SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Feraccru 30 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 30 mg iron (as ferric maltol).

Excipient(s) with known effect:
Each capsule contains
91.5 mg of lactose monohydrate
0.3 mg of Allura Red AC (E129)
0.1 mg of Sunset Yellow FCF (E110).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules, hard.

Red capsule (19 mm long x 7 mm diameter) printed "30".

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology
The recommended dose is one capsule twice daily, morning and evening, on an empty stomach (see section 4.5).

Treatment duration will depend on the severity of iron deficiency but generally at least 12-weeks treatment is required. It is recommended the treatment - is continued as long as necessary to replenish the body iron stores according to blood tests.

The 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 m^2).

No clinical data on the need to adjust the dose in patients with impaired hepatic function and/or renal impairment (eGFR ≥15 ml/min/1.73 m^2) are available (see section 4.4).

Paediatric population

The safety and efficacy of Feraccru in children (17 years and under) has not yet been established.
No data are available.

Method of administration
Oral use.

Feraccru capsules should be taken whole on an empty stomach (with half a glass of water), as the absorption of iron is reduced when it is taken with food (see section 4.5).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Haemochromatosis and other iron overload syndromes.
- Patients receiving repeated blood transfusions.

4.4 Special warnings and precautions for use

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 is not recommended for use in patients with inflammatory bowel disease (IBD) flare or in IBD- patients with haemoglobin (Hb) <9.5 g/dl.

Concomitant administration of ferric maltol with intravenous iron, dimercaprol, chloramphenicol or methyldopa is to be avoided (see section 4.5)

This medicinal product contains lactose: patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product also contains Allura Red AC (E129) and Sunset Yellow FCF (E110): these may cause allergic reactions.

This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with ferric maltol. Based on an in vitro study maltol is glucuronised through UGT1A6 (see section 5.2).

Food has been shown to inhibit uptake of Feraccru: The treatment should be taken on an empty stomach (see section 4.2).

Intravenous administration of iron salts
Concomitant administration of Feraccru and intravenous iron may induce hypotension or even collapse due to the fast release of iron resulting from saturation of transferrin caused by intravenous iron.

Medicinal products that may impact absorption and distribution of iron from Feraccru

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.

Impact of Feraccru on absorption of other medicinal products
Oral iron is known to reduce the absorption of penicillamine, bisphosphonates, ciprofloxacin, entacapone, levodopa, levofloxacin, levothyroxine (thyroxine) moxifloxacin, mycophenolate, norfloxacin and ofloxacin. These medicinal products 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.

Pharmacodynamic interactions
Concomitant use of iron and dimercaprol is nephrotoxic (see section 4.4).

Concomitant use of chloramphenicol will delay plasma iron clearance, incorporation of iron into red blood cells and interfere with erythropoiesis (see section 4.4).

Concomitant use of iron with methyldopa may antagonise the hypotensive effect of methyldopa (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breastfeeding

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 breast feeding if clinically needed.

Fertility

There are no data on the effect of ferric maltol on human fertility. No effects on fertility are anticipated since systemic exposure to ferric maltol is negligible

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
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%].

Tabulated list of adverse reactions

Table 1 presents all adverse reactions occurring during clinical studies to date with Feraccru.

Adverse reaction frequencies are defined as: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000) or very rare (<1/10000).

Table 1: Adverse reactions observed during clinical studies to date.

System organ class	Common	Uncommon
Nervous system disorders		Headache
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
General disorders and administration site conditions		Thirst
Investigations		Blood alkaline phosphatase increased Blood thyroid stimulating hormone increased Gamma-glutamyltransferase increased

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Iron overdose is dangerous and can be life-threatening in children, infants and toddlers requiring immediate attention.

Symptoms of iron overdose
Early signs and symptoms include nausea, vomiting, abdominal pain and diarrhoea. The vomit and stools may be grey or black. In mild cases early features improve but in more serious cases there may be evidence of hypoperfusion (cool peripheries and hypotension), metabolic acidosis and systemic toxicity. In serious cases there can be recurrence of vomiting and gastrointestinal bleeding, up to 12 hours after ingestion. Shock can result from hypovolaemia or direct cardiotoxicity. Evidence of hepatocellular necrosis appears at this stage with jaundice, bleeding, hypoglycaemia, encephalopathy and positive anion gap metabolic acidosis. Poor tissue perfusion may lead to renal failure. Rarely, gastric scarring causing stricture or pyloric stenosis (alone or in combination) may lead to partial or complete bowel obstruction 2-5 weeks after ingestion.

Ingestion of 20 mg/kg elemental iron is potentially toxic and 200-250 mg/kg is potentially fatal. No single method of assessment is entirely satisfactory - clinical features as well as laboratory analysis must be taken into account. Serum iron levels measured at about 4 hours after ingestion is the best laboratory measure of severity.

Management
Supportive and symptomatic measures reflecting best standard medical care should be implemented. The use of desferroxamine should be considered: for detailed information see product information provided by the manufacturer. Haemodialysis does not remove iron effectively but should be considered on a supportive basis for acute renal failure as this will facilitate removal of the iron-desferroxamine complex.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antianemic preparations Iron trivalent, oral preparation, ATC code: B03AB10.

Mechanism 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 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.

Clinical efficacy

IBD Studies
The safety and efficacy of Feraccru for the treatment of iron deficiency anaemia was studied in 128 patients (age range 18-76 years; 45 males and 83 females) with inactive to mildly active IBD (58 patients with Ulcerative Colitis [UC] and 70 patients with Crohn's disease [CD]) and baseline Hb concentrations between 9.5 g/dL and 12 / 13 g/dL for females / males. Patients were enrolled in one combined randomised, placebo-controlled clinical study (AEGIS 1/2). 69 % of the patients with UC had a SCCAI score ≤2 and 31 % a SCCAI score of 3.83 % of the patients with CD had a CDAI-score <150 and 17 % a CDAI-score >150-220. All patients had discontinued from prior oral ferrous product (OFP) treatment: more than 60 % of the subjects stopped taking prior OFP due to adverse events. The median time since last dose of OFP was 22 months in the experimental group and 17 months in the placebo arm. 52 % of the patients in AEGIS 1 and 33 % in AEGIS 2 had a disease flare in the previous 6 months. The median (min-max) time since last disease flare was around 7 months (0.0-450 months). Subjects were randomised to receive either 30 mg Feraccru twice daily or a matched placebo control for 12 weeks. The difference between the change from baseline for Feraccru compared to placebo at week 12 was 2.25 g/dL ($p<0.0001$). Following completion of the 12-week placebo-controlled phase of the studies, all subjects were switched to Feraccru 30 mg twice daily open-label treatment for a further 52 weeks.

The results for the other key efficacy endpoints are shown in Table 2.

Table 2: Summary of Other Key Efficacy Endpoints (AEGIS 1/2)

Endpoint	Hb change (g/dL) from Baseline* at Week 4 Mean (SE)	Hb change (g/dL) from Baseline* at Week 8 Mean(SE)	Proportion of subjects that achieved normalised Hb at Week 12 (%)	Proportion of subjects that achieved ≥1 g/dL change in Hb at Week 12 (%)	Proportion of subjects that achieved ≥2 g/dL change in Hb at Week 12 (%)
Feraccru (N=64)	1.06 (0.08)***	1.79 (0.11)***	66	78	56
Placebo (N=64)	0.02 (0.08)	0.06 (0.11)	12	11	0

* Hb at Baseline mean (SE): Feraccru 11.0 (1.027) g/dL, Placebo 11.1 (0.851) g/dL; ***$p<0.0001$ compared to placebo group;

An increase of ≥1 g/dL change in Hb at Week 12 was achieved in 90 % and 69 % of the ulcerative colitis (N=29) and Crohn's Disease (N=35) subgroups, respectively. An increase of ≥2 g/dL change in Hb at Week 12 was achieved in 62 % and 51 % of the ulcerative colitis and Crohn's Disease subgroups, respectively. Iron deficiency was also shown to be corrected by increase in ferritin levels in both studies. Mean ferritin (µg/L) levels in subjects taking feraccru improved steadily from baseline (mean 8.6 µg/L [SD 6.77]) to Week 12 (mean 26.0 µg/L [SD 30.57]), a mean overall improvement of 17.4 µg/L. Ferritin continued to rise over long-term treatment with Feraccru (mean 68.9 µg/L [SD 96.24] at 64 weeks, a mean overall improvement of 60.3 µg/L).

Chronic Kidney Disease (CKD) study
The efficacy, safety, tolerability and pharmacokinetics (PK) of Feraccru for the treatment of iron deficiency anaemia in adult subjects with chronic kidney disease (CKD) was studied in a phase III randomised placebo-controlled clinical study (AEGIS-CKD). 167 patients (age range 30-90 years; 50 males and 117 females) with an eGFR of ≥15 mL/min/1.73m^2 and <60 mL/min/1.73m^2 and baseline Hb ≥8.0 g/dL and <11.0 g/dL and ferritin <250 ng/mL with a transferrin saturation (TSAT) <25%, or ferritin <500 ng/mL with a TSAT of <15% were randomized 2:1 to receive either Feraccru 30 mg capsules twice daily or placebo twice daily for a treatment period of 16 weeks. This was followed by an open-label treatment phase, which included up to 36 weeks of treatment with Feraccru only.

Feraccru resulted in clinically and statistically significant increases in Hb compared to placebo during the double-blind 16-week treatment period. The least squares mean (LSM) change in Hb concentration from baseline to Week 16 was 0.50 g/dL for the ferric maltol group and -0.02 g/dL for the placebo group, with a statistically significant LSM difference of 0.52 (p=0.0149).

The LSM change in ferritin concentration from baseline to Week 16 with LOCF was 25.42 µg/L for the Feraccru group and -7.23 µg/L for the placebo group, with a statistically significant LSM difference of 32.65 (p=0.0007).

Paediatric Studies
The European Medicines Agency has deferred the obligation to submit the results of studies with Feraccru in one or more subsets of the paediatric population in iron deficient anaemia (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption and elimination
The pharmacokinetic properties of ferric maltolwas assessed through measurement of plasma and urine concentrations of maltol and maltol glucuronide, together with serum iron parameters after a single dose and at steady state (after 1 week) in 24 subjects with iron deficiency, randomised to receive 30 mg, 60 mg or 90 mg Feraccru twice daily. Blood and urine samples were assayed for maltol and maltol glucuronide. Serum samples were assayed for iron parameters.

Maltol was transiently measured in plasma with a AUC_{0-t} between 0.022 and 0.205 h.µg/mL across all dosing regimens and both study days. Non-clinical studies have shown that maltol is metabolised through UGT1A6 and by sulphation. It is not known if medical products that inhibit UGT enzymes have the potential to increase maltol concentration (see section 4.5). The maltol appeared to be rapidly metabolised to maltol glucuronide (AUC_{0-t} between 9.83 and 30.9 h.µg/mL across all dose regimens). Maximum maltol and maltol glucuronide concentrations were reached 1 to 1.5 hours after oral administration of Feraccru. Exposure to maltol glucuronide increased dose proportionally over the Feraccru 30 to 90 mg twice daily dosing range and there was no significant accumulation of either after 7 days treatment with Feraccru. Of the total maltol ingested, a mean of between 39.8 % and 60.0 % was excreted as maltol glucuronide. Peak transferrin saturation (TSAT) and total serum iron values were reached 1.5 to 3 hours after oral administration of Feraccru. Total serum iron concentrations and TSAT values were generally higher with increasing Feraccru doses. TSAT and total serum iron profiles were comparable between Day 1 and Day 8.

The pharmacokinetic properties of Feraccru were also investigated at steady state in 15 subjects who were already participating in the AEGIS1/2 study described above and who had been in the open-label treatment phase for at least 7 days (Feraccru 30 mg twice daily). Maltol was again transiently measured in plasma with a half-life of 0.7 hours, with a C_{max} of 67.3 $\pm$ 28.3 ng/mL. The maltol appeared to be rapidly metabolised to maltol glucuronide (C_{max} = 4677 $\pm$ 1613 ng/mL). Maximum maltol and maltol glucuronide concentrations were reached approximately 1 hour after oral administration of Feraccru. Maximum total iron serum concentrations were measured 1-2 hours after administration. The pharmacokinetic profiles of maltol/maltol glucuronide and iron parameters were independent of one another.

5.3 Preclinical safety data

Ferric maltol
Non-clinical studies revealed no special hazard for humans based on repeated dose toxicity and local tolerance studies conducted with ferric maltol.

Deposition of iron in the reticulo-endothelial system, liver and spleen was recorded in dogs administered 250 mg/kg/day ferric maltol.

No reproductive and developmental toxicity or carcinogenicity studies have been conducted with ferric maltol.

Maltol
Haemosiderin was observed in Kupffer cells of dogs administered 250 mg/kg/day maltol. At doses of 500 mg/kg/day testicular degeneration and toxic signs indicative of iron chelation were recorded. These effects were not observable in a second study in dogs receiving up to 300 mg/kg/day.

A possible potential genotoxic potential for maltol could not be fully ruled out. However, no carcinogenic effects were recorded in studies conducted in mice and rats receiving up to 400 mg/kg/day maltol.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

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

Printing Ink:
Shellac glaze-45% (20 % esterfied) in Ethanol
Iron oxide black
Propylene glycol
Ammonium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

Shelf-life after first opening container: 45 days.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

HDPE bottles with a child-proof polypropylene push-lock. Each bottle contains 50 or 56 capsules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Norgine Pharmaceuticals Limited
Norgine House
Widewater Place
Moorhall Road
Harefield
Uxbridge
UB9 6NS
UK

8. MARKETING AUTHORISATION NUMBER

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1st October 2021