.1 (13.5)) compared with the placebo group (38.5(12.3)), with a higher proportion of females in each group (63 vs 67% respectively). 45% (n=29) had UC in both FERACCRU® and placebo groups, with 55% (n=35) with CD. Baseline mean Hb was 11.0g/dL in the FERACCRU® group, and 11.1g/dL in the placebo group.

Hb endpoint:

For the primary efficacy analysis, a statistically significant increase in Hb concentration was observed with the FERACCRU® group, compared to placebo, at week 12. Absolute mean (SD) Hb concentrations improved from 11.00 (1.03) g/dL to 13.20 (1.04) g/dL at week 12 in the FERACCRU® group, compared to the placebo group, where Hb values were similar at week 12 compared to baseline (figure 4).

Using ANCOVA, the mean (SE) improvement in Hb for the FERACCRU® group versus placebo was 2.25 (0.12) g/dL, p<0.0001.

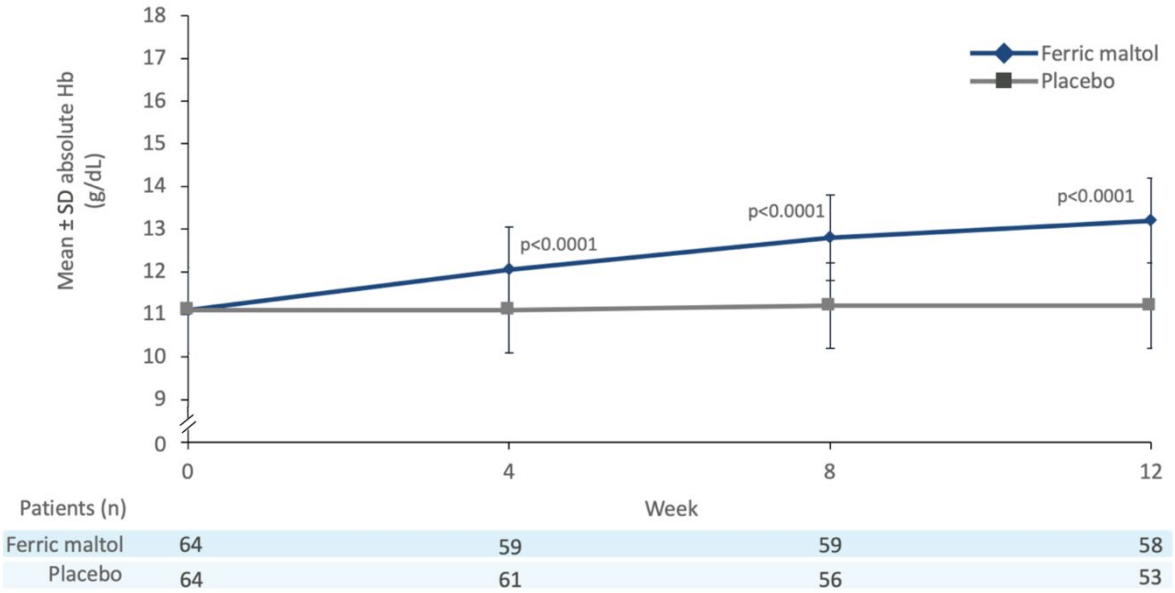


Figure 4: AEGIS 1 & 2: change in absolute Hb at Week 12

Figure 5 displays the results of the responder analysis for ≥1g/dL, ≥2g/dL and normalisation of Hb for both FERACCRU® and placebo groups. Ferric maltol versus placebo ORs were 41.8 (95% CI, 13.5–129.9) for ≥1 g/dL increases, not calculable for ≥2 g/dL increases, and 15.3 (95% CI, 5.9–39.3) for normalisation.

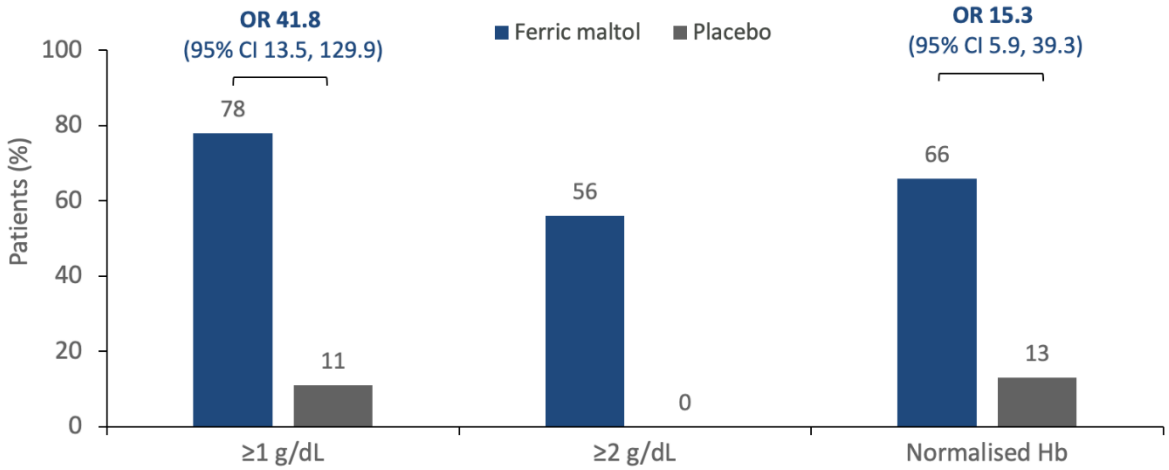


Figure 5: AEGIS 1 & 2: change from baseline and normalisation of Hb at Week 12 (responder analysis)

Iron indices:

Mean absolute levels of both serum ferritin and TSAT increased in the FERACCRU® group, with an improvement at 12 weeks, further details are provided along with the extension study data.

Safety & Tolerability

86% of the patients in the FERACCRU® group and 83% of the patients in the placebo group completed 12 weeks of treatment. 13 and 8% of patients discontinued due to adverse events, respectively. Adverse events were experienced by 58% of patients treated with FERACCRU® and 72% of patients treated with placebo.

Adverse events were mainly gastrointestinal in nature for both the FERACCRU® and placebo groups, the gastrointestinal TEAEs occurring in >2% of patients (either treatment arm) are included in the table below.

TEAEs occurring in >2% patients	Ferric maltol %	Placebo %
Abdominal pain	13.3	11.7
Diarrhoea	8.3	10
Constipation	8.3	1.7
Flatulence	6.7	0
Abdominal discomfort	5	0
Abdominal distension	3.3	0
Gastroesophageal reflux	3.3	0
Vomiting	1.7	3

Table 4: AEGIS 1 & 2: gastrointestinal TEAEs at Week 12

Ferric maltol therapy for iron deficiency anaemia in patients with inflammatory bowel disease: long-term extension data from a Phase 3 study[12]

Schmidt C, Ahmad T, Tulassay Z et al. 2016

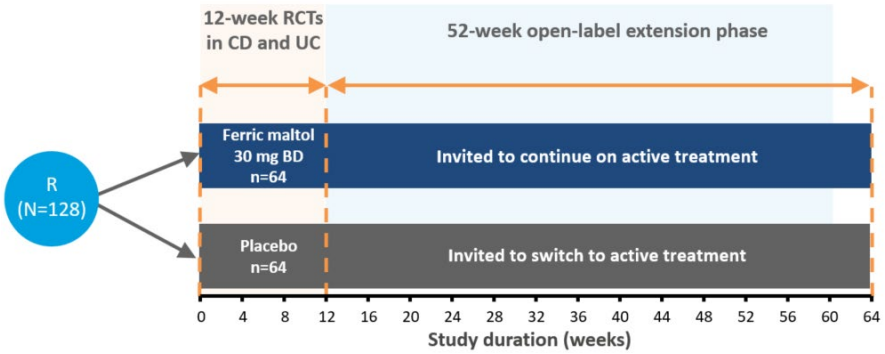
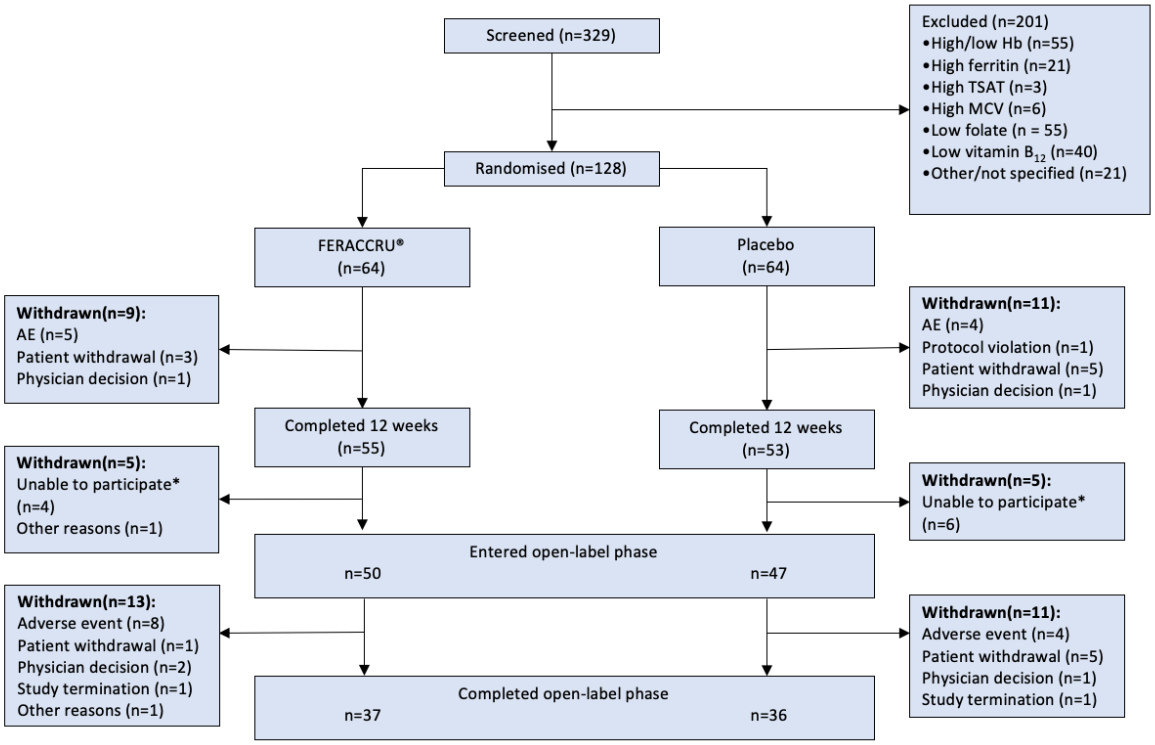
Study design	**A 52-week, open-label extension of the AEGIS 1 & 2 phase 3 study**	
Aim	To evaluate the long-term efficacy and safety with ferric maltol in inflammatory bowel disease patients in whom oral ferrous therapies had failed to correct iron deficiency anaemia	
Patients	**Key inclusion criteria**	**Key exclusion criteria**
	• All patients completing 12 weeks of randomised therapy from AEGIS 1 & 2	• N/A
Treatments		
Assessments	**Primary endpoint:** • Absolute change in Hb from baseline (day 0*) **Secondary endpoints:** • Proportion of patients achieving normalisation of Hb (Normalisation defined as Hb≥12g/dL for females or Hb≥13g/dL for males) • Absolute serum ferritin concentration/TSAT were measured at 4-12 weekly intervals • Disease specific quality of life (IBDQ) • General quality of life (SF-36) • Safety/adverse event monitoring *Day 0 refers to the beginning of randomised therapy	

Table 5: AEGIS 1 & 2 Extension Study design[12]

Study: Results

Patient population numbers



*Ten Austrian patients (4 initially randomised to FERACCRU® and 6 to placebo) did not have ethics approval to enter the open label phase.

Figure 6: AEGIS 1 & 2 Extension Patient Disposition[12]

50/64 patients initially randomised to receive FERACCRU® (the 'continued' group) and 47/64 patients initially randomised to placebo (the 'switch' group) entered the long-term extension.

Hb endpoints:

The mean (SD) Hb concentrations increased from 11.00 (1.03) g/dL at baseline to 13.95 (1.26) g/dL in the 'continued' group, and from 11.10 (0.85) g/dL at baseline to 13.33 (1.46) g/dL at week 64 in the 'switch' group (figure 7).

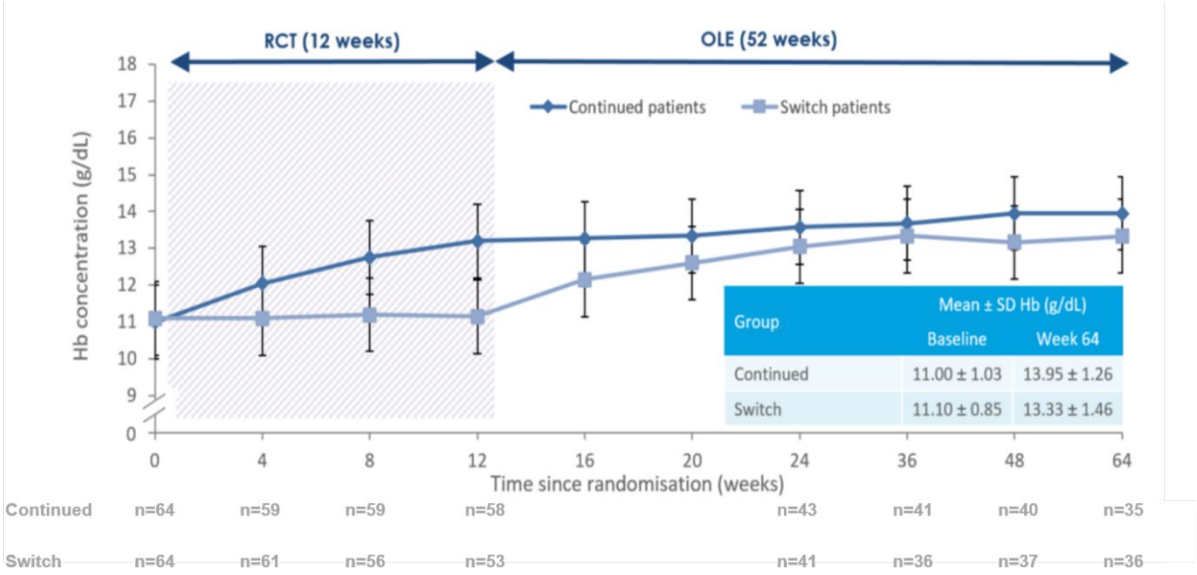


Figure 7: Absolute Hb concentrations in continued and switched patients up to Week 64[12]

78% of patients achieved normal Hb levels by week 16, which increased to 86% by week 64. (Normalisation defined as Hb ≥12g/dL for females or Hb ≥13g/dL for males)

Iron indices:

A numerical increase was seen for both serum ferritin and TSAT over the extension study, but without reaching statistical significance. Mean (SD) serum ferritin increased from 8.4 (6.6)µg/l (n=128) at baseline to 2.5 (42.9)µg/l (n=91) at week 16, and 57.4 (77.4)µg/l (n=72) up to week 64. Mean (SD) results for TSAT increased from 10% (10%) at baseline to 25% (17%) at week 16 and 29% (13%) up to week 64 (figure 8).

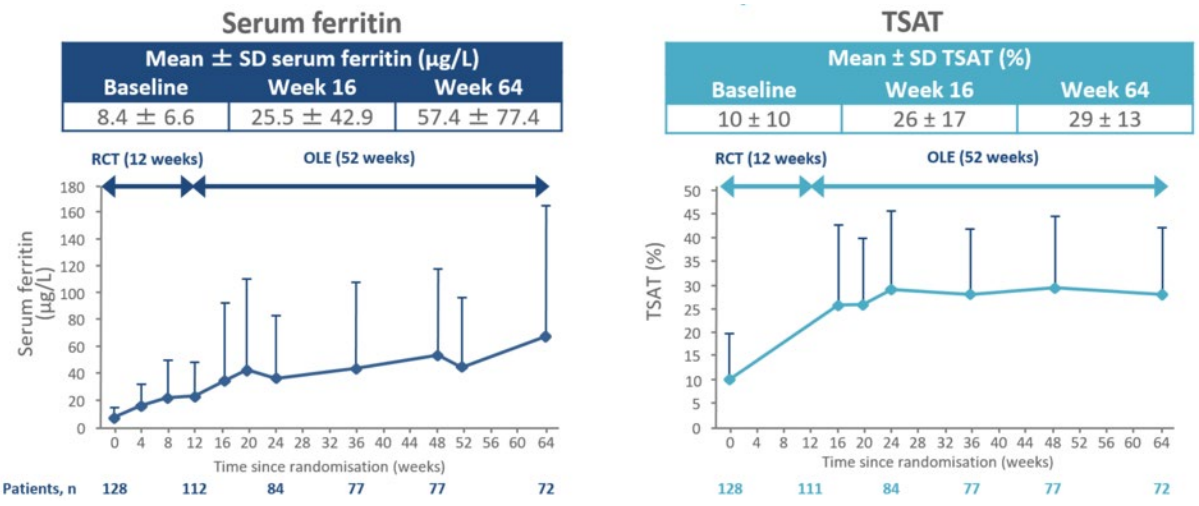


Figure 8: Absolute serum ferritin concentration and TSAT in patients treated with ferric maltol up to Week 64[12]

Prescribing Information and Adverse Event reporting is available at the end of this document

Disease activity and Quality of Life:

Ulcerative Colitis: mean (SD) total SCCAI scored decreased slightly from a baseline of 1.6 (1.140) to 1.3 (1.40) at Week 24 and 1.1 (1.29) at Week 64.

Crohn's Disease: mean (SD) total CDAI scored decreased slightly from a baseline of 95.9 (51.76) to 82.0 (61.10) at Week 24 and 64.4 (40.52) at Week 64.

No significant changes from baseline were observed for the quality of life measures in this study.

Safety and Tolerability:

AEs occurred in 63 (57%) of patients treated with FERACCRU® up to week 12, and 89 (80%) of patients treated over the entire study. 20 (18%) of AEs were considered to be related to study medication up to week 12, and 27 (24%) including the extension study. The most common AEs up to Week 64 were nasopharyngitis, abdominal pain and diarrhoea (see table 6).

N = 111	Incidence, n(%)	
	Up to Week 12	Up to Week 64
Nasopharyngitis	8 (7)	20 (18)
Abdominal Pain	15 (14)	18 (16)
Diarrhoea	12 (11)	16 (14)
Ulcerative Colitis (exacerbation)	2 (2)	11 (11)
Flatulence	6 (5)	9 (8)
Arthralgia	4 (4)	9 (8)
Crohn's Disease (exacerbation)	3 (3)	8 (7)
Constipation	6 (5)	7 (6)
Abdominal pain (upper)	4 (4)	6 (5)
Nausea	2 (2)	5 (5)

Table 6: Ten most frequent AEs reported up to Week 64[12]

Evidence for use: CKD Phase IIIb study

Oral Ferric Maltol for the Treatment of Iron-Deficiency Anemia in Patients With CKD: A Randomized Trial and Open-Label Extension[13]

Pergola P. and Kopyt N. 2021

Objective

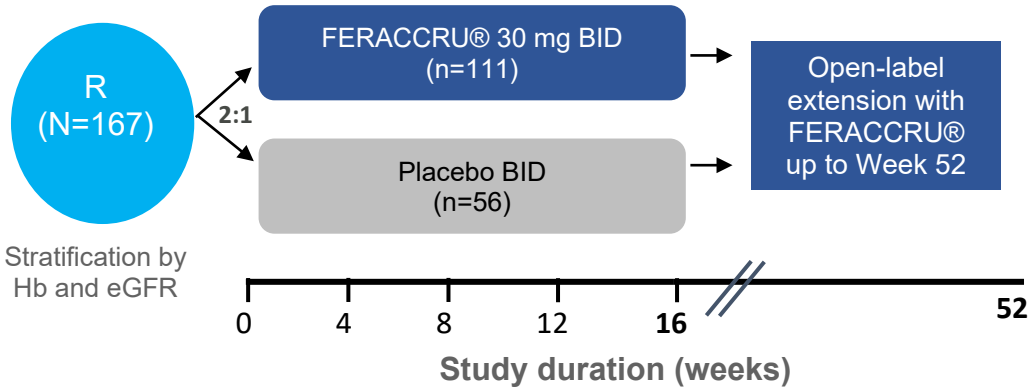
Evaluate the safety and efficacy of oral ferric maltol in patients with stage 3 or 4 CKD.

Methods

Study Design:

- Prospective, multicentre, phase 3b, double blind, randomised controlled trial with open label extension

Patients:



Key inclusion Criteria
• eGFR ≥15 to <60 mL/min/1.73 m^2
• Hb ≥8.0 to <11.0 g/dL *and* ferritin <250 µg/L + TSAT <25% *or* ferritin <500 µg/L + TSAT <15%

Table 7: Key inclusion criteria

Primary endpoint (week 16):

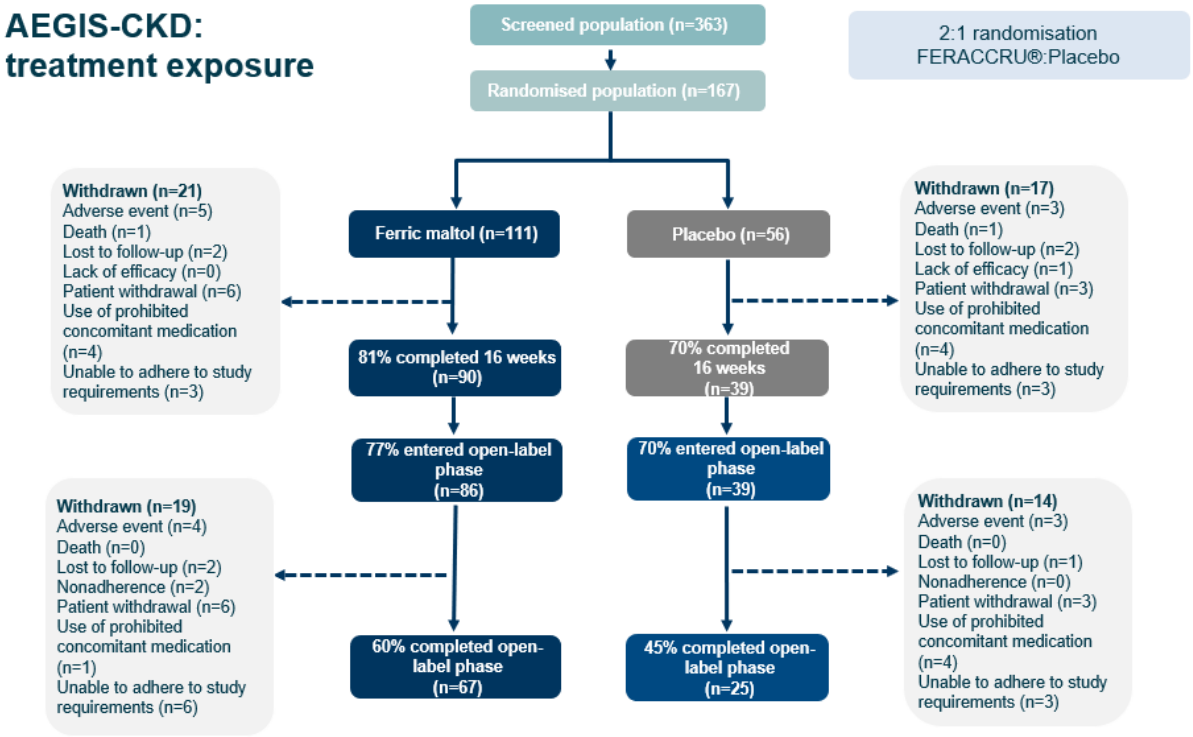
- Change in Hb concentration from baseline

Key secondary efficacy endpoints:

- ≥1 g/dL and ≥2 g/dL Hb increases at Week 16
- Hb ≥11 g/dL at Week 16
- Hb changes from baseline to Week 4 and Week 8
- Changes in ferritin, TSAT and serum iron
- Treatment-emergent AEs and SAEs

Study: Results

Patient population numbers



81% (90/111) patients allocated to receive FERACCRU® were able to complete 16 weeks of treatment, compared to 70% (39/56) of patients allocated to receive placebo.

125 patients started open-label FERACCRU®; of these 92 (74%) completed the open-label treatment period.

Hb endpoints:

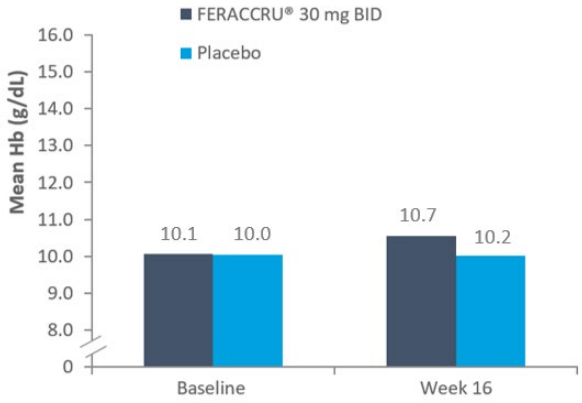


Figure 9: Primary endpoint: Hb change at week 16 (adapted from Pergola and Kopyt, 2021[13])

For the primary endpoint evaluating the mean change in Hb from baseline, the LSM (SE) difference for FERACCRU® vs placebo was reported as 0.6 ± 1.3 (SD) g/dL in the FERACCRU® group and −0.1 ± 1.0 g/dL in the placebo group (Fig 9). The difference between groups was statistically significant (least-squares mean [LSM], 0.5 g/dL; SE, p = 0.01).

Improvements in Hb in patients receiving FERACCRU® during double-blind treatment were maintained with continued open-label FERACCRU® to week 52 (Fig 10), with a total increase of 0.7 g/dL from baseline to week 52.[13] Changes in Hb for patients moving from placebo (double-blind period) to FERACCRU® in the open label period mirrored those seen with FERACCRU® during double-blind treatment (Fig 10), with a total increase of 0.5 g/dL by week 52.[13]

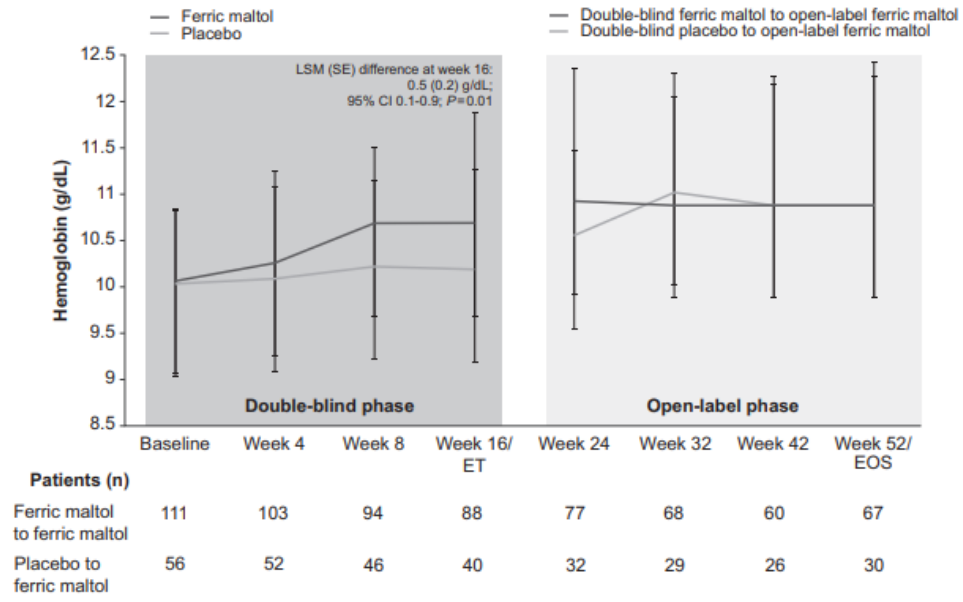


Figure 10: Hb measures over time (image from Pergola P. and Kopyt N. 2021[13])

Iron indices:

Changes from baseline to week 16	Ferric maltol	Placebo	P value
Ferritin, µg/dL	25.4	-7.2	<0.001
TSAT, %	3.8	-0.9	<0.001
Serum iron, µmol/L	1.6	-0.3	0.002

Table 8: Ferritin and TSAT changes over 16 weeks, comparing FERACCRU® to placebo[13]

Ferritin, TSAT, and serum iron values all increased from baseline to week 16 in the FERACCRU® group, and declined in the placebo group; differences between all groups were statistically significant (Table 8).

Improvements in these indices with FERACCRU® during double-blind treatment were maintained with open-label FERACCRU® to week 52 (Fig 11-13). Changes in iron indices for participants moving from placebo to FERACCRU® mirrored the changes seen with FERACCRU® during double-blind treatment (Fig 11-13).

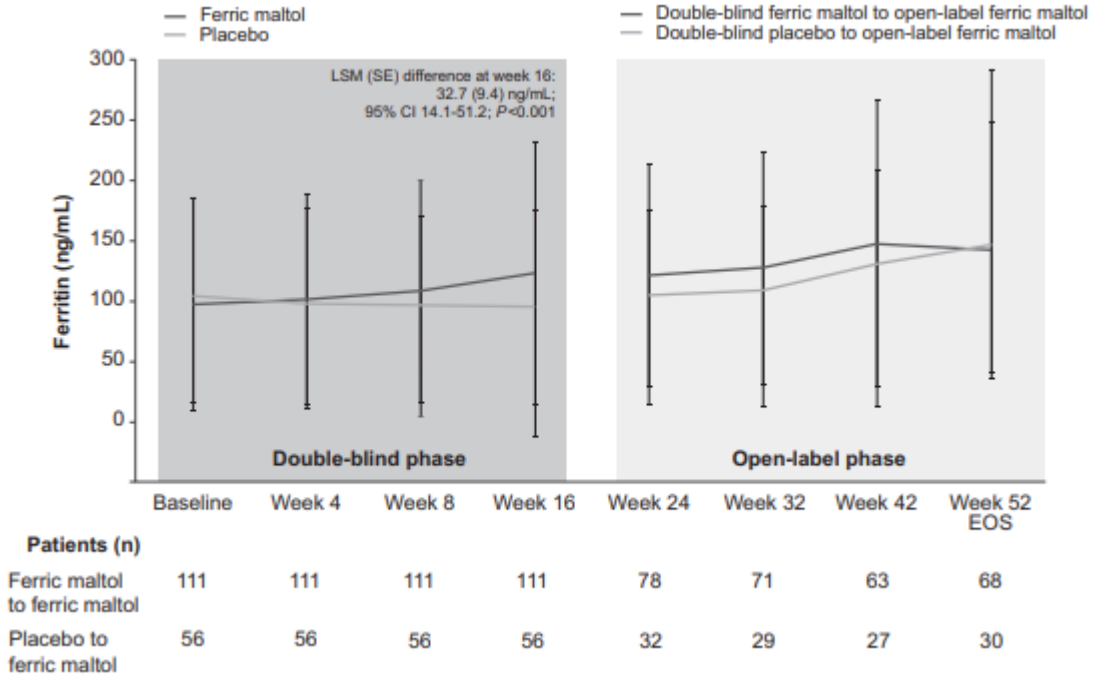


Figure 11: Ferritin over time (image from Pergola P. and Kopyt N. 2021[13]**)**

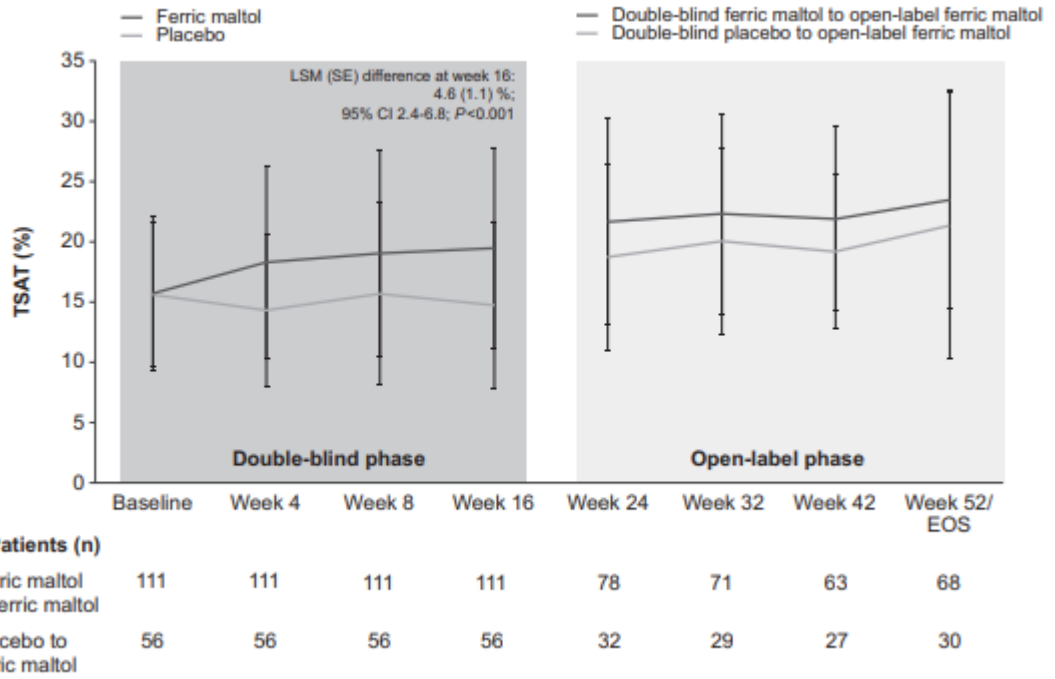


Figure 12: TSAT over time (image from Pergola P. and Kopyt N. 2021[13])

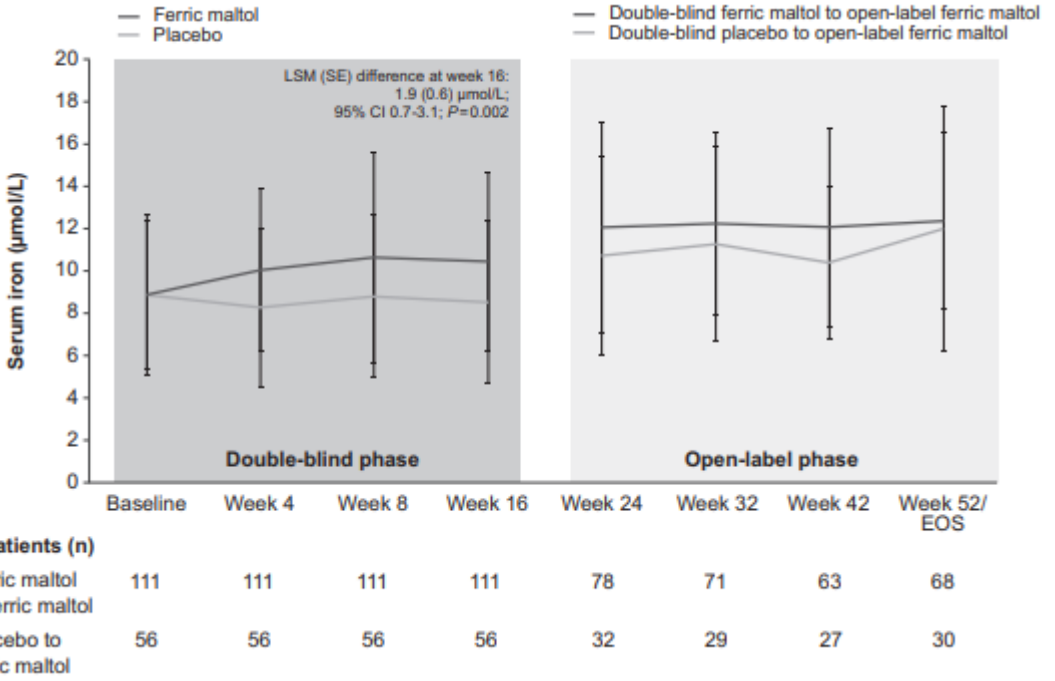


Figure 13: Serum iron over time (image from Pergola P. and Kopyt N. 2021[13])

Safety:

Adverse events to up week 16

Up to week 16, AEs occurred in 68% of patients treated with FERACCRU® (Table 9); of these, 19% were considered related to FERACCRU®[13].

SAEs occurred in twenty-three patients (21%) in the FERACCRU® group and 12 patients (21%) in the placebo group experienced, none of which were considered related to study drug.

There was one death each in the FERACCRU® and the placebo group; neither were considered related to study drug.

	Ferric Maltol (n=111)	Placebo (n=56)
	% patients	% patients
Any TEAE	68	75
Serious TEAE	21	21
TEAE related to study drug	19	11
TEAE resulting in treatment withdrawal	6	9
Death following TEAE	1	1

Table 9: Overview of TEAEs to week 16[13]

Gastrointestinal disorders were the most frequent adverse event in each group up to week 16 (Table 10). The most common drug-related adverse events in the FERACCRU® group being discoloured faeces (6%) and diarrhoea (5%).[13]

Adverse events affecting ≥5% of patients	Ferric Maltol (n=111)	Placebo (n=56)
	% patients	% patients
Blood and lymphatic system disorders	5	16
Anaemia (worsening)	4	11
Gastrointestinal disorders	41	30
Diarrhoea	9	9
Nausea	8	9
Constipation	8	4
Faeces discoloured	7	2
Infections and infestations	15	23
Urinary tract infection	6	9
Metabolism and nutrition disorders	19	23
Hyperkalemia	4	13
Renal and urinary disorders	9	11
Acute kidney injury	5	7
Blood and lymphatic system disorders	5	16

Table 10: Adverse events up to week 16[13]

Adverse events up to week 52

In the open label extension, similar proportions of patients originally randomised to FERACCRU® and placebo experienced adverse events (Table 11).

Serious adverse events occurred in 36 patients, 27 (31%) of whom originally received ferric maltol and 9 (23%) of whom originally received placebo; none were considered related to study drug. No treatment-related deaths occurred during the open-label extension.

	Double Blind Ferric Maltol to Open Label Ferric Maltol (n=86)	Double Blind Placebo to Open Label Ferric Maltol (n=39)
	% patients	% patients
Any TEAE	88	90
Serious TEAE	31	23
TEAE related to study drug	20	18
TEAE resulting in treatment withdrawal	9	8
Death following TEAE	0	0

Table 11: Overview of TEAEs to week 52[13]

The most common adverse events up to week 52 were gastrointestinal, which were proportionally more common in patients receiving FERACCRU® in the double blind phase (Table 12). The most common drug-related adverse events were gastrointestinal disorders.[13]

Adverse events affecting ≥5% of patients	Double Blind Ferric Maltol to Open Label Ferric Maltol (n=86) % patients	Double Blind Placebo to Open Label Ferric Maltol (n=39) % patients
Gastrointestinal disorders	56	46
Constipation	16	13
Diarrhoea	8	13
Faeces discoloured	8	3
Nausea	12	13
Vomiting	8	0
General disorders and administration site conditions	19	13
Fatigue	7	3
Oedema peripheral	8	5
Infections and infestations	45	49
Bronchitis	6	10
Nasopharyngitis	11	8
Pneumonia	8	5
Upper respiratory tract infection	9	10
Urinary tract infection	8	1
Injury, poisoning, and procedural complications	20	10
Fall	8	3
Metabolism and nutrition disorders	29	33

Prescribing Information and Adverse Event reporting is available at the end of this document

Hyperkalaemia	6	15
Respiratory, thoracic, and mediastinal disorders	22	18
Dyspnoea	6	5
Vascular disorders	19	13
Hypertension	6	8

Table 12: Adverse events up to week 52[13]

Evidence for use: Real World Data

Feraccru® Real world Effectiveness Study in Hospital practice (FRESH)[14]

Cummings JF et al. 2021

Methods

This observational cohort study aimed to understand the real-world effectiveness and tolerability of FERACCRU® in the UK for patients with mild-moderate IDA and IBD.

Key Inclusion Criteria[15]
Male and female patients aged ≥ 18 years
Patient presenting with mild to moderate IDA* that is secondary to either CD or UC
Serum ferritin concentration <30mcg/L or transferrin saturation <20%
Patient receiving FERACCRU® since the time of UK launch in June 2016

Key Exclusion Criteria[15]
Patient receiving FERACCRU® as part of an interventional clinical trial
Patients with severely active IBD or requiring corticosteroids at the time of initiation of FERACCRU®
Patient with an IBD flare, as determined by the clinician
Patient with medical records that are not available for review
Patient not willing or unable to consent to study participation, or patient is deceased at the start of data collection period

*Defined as Hb ≥9.5g/dL and <12.0g/dL in females, ≥9.5g/dL and <13.0g/dL in males

The primary outcome measure was the percentage of patients with normalised Hb levels at 12 weeks after initial of FERACCRU® from baseline. Secondary outcome measures included[15]:

- Change in Hb, serum ferritin and transferrin saturation at 4 and 12 weeks compared to baseline
- Time to normalisation* of Hb, serum ferritin and transferrin saturation
- Number of patients who discontinue FERACCRU®
- Type, severity and time of adverse events
- Percentage of patients with normalised serum ferritin and transferrin saturation at 12 weeks

*Normal Hb defined as ≥12g/dL (females) and ≥13g/dL (males), normal serum ferritin defined as ≥30mcg/L and ≤300mcg/L, normal transferrin saturation defined as between 20% and 50%

Study: Results

Patient population numbers
59 patients were included in the study, 38 (64%) were female, with a mean age of 42.9 years (interquartile range 18.5-83.5 years).

Previous iron therapy

Data was available in 25 (42%) of patients; who received a total of 27 courses of oral ferrous products (OFPs), the most common of which was ferrous sulphate (11 courses).

The most common reasons for discontinuing OFPs and initiating FERACCRU® were diarrhoea, nausea and lack of efficacy.

Hb endpoint:

30/59 patients had Hb data at baseline and week 12, therefore included in primary analysis.

Of these patients, 63% (19/30) of patients normalized their Hb at 12 weeks (Fig. 11). A further 27% (8/30) of patients without week 12 Hb data has normalised Hb at either week 4 or 8.

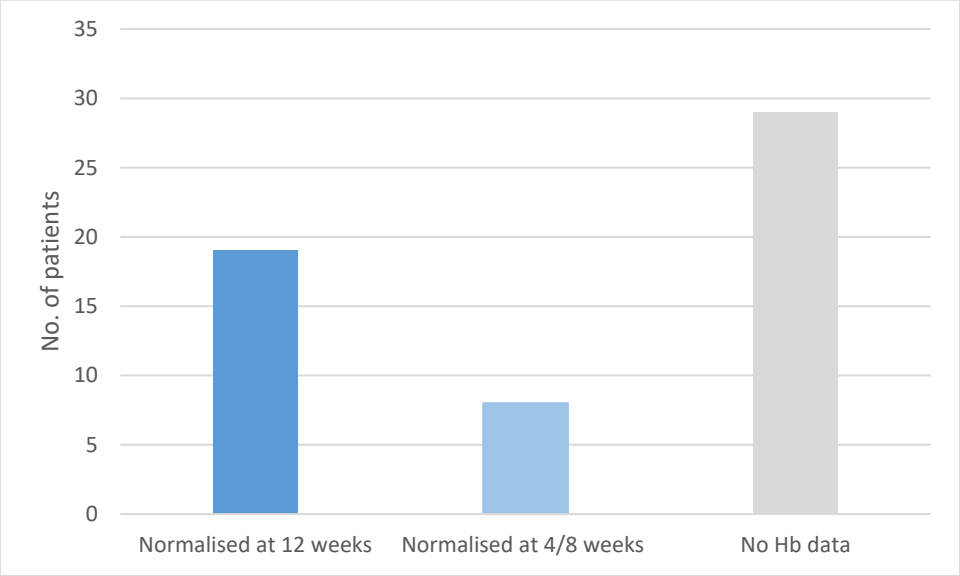


Figure 11: FRESH study primary endpoint – Normalisation of Hb[14]

Safety

Adverse events were recorded in 19 patients (32%), who had a total of 24 events (Table 13). Abdominal pain or discomfort (n=9, 15%) and constipation (n=3, 5%) were the most common AEs. One event (constipation) was judged definitely related to FERACCRU®; seven other events (all gastrointestinal) judged probably related to FERACCRU®. No serious adverse events judged by investigators to be related to FERACCRU®.

Adverse event	Patients (n=59) n (%)
Abdominal pain and discomfort*	9 (15)
Constipation	3 (5)
Diarrhoea	2 (3)
Nausea	1 (2)
Lower abdominal abscess	1 (2)
Shoulder and back pain	1 (2)
Perianal sepsis (exacerbation of underlying disease)	1 (2)
Increased frequency of bowel movements, with some mucus	1 (2)
Flare in underling condition	1 (2)
Clostridium difficile toxin and glutamate dehydrogenase deficiency causing exacerbation of ulcerative colitis flare	1 (2)
Right-sided buccal-space abscess requiring hospitalisation	1 (2)
'Feeling low'	1 (2)
Cellulitis	1 (2)

* Includes combined categories of abdominal pain, abdominal discomfort/distension and abdominal pain and gastritis

Contraindications and precautions

FERACCRU® is contraindicated:

- where there is known hypersensitivity to the active substance or to any of the excipients*
- in haemochromatosis or other iron overload syndromes
- in patients receiving repeated blood transfusions

FERACCRU® should not be used in patients with IBD flare or in IBD patients with Hb < 9.5g/dL

*please review details below or in the Summary of Product Characteristics (SmPC)

References
Feraccru 30mg hard capsules - Summary of Product Characteristics (SmPC). Available from:
https://www.medicines.org.uk/emc
https://www.emcmedicines.com/en-GB/northernireland

Contraindications[1,2]
FERACCRU® is contraindicated where there is known hypersensitivity to the active substance or to any of the excipients:

Capsule Contents:	Capsule Shell:
Lactose monohydrate	Hypromellose
Sodium laurilsulfate	Brilliant Blue (E133)
Magnesium stearate	Allura Red AC (E129)
Colloidal anhydrous silica	Titanium dioxide (E171)
Crospovidone (Type A)	Sunset Yellow FCF (E110)

It is also contraindicated in haemochromatosis or other iron overload syndromes, as well as in patients receiving repeated blood transfusions.

Special warnings and precautions for use:
FERACCRU® should not be used in patients with IBD flare or in IBD patients with haemoglobin (Hb) <9.5 g/dl.

FERACCRU® is licensed for use in adults only. The safety and efficacy of Feraccru in children (17 years and under) has not yet been established. No data are available.

Special care should be taken if other dietary and/or iron salt supplementation are used concurrently.

Iron deficiency or iron deficiency anaemia (IDA) diagnosis should be made based on blood tests; it is important to investigate the cause of the iron deficiency and to exclude underlying causes of anaemia other than iron deficiency.

FERACCRU® has not been studied in patients with impaired renal (eGFR<15 ml/min/1.73 m^2) and/or impaired hepatic function.

This medicinal product contains lactose: patients with rare hereditary problems of galactose intolerance, total lactase deficiency 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.

Information relating to drug interactions can be found in table 1.

Safety

Common adverse reactions include gastrointestinal symptoms such as abdominal pain, flatulence, constipation, abdominal discomfort/distension, diarrhoea, discoloured faeces and nausea.

The phase III study (Gasche *et al.* 2015), which investigated the use of FERACCRU® compared to placebo in patients with mild to moderate IDA and IBD, reported treatment emergent adverse events in 35 patients (58%) in the ferric maltol group and in 43 patients (72%) in the placebo group. No treatment related serious adverse events were attributed to FERACCRU at 12 weeks.

References:
Feraccru 30mg hard capsules - Summary of Product Characteristics (SmPC). Available from:
https://www.medicines.org.uk/emc
https://www.emcmedicines.com/en-GB/northernireland

Gasche C, Ahmad T, Tulassay Z, Baumgart DC, Bokemeyer B, Büning C, 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. Inflammatory Bowel Diseases. 2015 Mar;21(3):579–88

Table 10 lists the undesirable effects that have been associated with FERACCRU®, and stated in the SmPC[1,2].

	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)
Gastrointestinal disorders	• Abdominal pain (including upper abdomen) • Flatulence • Constipation • Abdominal discomfort/ distension • Diarrhoea • Discoloured faeces • Nausea	• Small intestinal bacterial overgrowth • Vomiting
Skin and subcutaneous tissue disorders		• Acne • Erythema
Musculoskeletal and connective tissue disorders		• Joint stiffness • Pain in extremity
Nervous system disorders		• Headache
General disorders and administration site conditions		• Thirst
Investigations		• Blood alkaline phosphatase increased • Blood thyroid stimulating hormone increased • Gamma-glutamyltransferase increased

Table 10: Undesirable effects associated with FERACCRU®[1,2]

Fertility, pregnancy and lactation

FERACCRU® may be used in pregnancy or during breastfeeding if necessary

References:
Feraccru 30mg hard capsules - Summary of Product Characteristics (SmPC). Available from:
https://www.medicines.org.uk/emc
https://www.emcmedicines.com/en-GB/northernireland

A moderate amount of data on the oral use of ferric iron in pregnant women indicate no malformative nor feto/neonatal toxicity. Systemic exposure to the intact ferric maltol complex is negligible. Feraccru may be considered during pregnancy if necessary.

No effects of oral ferric iron have been shown in breastfed newborns/infants of treated mothers. Ferric maltol is not available systemically and is therefore unlikely to pass into the mother's milk. Feraccru can be used during breastfeeding if clinically needed.

There are no data on the effect of ferric maltol on human fertility.

Health Technology Assessments (HTAs)

Submissions for both the SMC and AWMSG are expected to be made by the manufacturer for FERACCRU® in early 2022, following prior 'not recommended' advice in 2016; the outcome of these submissions could be positive or negative.

References:
ferric maltol (Feraccru) [Internet]. Scottish Medicine Consortium. Available from: https://www.scottishmedicines.org.uk/medicines-advice

All Wales Medicines Strategy Group (AWMSG) - ferric maltol (Feraccru) [Internet]. Available from: https://awmsg.nhs.wales/medicines-appraisals-and-guidance

	Past review	Future review
NICE	No review conducted	No HTA review expected
SMC[16]	Reviewed FERACCRU® in 2016, 'not recommended' advice issued	Resubmission to SMC expected early 2022
AWMSG[17]	Reviewed FERACCRU® in 2016, 'not recommended' advice issued	Resubmission to AWMSG expected early 2022

Table 11: HTA Status Summary

FERACCRU® was launched in the UK in 2016. Initially it was licensed for treatment of IDA in adult patients with IBD, with its licence expanded to ID in adults in 2018[1,2]. In late 2018 Norgine acquired the marketing authorisation for FERACCRU® in Europe and have taken responsibility for commercialisation in the UK and Ireland.

In Scotland, FERACCRU® was reviewed by the SMC in 2016. This submission was limited to IDA in IBD. Following review it was not recommended by the SMC[16]. FERACCRU® was similarly not recommended by the AWMSG in Wales[17]. NICE have not selected FERACCRU® for review and therefore will not review as part of the technology appraisal programme, consequently it will not have mandatory funding associated with it in England.

Resubmissions to both the SMC and AWMSG are anticipated in early 2022 ; the outcome of these submissions could be positive or negative.

Appendix

Disease Activity Scores

The phase III studies that investigated the treatment of IDA in patients with IBD used disease activity scores to define eligibility criteria, as well as to monitor for evidence of changes in disease activity during the studies[3,12]. For assessing disease activity in UC,the SCCAI was used, and in CD the CDAI was used (see below):

Simple Clinical Colitis Activity Index (SCCAI)[18]
• Used to assess severity of symptoms in UC
• Active disease defined as a score of 5 or more

• Assesses 5 categories:
  ○ Bowel frequency (day)
  ○ Bowel frequency (night)
  ○ Urgency of defecation
  ○ Blood in stool
  ○ General well being
  ○ Extra-colonic features

• AEGIS-IBD required SCCAI <4 at screening and randomisation for UC patients[3] • A flare was defined as SCCAI ≥5[3]

Crohn's Disease Activity Index (CDAI)[19]
• Used to assess severity of symptoms in CD
• Range 0 to over 600 • Based on a diary kept by the patient for 7 days, along with other measurements
• Remission is CDAI <150 • Moderate to severe disease is CDAI > =220 • Severe active disease usually corresponds to CDAI of 300 or more

• CDAI consists of questions across several categories, the scores of each are added (after applying a weighting factor), examples include:
  ○ Number of liquid or soft stools each day for 7 days
  ○ Abdominal pain graded each day for 7 days
  ○ General well-being each day for 7 days
  ○ Presence of complications e.g. arthritis
  ○ Taking medicines for diarrhoea
  ○ Presence of abdominal mass
  ○ Haematocrit
  ○ Percentage deviation from standard weight

• AEGIS-IBD required CDAI <220 at randomisation for CD patients[3] • A flare was defined as CDAI ≥320[3]

References

1. emc. Feraccru 30mg hard capsules - Summary of Product Characteristics (SmPC) [Internet]. Available from: https://www.medicines.org.uk/emc/medicine/31722

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3. Gasche C, Ahmad T, Tulassay Z, Baumgart DC, Bokemeyer B, Büning C, 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. Inflammatory Bowel Diseases. 2015 Mar;21(3):579–88.

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Prescribing Information - FERACCRU®

PRESCRIBING INFORMATION: Feraccru 30mg hard capsules (ferric maltol)

Please refer to the full Summary of Product Characteristics (SmPC) before prescribing.

Presentation: Red hard capsules. Each capsule contains 30 mg iron (as ferric maltol).

Indication: Feraccru is indicated in adults for the treatment of iron deficiency.

Dosage and administration: Adults: Feraccru should be taken orally. The whole capsule should be taken on an empty stomach (with half a glass of water). The recommended dose is one capsule twice daily, in the morning and evening. The absorption of iron is reduced when Feraccru is taken with food. Treatment duration will depend on 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 **Children:** The safety and efficacy of Feraccru in children (17 years and under) has not yet been established. No data are available. **Elderly and patients with hepatic or renal impairment:** No dose adjustment is needed in elderly patients or patients with renal impairment (eGFR ≥15 ml/min/1.73 m2). There is no clinical data on patients with impaired hepatic function and/or renal impairment (eGFR <15 ml/min/1.73 m2).

Contraindications: Hypersensitivity to the active substance or to any of the excipients; haemochromatosis and other iron overload syndromes; patients receiving repeated blood transfusions.

Warnings and precautions: Not recommended for use in patients with inflammatory bowel disease (IBD) flare or in IBD patients with haemoglobin (Hb) levels <9.5 g/dl. Iron deficiency or iron deficiency anaemia (IDA) diagnosis should be made based on blood tests; it is important to investigate the cause of the iron deficiency and to exclude underlying causes of anaemia other than iron deficiency. Feraccru contains lactose and so patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine. This product also contains Allura Red AC (E129) and Sunset Yellow FCF (E110); these may cause allergic reactions.

Interactions: Food has been shown to inhibit uptake of Feraccru and so treatment should be taken on an empty stomach. Avoid concomitant administration of Feraccru and IV iron, dimercaprol, chloramphenicol and methyldopa. Feraccru should be given at least 2 to 3 hours apart from: penicillamine, bisphosphonates, ciprofloxacin, entacapone, levodopa, levofloxacin, levothyroxine (thyroxine), moxifloxacin, mycophenolate, norfloxacin, ofloxacin, tetracyclines, calcium and magnesium salts e.g. magnesium trisilicate.

Fertility, pregnancy and lactation: A moderate amount of data on the oral use of ferric iron in pregnant women indicate no malformative nor feto/ neonatal toxicity. Systemic exposure to the intact ferric maltol complex is negligible. Feraccru may be considered during pregnancy if necessary. No effects of oral ferric iron have been shown in breastfed newborns/infants of treated mothers. Ferric maltol is not available systemically and is therefore unlikely to pass into the mother's milk. Feraccru can be used during breastfeeding if clinically needed. There are no data on the effect of ferric maltol on human fertility.

Effects on ability to drive and use machines: Feraccru has no or negligible influence on the ability to drive and use machines.

Undesirable effects: Common side effects: Abdominal pain, flatulence, constipation, abdominal discomfort/distension, diarrhoea, discoloured faeces and nausea. Refer to the SmPC for a full list and frequency of adverse events.

Price and pack sizes: £47.60 for 56 capsules.

Legal category: Prescription Only Medicine.

Marketing Authorisation Number: EU/1/15/1075/001

Marketing Authorisation Holder: Norgine B.V., Antonio Vivaldistraat 150, 1083 HP Amsterdam, Netherlands.

Date of preparation: December 2020

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Company reference: UK-HAE-FER-2000095

United Kingdom - Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Norgine Pharmaceuticals Ltd on:
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