Promotional supplement
Primary care management of iron deficiency anaemia

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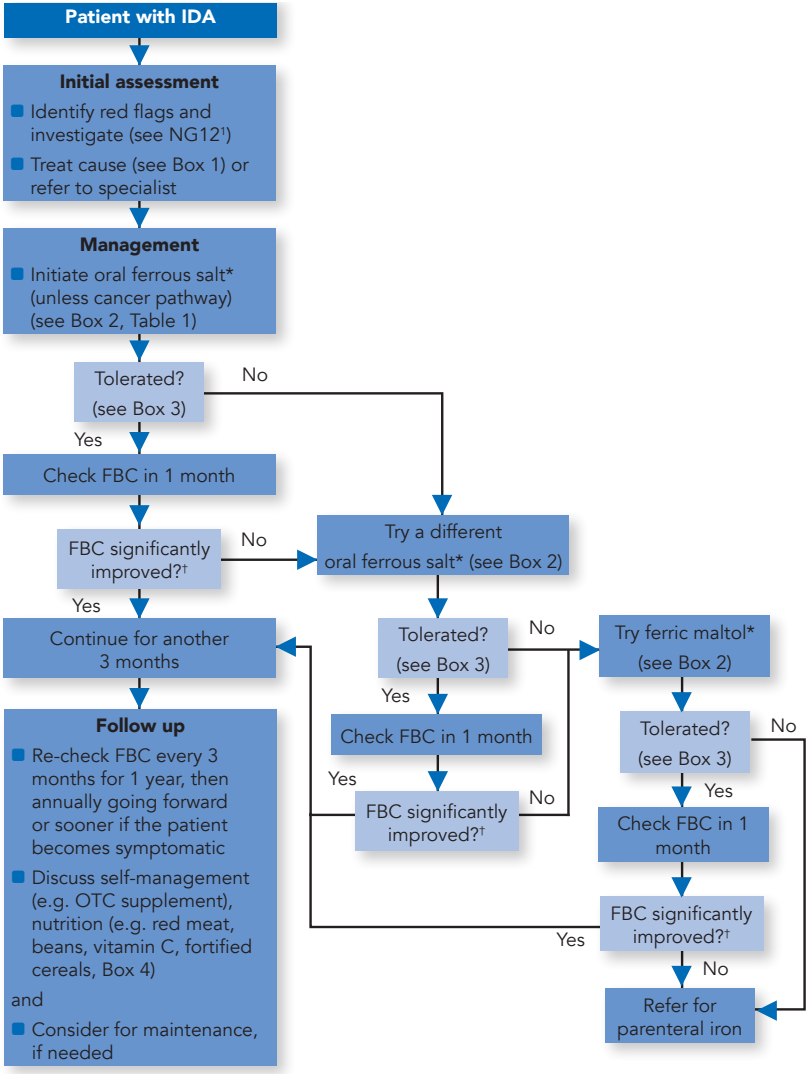
This management algorithm supplement was commissioned and funded by Norgine Pharmaceuticals Limited, and developed by a multidisciplinary expert panel: Barrett K et al. See inside for full disclaimer.
Prescribing information can be found on page 7.

Guidelines



BNF=British National Formulary; FBC=full blood count; OTC=over the counter; SmPC=summary of product characteristics.
*Refer to SmPC, BNF or local formulary for dosing and interactions; Table 1 lists key drug interactions.
†If no improvement within 3 months, check compliance, consider switching to another oral iron and further investigations. If anaemia worsens or patient becomes moderately or severely symptomatic, refer to secondary care for further investigations, if not already investigated, and for consideration of parenteral iron rather than trying alternative oral iron.

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Background

- Iron deficiency anaemia (IDA) occurs when production of red blood cells is diminished due to a long-term negative balance of stored iron,[2] or due to chronic gastrointestinal bleeding, and is a common cause of referral to gastroenterologists[2]
- The underlying cause of IDA should be determined and treated, but it is important to intervene in primary care to restore haemoglobin and red blood cells to normal levels, and to replenish iron stores while the underlying cause is investigated[2]
- Published guidelines suggest starting treatment of IDA with oral ferrous salts (OFS); if these are not tolerated or the patient does not respond, parenteral iron is the suggested next step[3,4]
- An option not considered in existing UK guidelines before escalating to parenteral iron is ferric maltol. In a phase III randomised double-blind clinical trial in patients with inflammatory bowel disease who previously failed to respond to, or were intolerant to OFS, ferric maltol showed clinically meaningful improvements in haemoglobin concentrations, and gastrointestinal side effects reported were similar to those seen with placebo; the most common adverse reactions were gastrointestinal in nature, and of mild or moderate severity[5]
- A working party group was brought together to develop an algorithm that includes the option of ferric maltol for the treatment of IDA based on existing clinical guidance, local UK pathways and protocols, and expert consensus. This algorithm excludes:
  - pregnant women, who should be managed as per local guidance and according to the recommendations of the Royal College of Obstetricians & Gynaecologists[6]
  - patients with chronic kidney disease, who should be managed according to NICE Guideline 8[7]
  - patients with compromised cardiovascular systems, who require hospital admission

Management of patients with IDA

Initial assessment

- In patients confirmed to have IDA:
  - identify and investigate red flags according to NICE Guideline 12[1]
  - treat underlying cause of IDA (Box 1) or refer to specialist

Management of IDA

- Start iron treatment while investigations for the underlying cause are underway or while specialist referral is awaited

Box 1: Possible causes of iron-deficiency anaemia

- Dietary deficiency
- Menorrhagia
- Gastroenterological causes (e.g. coeliac disease, inflammatory bowel disease)
- Renal causes (e.g. chronic kidney disease, bladder cancer)
- Medications (e.g. non-steroidal anti-inflammatory drugs)
- Blood donation
- Acute blood loss

Box 2: Examples of available iron preparations (with amount of elemental iron per dose)[8]

- Ferrous fumarate (preferably prescribed as non-proprietary formulation)
  - 210mg tablets (contains 65-70mg elemental iron per tablet)
  - 322 mg tablet (contains 100 mg elemental iron per tablet)
  - 140mg/ml syrup (contains 45mg elemental iron per 5ml)
- Ferrous gluconate (preferably prescribed as non-proprietary formulation)
  - 300 mg tablet (contains 35 mg elemental iron per tablet)
- Ferrous sulphate (preferably prescribed as non-proprietary formulation)
  - 200 mg tablet (contains 65 mg elemental iron per tablet)
- Sodium feredetate (sodium iron edetate) (preferably prescribed as non-proprietary formulation)
  - 190mg/5ml oral solution (contains 27.5mg of elemental iron/5ml)
  - 27.5mg/5ml oral solution (contains 27.5 mg of iron)
- Ferric maltol
  - 30 mg capsule contains 30 mg elemental iron

Table 1: Drug-drug interactions[8]

Medication affected by iron supplement absorption	Interaction/advice
Biphosphonates	■ Complex formation with iron and decrease in bioavailability of biphosphonates ■ Avoid iron supplements 6 hours before or 1–2 hours after biphosphonates
Levodopa/beneldopa/carbidopa	■ Decrease in bioavailability of carbidopa and/or levodopa ■ Separate times between iron and these drugs by as long as possible
Levothyroxine	■ Decrease in bioavailability of thyroxine (thyroxine and iron form a poorly soluble complex in vitro) ■ Separate absorption by at least 4-5 hours
Bictecravir	■ Iron interferes with gastrointestinal absorption of bictegravir ■ Bictecravir should be administered at least 2 hours before iron supplements or taken together with food
Dolutegravir	■ Chelation of dolutegravir by divalent cations ■ Administer dolutegravir 2 hours before or 6 hours after iron ■ Alternatively, dolutegravir can be taken simultaneously with iron supplements or with food
Methyldopa	■ Decrease in bioavailability of methyldopa ■ Take methyldopa 2 hours before taking iron supplements
Penicillamine	■ Oral absorption of penicillamine may be reduced by concomitant administration of iron ■ Separate administration by 2 hours
Quinolones	■ Reduced absorption of quinolones ■ Quinolones should be administered 1–2 hours before or at least 4 hours after iron supplements
Tetracyclines	■ Absorption of tetracycline from gastrointestinal tract is impaired by concomitant administration of divalent and trivalent cations such as iron ■ Take 2–3 hours after iron supplement
Antacids	■ Reduced absorption of iron ■ Take iron 1 hour before or 2 hours after antacids
Calcium supplements	■ Reduced absorption of iron ■ Allow a minimum period of 4 hours before taking calcium
Chloramphenicol	■ Unlikely to occur with ophthalmic preparations

(continues on next page)

Table 1: Drug-drug interactions[8] (continued)

Medication affected by iron supplement absorption	Interaction/advice
Citric or ascorbic acid and acidic fruit juices (orange juice)	■ Increase absorption of iron ■ Ascorbic acid seems to have an important role in metal ion metabolism, including gastrointestinal absorption of iron and its transport between plasma and storage organs
Other interactions	
Entacapone	■ Entacapone may chelate with iron in gastrointestinal tract leading to reduction in absorption of both medications ■ Entacapone and iron preparations should be taken at least 2–3 hours apart
Trientine	■ Trientine may chelate with iron in gastrointestinal tract leading to reduction in absorption of both medications ■ Trientene and iron preparations should be taken at least 2–3 hours apart
Zinc	■ Zinc and iron supplements decrease absorption of each other
For further information on interactions, please refer to the individual SmPCs available at medicines.org.uk	

- Box 2 provides examples of the ferrous products available, with the amount of elemental iron per dose[8]

Oral ferrous salts

- Initiate OFS (unless the patient is being referred through the cancer pathway)
  - refer to summary of product characteristics (SmPCs), British National Formulary (BNF), or local formulary for dosing and drug interactions
    - Table 1 provides a summary of common drug–drug interactions[8]
    - Box 3 provides information on optimising tolerability
  - check tolerability
    - if tolerated, continue treatment
    - if not tolerated, try a different oral ferrous salt (see Box 1)
  - check full blood count (FBC) in 1 month
    - if FBC is significantly improved on first-line OFS, continue for another 3 months
    - if no improvement within 3 months:
      - check compliance
      - consider switching to another oral ferrous salt and further investigations
    - if anaemia worsens or patient is moderately or severely symptomatic, refer to secondary care for:
      - further investigations, if not already investigated
      - consideration of parenteral iron rather than trying an alternative oral iron
- Try an alternative OFS if the patient has poor tolerability or poor response to the first-line OFS:
  - refer to SmPCs, BNF, or local formulary for dosing and drug interactions, as described above (see Table 1; Box 3)
  - check tolerability, as described above
    - if tolerated, continue treatment
    - if not tolerated, try ferric maltol (see Box 1)
  - check FBC in 1 month
    - if FBC is significantly improved on second-line OFS, continue for another 3 months
    - if no improvement within 3 months:
      - check compliance
      - consider switching to ferric maltol and further investigations

Box 3: Tips for improving tolerability and absorption[9]

- Iron preparations are best absorbed on an empty stomach, to reduce gastrointestinal side-effects:
  - taking with a small amount of food (without high fibre, bran or caffeine, particularly tea, milk or antacid) improves tolerability
  - taking with orange or vitamin C improves absorption
- Iron supplements are prescribed for about 6 months and maintenance on a single daily dose, but alternate-day dosing can be effective for patients with poor tolerability[10]
- Switching to a preparation with a lower elemental content may increase tolerability (see Box 1)
- Ferrous sulphate works best when taken on an empty stomach; however, if it upsets the stomach it can be taken with or after food
- Recommend taking ferrous sulphate with orange juice or a vitamin C supplement—vitamin C is believed to increase the amount of iron absorbed by the body
- The tablet or capsule should be swallowed whole with a glass of water; they should not be sucked, chewed, or kept in the mouth
- Supplements should not be taken with tea, coffee, eggs, dairy products, and soybean products, as they can reduce the amount of iron that gets into the system; when taking ferrous sulphate (or when eating foods that are high in iron), a 2-hour gap should be left before having these foods or drinks

Box 4: Good sources of iron[11]

- Liver (should be avoided during pregnancy)
- Meat
- Pulses (beans, peas and lentils)
- Nuts
- Dried fruit (e.g. dried apricots)
- Wholegrains (e.g. brown rice)
- Fortified cereals and breads (with extra iron)
- Soybean flour
- Most dark-green leafy vegetables (e.g. watercress and curly kale)

    - if anaemia worsens or patient is moderately or severely symptomatic, refer to secondary care for:
      - further investigations, if not already investigated
      - consideration of parenteral iron rather than trying alternative oral iron

Ferric maltol

- If the patient fails to respond to two different OFS, consider ferric maltol
  - refer to SmPC, BNF, or local formulary for dosing and drug interactions, as described above (Table 1; Box 3)
  - check tolerability, as described above
    - if tolerated, continue treatment
    - if not tolerated, consider parenteral iron
  - check FBC in 1 month
    - if FBC is significantly improved on ferric maltol, continue for another 3 months
    - if no improvement within 3 months:
      - check compliance
      - consider parenteral iron and further investigations
    - if anaemia worsens or patient is moderately or severely symptomatic, refer to secondary care for:
      - further investigations, if not already investigated
      - consideration of parenteral iron rather than trying another alternative oral iron

Parenteral iron

- If the patient fails to respond to or tolerate OFS or ferric maltol, refer for parenteral iron
- If anaemia worsens or the patient is moderately or severely symptomatic, refer to secondary care for further investigations, if not already investigated

Follow up

- Re-check FBC every 3 months for 1 year and then annually going forward (or sooner if the patient becomes symptomatic)

- Discuss self-management—for example, with over-the-counter iron products and improved nutrition (see Box 4)
- Consider iron for maintenance, if needed

References

1. NICE. *Suspected cancer: recognition and referral*. NICE Guideline 12, 2017. Available at: www.nice.org.uk/ng12

2. NICE. *Anaemia—iron deficiency*. Clinical Knowledge Summary, 2018. Available at: cks.nice.org.uk/anaemia-iron-deficiency

3. Goddard A, James M, McIntyre A et al. Guidelines for the management of iron deficiency anaemia. *Gut* 2011; **60**: 1309–1316.

4. Royal College of Nursing. *Iron deficiency anaemia in adults—guidance for nursing practice*. London, 2019. Available at: www.rcn.org.uk/professional-development/publications/pub-007460#detailTab

5. Gasche C, Ahmad T, Tulassay Z et al. Ferric maltol is effective in correcting iron deficiency anemia in patients with inflammatory bowel disease: results from a phase-3 clinical trial program. *Inflamm Bowel Dis* 2015; **21**: 579–588.

6. Royal College of Obstetricians & Gynaecologists. *Anaemia*. elearning.rcog.org.uk//principles-antenatal-care/screening-maternal-disease/screening-clinical-1

7. NICE. *Chronic kidney disease: managing anaemia*. NICE Guideline 8, 2015. Available at: www.nice.org.uk/ng8

8. Electronic Medicines Compendium. www.medicines.org.uk/emc

9. Auerbach M. *Treatment of iron deficiency anemia in adults*. Available at: www.uptodate.com/contents/treatment-of-iron-deficiency-anemia-in-adults

10. Stoffel N, Cercamondi C, Brittenham G et al. Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice-daily split dosing in iron-depleted women: two open-label, randomised controlled trials. *Lancet Haematol* 2017; **4** (11): e524–e533.

11. NHS. *Iron*. Available at: www.nhs.uk/conditions/vitamins-and-minerals/iron/

Useful resources

- NICE. *Suspected cancer: recognition and referral.* NICE Guideline 12:
  - www.nice.org.uk/ng12
- NICE. *Anaemia—iron deficiency.* Clinical Knowledge Summary:
  - cks.nice.org.uk/anaemia-iron-deficiency
- NICE. *Chronic kidney disease: managing anaemia*. NICE Guideline 8:
  - www.nice.org.uk/ng8
- Royal College of Obstetricians & Gynaecologists. *Iron deficiency anaemia in adults—guidance for nursing practice*
  - www.rcn.org.uk/professional-development/publications/pub-007460#detailTab

about this management algorithm …

This management algorithm has been commissioned and funded by Norgine Pharmaceuticals Ltd and developed in partnership with *Guidelines*. Norgine Pharmaceuticals Ltd reviewed and approved the scope and pre-meeting documents, suggested a Chair and the experts for the group, and carried out full medical approval on all materials to ensure compliance with regulations. The sponsorship fee included honoraria for the participants. The views and opinions of the participants are not necessarily those of Norgine Pharmaceuticals Ltd, *Guidelines*, its publisher, advisers, or advertisers.

Group members — Dr Kevin Barrett (Chair, GP with Special interest in Gastroenterology), Dr Sonica Goel (GP), Dr Christian Selinger (Consultant Gastroenterologist), and Anja St Clair-Jones (Consultant Pharmacy Gastroenterology).

Conflicts of interest — The group members received an honorarium from Norgine Pharmaceuticals Ltd to develop this management algorithm. Some of the group members have also received consultancy fees from other pharmaceutical companies, which might include Norgine Pharmaceuticals Ltd, for activities other than the development of this management algorithm.

UK-HAE-FER-2100046 Date of preparation: April 2021

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 m^2). There is no clinical data on patients with impaired hepatic function and/or renal impairment (eGFR <15 ml/min/1.73 m^2).

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

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: Tel. +44 (0)1895 826 606 E-mail medinfo@norgine.com

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