Ferric carboxymaltose (Ferinject)
for iron-deficiency anaemia

**KEY POINTS**

**Rapid correction of iron deficiency**
A maximum dose of 1000 mg iron can be delivered intravenously over 15 minutes, which may make it a suitable treatment for iron-deficiency anaemia outside of the hospital setting.

**Comparable efficacy to that of IV iron sucrose**
In key trials, ferric carboxymaltose increased Hb levels and replenished iron stores as effectively as IV iron sucrose but requiring fewer doses.

**Efficacy relative to IV iron polymaltose is assumed but not established**
There are no head-to-head comparisons with IV iron polymaltose.

**Ferric carboxymaltose can improve Hb levels and iron stores for iron-deficiency anaemia associated with a variety of conditions**
Prospective trials have demonstrated efficacy in patients with inflammatory bowel disease, chronic kidney disease, menorrhagia and postpartum anaemia.

**Ensure cardiopulmonary resuscitation equipment is available**
Life-threatening hypersensitivity reactions are a known risk with all IV iron preparations. Monitor patients during, and for 30 minutes after, administration of ferric carboxymaltose.

**Ferric carboxymaltose is approved for IV administration only**
Minimise the risk of injection-site leakage or extravasation (which can cause irritation and permanent discouleration of the skin) by flushing with 0.9% saline before and after administration.

**PBS listing**

**Unrestricted benefit**
Ferric carboxymaltose (Ferinject) is PBS listed for the treatment of iron-deficiency anaemia, where oral iron preparations are not tolerated, ineffective or otherwise inappropriate. The diagnosis must be based on laboratory tests.

**May be prescribed by nurse practitioners within collaborative arrangements**
Authorised nurse practitioners may prescribe this medicine on the PBS. See the PBS website for more information on nurse practitioner PBS prescribing.

**What is it?**
Ferric carboxymaltose (FCM) is another colloidal iron preparation for the parenteral treatment of iron-deficiency anaemia (IDA). It is pH neutral (5.0–7.0), has physiological osmolarity and can rapidly deliver high-dose iron in a single infusion (up to a maximum single dose of 1000 mg iron administered over 15 minutes).²,³

An iron (III)-hydroxide core contained in a carbohydrate shell confers stability to the FCM complex, allowing a slow and controlled release of iron from within the cells of the reticuloendothelial system.³,¹ This stability is also reported to limit the amount of labile (unbound) iron entering the circulation. Labile iron is toxic to cells.⁴,⁵
FCM is a parenteral iron preparation with characteristics that allow larger single doses to be administered over a shorter infusion period compared with existing IV iron preparations.

FCM can correct IDA across a range of clinical conditions, with efficacy and tolerability similar to those of IV iron sucrose and superior to those of oral iron supplementation.

While head-to-head data for FCM versus IV iron sucrose are available, there are no published studies to establish efficacy of FCM relative to IV iron polymaltose (the other parenteral iron formulation available in Australia) for the treatment of IDA.

FCM is Category B3 — studies of efficacy and safety in pregnancy remain limited. There are no data regarding use of FCM in children aged < 14 years.

Although Ferinject has been available on private script in Australia for more than 3 years and in Europe for more than 6 years, efficacy and safety associated with its long-term use for correcting IDA are not yet known. The longest study duration published to date is 24 weeks.

Reductions in serum phosphate concentrations (hypophosphataemia) to < 0.6 mmol/L (< 2.0 mg/dL) have been consistently reported in FCM trials. As nearly all these events have been transient and asymptomatic, the overall clinical implication of the reductions remains unclear.

FCM is an alternative iron preparation to consider in people aged 14 years or over with iron-deficiency anaemia who require rapid iron repletion.

The ability to deliver a high dose of iron within a short time frame may make FCM suitable for use in a primary care setting. However, FCM is unlikely to provide any advantage compared with existing IV agents for correcting IDA in patients with haemodialysis-dependent chronic kidney disease (CKD).

Closely monitor patients for signs of hypersensitivity during and for 30 minutes after the injection. FCM is for IV use only; do not administer as a subcutaneous or intramuscular injection.

Who is it for?
FCM is a treatment option for people aged 14 years or older with IDA who require rapid iron repletion but are unable to take, or fail to respond to, oral iron preparations. The PBS listing restriction requires that diagnosis must be based on laboratory tests (Table 1).²

Precautions and contraindications
FCM is not recommended in the first trimester of pregnancy and should be used with caution during the second and third trimesters.²

FCM is contraindicated for use:²
- in persons with known sensitivity to ferric carboxymaltose or any of its excipients
- in anaemia not attributed to iron deficiency (eg, other microcytic anaemia)
- when there is evidence of iron overload or disturbances in iron utilisation.
Iron deficiency is a common cause of anaemia. In Australia current clinical management recommends use of oral iron (in appropriate doses and for sufficient duration) as first-line therapy for most patients presenting with IDA. However, oral iron therapy may be of limited benefit to some people, including those with impaired intestinal iron absorption (e.g., irritable bowel disease IBD or CKD) or who experience GI side effects that reduce adherence (e.g., nausea, constipation and abdominal pain).

Oral iron therapy may also be inappropriate in cases of severe IDA, in which rapid iron repletion is required to prevent physiological decompensation or the need for blood transfusion.

An alternative IV treatment for correcting iron deficiency

FCM has been available on private script in Australia for more than 3 years and in Europe for more than 6 years. It is the third parenteral iron formulation and the fourth product to be listed on the PBS for IV correction of iron-deficiency anaemia (Table 2).

### Table 1. Laboratory blood test results that suggest a diagnosis of IDA*7

<table>
<thead>
<tr>
<th>Hb (g/L)</th>
<th>Mean cell volume and mean cell Hb</th>
<th>Serrum ferritin (micrograms/L)</th>
<th>Transferrin or total iron-binding capacity</th>
<th>Transferrin saturation</th>
<th>Serum iron</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 130 g/L (men)</td>
<td>Low (or normal in early IDA)*</td>
<td>&lt; 15–30 adults†</td>
<td>High*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 120 g/L (women)</td>
<td></td>
<td>&lt; 10–12 children</td>
<td></td>
<td></td>
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<tr>
<td>&lt; 110 g/L (pregnant women and preschool children)</td>
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</table>

**Hb** Haemoglobin

* Compared with laboratory reference range for age, sex and gestation if applicable
† In an anaemic adult, a serum ferritin concentration < 15 micrograms/L is diagnostic of IDA and a level of 15–30 micrograms/L is highly suggestive
‡ Ideally performed on fasting morning sample
§ Serum iron level is markedly labile, with a significant diurnal variation, is low in both iron deficiency and inflammation, and should not be used to diagnose iron deficiency

### Table 2. PBS-listed parenteral iron preparations available in Australia

<table>
<thead>
<tr>
<th>Name/product</th>
<th>Formulation</th>
<th>Elemental iron content</th>
<th>PBS indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferinject</td>
<td>Ferric carboxymaltose</td>
<td>500 mg/10 mL ampoule</td>
<td>For treatment of iron deficiency when oral iron preparations are ineffective or cannot be used. The diagnosis must be based on laboratory tests</td>
</tr>
</tbody>
</table>
| Ferrum H     | Iron polymaltose | 100 mg/2 mL ampoule | For the treatment of iron-deficiency anaemia in the following circumstances:  
  ➢ when oral therapy is contraindicated  
  ➢ when enteric absorption of iron is defective  
  ➢ when patient non-compliance or persistent GI intolerance makes oral therapy impractical |
| Ferrosig     | Iron polymaltose | 100 mg/2 mL ampoule | |
| Venofer      | Iron sucrose | 100 mg/5 mL ampoule | For the treatment of iron-deficiency anaemia in patients undergoing chronic haemodialysis and who are receiving supplemental erythropoietin therapy. The diagnosis of iron deficiency must be based on appropriate laboratory tests (e.g., serum ferritin, serum iron, transferrin saturation and hypochromic red cells) |
It may be a suitable alternative in many people unable to tolerate oral therapy, who have poor compliance or who require rapid replenishment of iron stores.

After IV administration of FCM, iron is incorporated into red blood cells within 6–9 days. In one study, after 24 days, iron utilisation was 91–99% in iron-deficiency anaemia and 61–84% in renal anaemia.2

**Large rapid dosing suitable for non-hospital setting**

FCM can be rapidly infused (15 minutes or less) in large single doses (up to 1000 mg; 20 mg/kg).2

Large total-dose infusions of IV iron polymaltose (commonly 1000–2500 mg for an adult), given at rates recommended in the approved Product Information, require around 5 hours.2,11

Accelerated rates of infusion for large iron polymaltose doses have been described but these are predominantly anecdotal reports.7,13

Further, although both iron polymaltose and iron sucrose can be infused over a short time frame of 10–15 minutes, the dose of iron that can be delivered is substantially lower (100–200 mg).10,13 For these products, multiple patient visits may be required to achieve a therapeutic dose.

**No advantage for patients with IDA receiving haemodialysis**

For patients with IDA who require haemodialysis, iron repletion can be administered concomitantly during the dialysis session.

As iron sucrose and iron polymaltose already provide treatment in this setting,10,13 the availability of FCM for rapid infusion is unlikely to offer any additional healthcare resource benefits.

Moreover, while two formulations of FCM are available (2 mL/100 mg iron and 10 mL/500 mg iron), only the latter has been listed for PBS reimbursement.1 This is of some relevance, as a single daily injection of FCM should not exceed 200 mg iron in patients with haemodialysis-dependent CKD.2

In all other patient groups, administration of FCM for treating IDA should not exceed 1000 mg iron per week.2 People requiring a cumulative iron dose above this will need to have a minimum of two infusions spaced at least 1 week apart. This dose restriction may limit the benefit of FCM for some patients in non-hospital or community settings.

**How does it compare?**

The efficacy of FCM for correcting IDA has been evaluated across a range of clinical conditions including IBD,14,15 CKD,16,17 chronic heart failure,18 menorrhagia19 and postpartum anaemia.20–22

**Haemoglobin response similar to that with iron sucrose, but with fewer doses**

Results from prospective and retrospective trials have confirmed that large doses of FCM given in fewer injections can increase Hb levels with efficacy comparable to that of multiple small dose injections of iron sucrose.5,23–25

In the 8-week REPAIR-IDA trial,23 involving IDA patients with non-dialysis-dependent CKD, two doses of FCM (750 mg/dose, n = 1276) were shown to be non-inferior to a typical dosing strategy of iron sucrose (five or fewer infusions of 200 mg, n = 1285).

More people treated with FCM had a sustained Hb increase of ≥ 10 g/L from baseline to study end than for those given iron sucrose (48.6% vs 41.0%, 95% CI 3.6% to 11.6%).23

Mean increases in serum ferritin and transferrin saturation were also significantly greater in the FCM group compared with the iron sucrose group. The mean total iron dose received over the treatment phase was 1464 ± 158 mg in the FCM group and 963 ± 138 mg in the iron sucrose group.23

Similarly, among patients with IDA and associated IBD, three or fewer 500–1000 mg FCM infusions showed improved efficacy compared with iron sucrose (up to 11 infusions of 200 mg iron) in the 12-week FERGicor trial.15
A small difference in mean total dose was reported for these treatment groups; 1377 ± 381 mg (FCM) and 1160 ± 316 mg (iron sucrose). At the end of the study, 66% of the FCM cohort had experienced a ≥ 2 g/dL Hb increase compared with 54% of the iron sucrose arm (p = 0.004). More people in the FCM treatment group experienced correction of anaemia compared with the iron sucrose group at study end (73% vs 62%, respectively, p = 0.015). The simpler FCM dosing regimen was also associated with greater patient compliance compared with iron sucrose (p < 0.001).

Improves anaemia as well as, or better than, oral iron and standard medical care

The efficacy of FCM for the treatment of iron-deficiency anaemia was compared with oral iron (ferrous sulphate) in several randomised open-label trials. Overall, FCM (≤ 1000 mg per infusion) was at least as effective, or more effective, than oral iron (ferrous sulphate 325 mg three times daily or 100 mg twice daily) at correcting haemoglobin, ferritin and transferrin saturation levels. Perhaps not surprisingly, haemoglobin increases were more rapid with FCM than with oral iron therapy.

The comparative effectiveness of FCM in treating iron-deficiency anaemia versus standard medical care (including IV iron formulations) has also been investigated in several randomised controlled trials. Clinically meaningful improvements in haemoglobin and iron indices have been observed compared with standard medical care in patients with IDA associated with conditions such as CKD, menorrhagia, IBD and after post-bariatric surgery or delivery.

Clinical equivalence with IV iron polymaltose is not known

To date, there have been no head-to-head comparisons of FCM with iron polymaltose, which is FDM’s main IV iron formulation comparator in Australia.

Indirect comparisons between FCM and iron polymaltose, based on their efficacy relative to oral iron, are also not possible due to marked heterogeneity in patients and outcomes.

Safety issues

Pooled safety information for FCM comprising the total short-term phase II/III database of 20 trials has recently been published, and is the largest database reported thus far for any IV iron formulation.

In this set of patients administered FCM (n = 5799), treatment-related side effects that occurred in more than 1% of the group included:

- nausea (3.1%)
- hypophosphataemia (1.9%)
- injection-site reactions (1.6%)
- headache (1.4%)
- hypertension (1.3%)
- dizziness (1.2%)

The safety of FCM beyond 24 weeks is yet to be established.

For information about reporting adverse reactions to the TGA, or to report suspected adverse reactions online, see the TGA website or use the ‘Blue Card’ distributed with the October issue of Australian Prescriber.

Monitor patients for hypertension

In recently completed FCM trials, protocol-defined hypertensive events have been reported to occur more frequently among FCM-treated patients compared with those receiving other iron preparations (oral and IV). Most of these events occurred during the observation period following iron injection/infusion.

Monitor patients closely, especially when large single doses > 200 mg iron are administered.

Hypophosphataemia occurs but is transient

An increased risk of transient asymptomatic hypophosphataemia has been observed in trials of FCM and appears to occur more often in association with FCM than with other iron preparations.
Severe cases with clinical sequelae are rare.\textsuperscript{30} Patients at increased risk of this adverse event include those with a concomitant disorder of phosphate homeostasis such as hyperparathyroidism or vitamin D deficiency.\textsuperscript{30}

Cardiopulmonary equipment must be available for managing anaphylaxis before administering FCM

All IV iron preparations carry a small risk of causing life-threatening hypersensitivity reactions.\textsuperscript{2} In the pooled database of short-term phase II/III trials the rate of hypersensitivity or allergic reactions potentially due to FCM treatment was 0.9\% (n = 51/5799) for FCM compared with 0.8\% (n = 42/5272) for all comparators and 1.5\% for other IV iron preparations (n = 37/2439).\textsuperscript{8,29} Patients should be monitored during and immediately after infusion.

**Reason for PBS listing**

In March 2013 the PBAC recommended listing FCM on the PBS as an unrestricted benefit for the treatment of IDA.\textsuperscript{1} Despite a lack of formal comparative data the listing was recommended based on cost-minimisation compared with IV iron polymaltose.\textsuperscript{1}

A subsequent submission made in November 2013 reduced the cost of the 500 mg vial to address the potential use of doses > 1000 mg and requested listing for a single strength of 500 mg only.\textsuperscript{1} This proposed listing differed from the original sponsor submission, which requested an Authority required restriction and also included a 100 mg vial size.\textsuperscript{1}

The PBAC acknowledged that FCM would likely have an advantage over IV iron polymaltose in terms of administration time and would be addressing a clinical need in Australia.\textsuperscript{1}

Do not administer subcutaneously or via intramuscular route

Administer FCM by the IV route ONLY as either an undiluted injection or drip infusion.\textsuperscript{2}

Minimise the risk of injection-site leakage or extravasation (which can cause irritation and permanent discoloration of the skin) by flushing with 0.9\% saline before and after infusion.\textsuperscript{31} If paravenous leakage occurs, stop IV infusion of FCM immediately.\textsuperscript{2}

FCM must only be diluted in sterile 0.9\% saline

Given the potential for FCM precipitation and/or interaction with other dilution agents, use only sterile 0.9\% saline to dilute FCM.\textsuperscript{2}

Dose not to exceed 1000 mg per week

Do not administer more than a maximum single dose of 1000 mg iron (maximum 20 mg iron per kilogram body weight) per week. If the total required dose of iron exceeds 1000 mg, additional doses up to 1000 mg must be given at least 1 week apart.\textsuperscript{2}

**Dosing issues**

Two methods can be used to calculate the individual cumulative dose of iron required for repletion; the Ganzoni Method and the Simplified Method. Both are based on body weight and Hb level. Further instructions regarding these calculations can be found in the Ferinject Product Information.\textsuperscript{2}

**Information for patients**

Advise patients to:

- notify a health professional immediately if they experience breathing difficulties, dizziness or neck or mouth swelling during FCM administration
- plan extra time into their visit, as they will need to be monitored for at least 30 minutes after their injection
- call 000 or have someone take them to the nearest hospital with an emergency department if they experience difficulty breathing, dizziness or neck or mouth swelling in the hours or days after the FCM injection.

Make sure patients:

- understand what injection-site reactions are, and what they need to do if they think they have one
- inform their health professional if they are pregnant.

Discuss the Ferinject Consumer Medicine Information (CMI) leaflet\textsuperscript{1} with the patient.

\textsuperscript{1} Available at www.nps.org.au/medicines/ferinject
REFERENCES


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