

AUSTRALIAN PRODUCT INFORMATION - FERINJECT® (FERRIC CARBOXYMALTOSE) SOLUTION FOR INJECTION

1 NAME OF THE MEDICINE

Ferric carboxymaltose

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2 mL vial contains 100 mg of iron as ferric carboxymaltose.

Each 10 mL vial contains 500 mg of iron as ferric carboxymaltose.

Each 20 mL vial contains 1000 mg of iron as ferric carboxymaltose.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Solution for intravenous use. FERINJECT is a dark brown, non-transparent, colloidal solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

FERINJECT is indicated for treatment of iron deficiency when oral iron preparations are ineffective or cannot be used.

The diagnosis must be based on laboratory tests.

4.2 DOSE AND METHOD OF ADMINISTRATION

Determination of the cumulative iron dose

The cumulative dose for repletion of iron using FERINJECT is determined based on the patient's body weight and Hb level and must not be exceeded. There are two methods for determining the cumulative dose, the Ganzoni Method and the Simplified Method. Caution is recommended with the Simplified Method since it is based on experience in a single trial in adults with median Hb 104 g/L (range 61-146 g/L) and body weight ≥ 35 kg – see section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials.

Patients should be closely monitored when large single doses of FERINJECT (>200 mg iron) are administered since the safety data are limited.

Post repletion, regular assessments should be done to ensure that iron levels are corrected and maintained.

Ganzoni Method

Cumulative Iron Dose = Body Weight *kg* x (Target Hb – Actual Hb *g/L*) x 0.24 + Iron Stores *mg*

where

Target Hb = 130 g/L for body weight <35 kg and 150 g/L for body weight ≥35 kg

Iron Stores = 15 mg/kg body weight for body weight <35 kg and 500 mg for body weight ≥35 kg.

Round down to nearest 100 mg if body weight ≤66 kg and round up to nearest 100 mg if body weight >66 kg.

Simplified Method (for patients of body weight ≥35 kg)

The cumulative iron dose is determined according to the following table:

Hb g/L	Body weight 35 to <70 kg	Body weight ≥70 kg
<100	1500 mg	2000 mg
≥100	1000 mg	1500 mg

For patients with an Hb value ≥140 g/L, an initial dose of 500 mg iron should be given and iron parameters should be checked prior to repeat dosing.

Intravenous injection

FERINJECT may be administered by intravenous injection using undiluted solution up to a maximum single dose of 1,000 mg iron (up to a maximum of 20 mg iron/kg body weight). For doses greater than 200 and up to 500 mg iron, FERINJECT should be administered at a rate of 100 mg iron/min. For doses greater than 500 and up to 1,000 mg iron, FERINJECT should be administered over 15 minutes. Do not administer more than 1,000 mg of iron per week.

Intravenous infusion

FERINJECT may be administered by intravenous infusion up to a maximum single dose of 1,000 mg iron (up to a maximum of 20 mg iron/kg body weight). Do not administer more than 1,000 mg iron per week.

Haemodialysis-dependent chronic kidney disease

In haemodialysis-dependent chronic kidney disease patients, a single daily injection of FERINJECT should not exceed 200 mg iron.

Pregnancy

It is recommended that the maximum cumulative dose in pregnant patients is restricted to 1,000mg for patients with Hb ≥90 g/L, or 1,500 mg in patients with Hb <90 g/L. Do not administer more than 1,000 mg iron per week.

Method of administration

FERINJECT must be administered only by the intravenous route: by bolus injection, or during a haemodialysis session undiluted directly into the venous limb of the dialyser, or by infusion. In case of infusion FERINJECT must be diluted only in sterile 0.9% m/V sodium chloride solution as follows:

Dilution plan of FERINJECT for intravenous infusion

FERINJECT	Iron	Maximum amount of sterile 0.9% m/V sodium chloride solution	Minimum administration time
2 to 4 mL	100 to 200 mg	50 mL	3 minutes
>4 to 10 mL	>200 to 500 mg	100 mL	6 minutes
>10 to 20 mL	>500 to 1,000 mg	250 mL	15 minutes

Note: For stability reasons, dilutions to concentrations less than 2 mg iron/mL (not including the volume of the ferric carboxymaltose solution) are not permissible.

FERINJECT must not be administered by the subcutaneous or intramuscular route.

Inspect vials visually for sediment and damage before use. Use only those containing sediment-free, homogeneous solution.

Each vial of FERINJECT is intended for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

FERINJECT must only be mixed with sterile 0.9% m/V sodium chloride solution. No other intravenous dilution solutions and therapeutic agents should be used, as there is the potential for precipitation and/or interaction. For dilution instructions, see above.

This medicinal product must not be mixed with other medicinal products than those mentioned above. The compatibility with containers other than polyethylene and glass is not known.

4.3 CONTRAINDICATIONS

The use of FERINJECT is contraindicated in cases of:

- hypersensitivity to ferric carboxymaltose complex, to FERINJECT or to any of its excipients
- anaemia not attributed to iron deficiency, e.g. other microcytic anaemia
- evidence of iron overload or disturbances in utilisation of iron

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**Iron Overload/Haemosiderosis**

Body iron excretion is limited and excess tissue iron can be hazardous causing haemosiderosis. Patients receiving FERINJECT require regular monitoring of red cell indices and serum ferritin to detect iron overload. If there is evidence of iron overload, iron therapy should be withheld.

Patients with Infections

Parenteral iron must be used with caution in case of acute or chronic infection, asthma, eczema or atopic allergies. It is recommended that the administration of FERINJECT is stopped in patients with ongoing bacteraemia. In patients with chronic infection a risk/benefit evaluation has to be performed, taking into account the suppression of erythropoiesis.

Hypersensitivity Reactions

Parenterally administered iron preparations can cause hypersensitivity reactions including anaphylactoid reactions, which may be fatal. Therefore, facilities for cardio-pulmonary resuscitation must be available. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately. Hypersensitivity reactions have also been reported after previously uneventful doses of any parenteral iron complexes, including ferric carboxymaltose. Each patient should be observed for adverse effects for at least 30 minutes following each FERINJECT administration.

Hypophosphataemia

Parenterally administered iron preparations can cause hypophosphataemia which in most cases is transient and without clinical symptoms. Cases of hypophosphataemia requiring medical attention were reported, mainly in patients with existing risk factors and after prolonged exposure to high-dose IV iron.

Paravenous Leakage

Caution should be exercised to avoid paravenous leakage when administering FERINJECT. Paravenous leakage of FERINJECT at the administration site may lead to potentially long lasting brown discolouration and irritation of the skin. In case of paravenous leakage, the administration of FERINJECT must be stopped immediately.

Sodium Content

One mL of undiluted FERINJECT contains up to 5.5 mg (0.24 mmol) of sodium. This should be considered when prescribing FERINJECT to patients on sodium-controlled diets.

Use in hepatic impairment

In patients with liver dysfunction, parenteral iron should only be administered after careful risk/benefit assessment. Parenteral iron administration should be avoided in patients with hepatic dysfunction where iron overload is a precipitating factor, in particular Porphyria Cutanea Tarda (PCT).

Use in the elderly

No data available.

Paediatric use

The use of FERINJECT has not been studied in children and therefore is not recommended in children under 14 years.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

As with all parenteral iron preparations the absorption of oral iron is reduced when administered concomitantly. Therefore, if required, oral iron therapy should not be started for at least 5 days after the last administration of FERINJECT.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Reduced weights of reproductive organs (prostate, seminal vesicle, epididymides, testis or uterus) were seen in rats and dogs at maternally toxic doses following repeated IV dosing with ferric carboxymaltose. There were no effects of ferric carboxymaltose on the fertility or reproductive performance of rats given thrice weekly IV doses of up to 30 mg/kg roughly equal to the maximum weekly clinical dose, based on body surface area (BSA).

Use in pregnancy (Category B3)

Studies in rats have shown that iron released from ferric carboxymaltose can cross the placental barrier.

In pregnant and iron-replete rabbits and rats, embryotoxicity (decreased placental or litter weights and increased resorptions) and increases in fetal skeletal abnormalities (thickened/kinked ribs in rats and cranial, forepaw and/or limb abnormalities in rabbits) were observed at maternally toxic IV iron doses from 9 or 30 mg/kg/day, respectively given during organogenesis (1-2 times the maximum weekly clinical dose, based on body surface area (BSA)). No effects were observed at IV iron doses up to 4.5 or 9 mg/kg/day, respectively (0.5 times the maximum weekly clinical dose, based on BSA).

There is no efficacy and safety data on the use of FERINJECT in human pregnancy less than 16 weeks' gestation. Iron deficiency occurring in the first trimester of pregnancy can in many cases be treated with oral iron.

There are limited data from the use of FERINJECT in women in pregnancy beyond 16 weeks' gestation. A careful risk/benefit evaluation is required before use during pregnancy and FERINJECT should not be used during pregnancy unless clearly necessary.

If the benefit of FERINJECT treatment is judged to outweigh the potential risk to the fetus, it is recommended that treatment in pregnancy should be confined to women beyond the 16th week of gestation.

Use in lactation

Clinical studies showed that transfer of iron from FERINJECT to human milk was negligible ($\leq 1\%$).

Evidence of delayed postnatal growth and development has been observed in rats exposed to ferric carboxymaltose. Milk transfer of administered iron from ferric carboxymaltose was demonstrated in lactating rats. Caution should be exercised when FERINJECT is used in lactating woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical studies experience

Adverse drug reactions reported in patients treated with ferric carboxymaltose (n=7,391) from completed clinical trials are summarized in the table below.

System Organ Class		Common (≥1/100, <1/10)	Uncommon (≥1/1,000, <1/100)	Rare (≥1/10,000, <1/1,000)
Immune System Disorders		–	Hypersensitivity	Anaphylactoid reactions
Nervous System Disorders		Headache, dizziness	Paraesthesia, dysgeusia	–
Cardiac Disorders		–	Tachycardia	–
Vascular Disorders		Hypertension, flushing	Hypotension	–
Respiratory, Thoracic and Mediastinal Disorders		–	Dyspnoea	–
Gastrointestinal Disorders		Nausea	Vomiting, dyspepsia, flatulence, abdominal pain, constipation, diarrhoea	–
Skin and Subcutaneous Tissue Disorders		–	Pruritus, urticaria, erythema, rash ⁽¹⁾	–
Musculoskeletal and Connective Tissue Disorders		–	Myalgia, back pain, arthralgia, pain in extremity, muscle spasms	–
General Disorders and Administration Site Conditions		Injection/Infusion site reactions ⁽²⁾	Pyrexia, fatigue, chest pain, oedema peripheral, pain, chills	Malaise
Investigations		-	Alanine aminotransferase increased, aspartate amino transferase increased, gamma-glutamyltransferase increased, blood lactate dehydrogenase increased, blood alkaline phosphatase increased	–
Metabolism and Nutritional Disorders		Hypophosphataemia [#]	–	–

#: based on laboratory findings

- 1 Includes the following preferred terms: rash (individual ADR frequency determined as uncommon) and rash erythematous, -generalised, -macular, -maculo-papular, -pruritic (all individual ADRs frequencies determined as rare).
- 2 Includes, but is not limited to the following preferred terms: injection/infusion site -pain, -haematoma, -discolouration, -extravasation, -irritation, reaction, (all individual ADRs frequencies determined as uncommon) and -paraesthesia (individual ADR frequency determined as rare).

Note: ADR = Adverse drug reaction.

The most commonly reported ADR is nausea, occurring in 2.9% of the patients.

Undesirable Effects from Post-marketing Spontaneous Reporting

As part of the continuing post-marketing surveillance of ferric carboxymaltose, the following adverse reactions have been observed:

Post-marketing Spontaneous Reports

System Organ Class	Preferred Terms ⁽¹⁾
Nervous System Disorders	Loss of consciousness and vertigo
Psychiatric Disorders	Anxiety
Cardiovascular Disorders	Syncope, Pre-syncope
Skin and Subcutaneous Tissue Disorders	Angioedema, dermatitis, pallor, and face oedema
Respiratory, Thoracic and Mediastinal Disorders	Bronchospasm
General Disorders and Administration Site Conditions	Influenza like illness

¹ Frequency not known.

Post-marketing Spontaneous Reports in Pregnancy Cases

System Organ Class	Preferred Terms ⁽¹⁾
Immune System Disorders	Hypersensitivity, anaphylactoid reactions
Nervous System Disorders	Headache, dizziness
Vascular Disorders	Hypotension, Blood pressure systolic decreased
Skin and Subcutaneous Tissue Disorders	Rash, urticaria
Respiratory, Thoracic and Mediastinal Disorders	Dyspnoea
General Disorders and Administration Site Conditions	Extravasation, infusion site discolouration, injection site discolouration

¹ Frequency not known.

There have been individual case reports of temporally-related, but not causally-related, events of: antenatal fetal ductus venosus thrombosis, uterine hypertonia or contractions and fetal demise when Ferinject has been used in pregnancy.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Administration of FERINJECT in quantities exceeding the amount needed to correct iron deficit at the time of administration may lead to accumulation of iron in storage sites eventually leading to haemosiderosis. Monitoring of iron parameters such as serum ferritin and transferrin saturation may assist in recognising iron accumulation. If iron accumulation has occurred, the use of an iron chelator may be considered.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Ferric carboxymaltose (FCM) solution for injection/infusion contains iron in a stable ferric state as a complex with a carbohydrate polymer designed to provide iron for the iron transport and storage proteins in the body (transferrin and ferritin). FCM was effective in increasing haemoglobin (Hb) and serum ferritin concentrations in patients with mild to moderate iron-deficiency anaemia. The intravenous (IV) iron dose was 500 mg weekly for up to 4 weeks (n=20) or 1,000 mg weekly for up to 2 weeks (n=26). With the 500 mg iron dose, 37% of patients achieved normal Hb levels within 8 weeks and 75% achieved a ≥ 20 g/L increase in Hb on at least one occasion. With 1,000 mg iron, 48% of patients achieved normal Hb levels within 6 weeks and 73% achieved a ≥ 20 g/L increase in Hb on at least one occasion. The target serum ferritin concentration 100-500 $\mu\text{g/L}$ was reached with both doses and remained within the target range at 2 weeks follow-up (at 6 and 4 weeks respectively for the two dose groups)-data were only available for about half the 500 mg iron dose group.

Clinical trials

Clinical studies showed that the haematological response and the filling of the iron stores was faster after intravenous administration of FCM than with orally administered comparators.

The phase III studies undertaken with FCM included patients with iron deficiency (ID) of different aetiologies, i.e. associated with non-dialysis and dialysis dependent chronic kidney disease (CKD), inflammatory bowel disease, heavy menstrual bleeding, post-partum iron deficiency anaemia (IDA), pregnancy (second and third trimester) or patients with chronic heart failure and iron deficiency.

IDA associated with haemodialysis-dependent chronic kidney disease

The efficacy and safety of FCM compared to Venofer[®] (iron sucrose, intravenous) for the treatment of IDA secondary to chronic renal failure was assessed in a multi-centre, open-label, randomised, parallel-group, Phase III study in 237 patients on haemodialysis or haemodiafiltration. IDA was defined as Hb ≤ 115 g/L in addition to transferrin saturation (TSAT) $< 20\%$ and/or serum ferritin < 200 $\mu\text{g/L}$. Patients received 200 mg iron 2 or 3 times weekly (depending on the timing of dialysis sessions) until their individual calculated cumulative dose had been reached. The mean duration of treatment was 15.8 days (range 1 to 27) and 16.2 days (range 1 to 43 days) for the FCM and Venofer[®] groups, respectively.

Patients treated with erythropoietin (EPO) should have had received this treatment for at least 8 weeks prior to inclusion in the study and increases in the dose of EPO were not permitted. The primary efficacy endpoint was defined as the percentage of patients reaching an increase in Hb of ≥ 10 g/L at 4 weeks. The percentage of responders was 44.1% (52/118) in the FCM group and 35.3% (41/116) in the Venofer[®] group; the difference between groups was not statistically significant ($\chi^2 = 0.2254$). At follow-up 4 weeks after the final dose of medication, secondary efficacy parameters (Hb ≥ 110 -120 g/L, serum ferritin 200-800 $\mu\text{g/L}$, TSAT 20-50%) demonstrated successful increase in iron stores for both treatment groups.

IDA associated with non-dialysis-dependent chronic kidney disease

A multi-centre, randomised, open-label, controlled, 8-week, Phase III study in 255 patients was conducted to compare the safety and efficacy of intravenous infusions of the FCM solution with oral administration of ferrous sulphate, independent of Hb response to EPO, in treating IDA in non-dialysis-dependent chronic kidney disease (ND-CKD). IDA was defined as Hb ≤ 110 g/L, TSAT $\leq 25\%$, and serum ferritin ≤ 300 $\mu\text{g/L}$. Patients treated with EPO should have had received this treatment for at least 8 weeks prior to inclusion in the study and increases in the dose of EPO were not permitted. Patients randomised to FCM treatment received 1 to 3 doses of FCM solution intravenously at 2-4 week intervals: 15 mg iron/kg for weight ≤ 66 kg to a maximum of 1,000 mg iron for the initial dose and a maximum of 500 mg iron for subsequent doses. Patients randomised to oral iron treatment received ferrous sulphate tablets (65 mg iron) 3 times daily for 8 weeks.

In a modified intent-to-treat analysis which excluded 8 FCM patients and 2 ferrous sulfate patients, the primary efficacy endpoint, defined as the percentage of patients with an increase in Hb ≥ 10 g/L at any time between baseline and end of study, or time of intervention, was reached by 60.4% (87/144) of FCM-treated patients compared to 34.7% (35/101) of oral iron-treated patients ($p < 0.001$; 95% confidence interval (CI) 13.0, 38.5). The modified intent-to-treat population comprised patients with at least one dose of study medication, stable erythropoietin dose, at least one post-baseline Hb assessment and GFR ≤ 45 mL/min/1.73 m². FCM was also demonstrated to be superior to oral iron across all secondary ranked efficacy endpoints: Hb change ≥ 10 g/L and a serum ferritin change ≥ 160 $\mu\text{g/L}$ at any time during the study (60.4% versus 0.0%, respectively; $p < 0.001$; 95% CI 48.2, 72.6) or a Hb change ≥ 10 g/L before Day 42 (54.2% versus 28.7%, respectively; $p < 0.001$; 95% CI 12.8, 38.1).

In a 44-week extension to this study, the efficacy of FCM in the long-term maintenance treatment of anaemia in ND-CKD was evaluated in 140 patients. Clinical success (Hb ≥ 110 g/L, serum ferritin 100-800 $\mu\text{g/L}$, TSAT 30-50%) was achieved in 51.4% (72/140) of patients, with 10% (14/140) exhibiting sustained clinical success at 50% or more of the assessments.

In the ND-CKD subgroup of another study, the safety and efficacy of IV injection of FCM solution, 15 mg iron/kg body weight up to 1,000 mg iron administered over 15 min. was assessed. The comparator was standard medical care (SMC) as determined by the investigator.

The primary endpoint was the incidence of treatment-emergent serious adverse events from Day 0 to 30 days after the last dose of study drug. The safety population contained 204 FCM subjects and 212 SMC subjects. The majority had mild anaemia (mean Hb 104 g/L in FCM group and 102 g/L in control group). There were no serious adverse events assessed as related to FCM. Based on these limited data and the lack of specific serious drug-related adverse reactions, the safety of single FCM doses of 1,000 mg iron appeared equal to SMC.

Efficacy was assessed in a modified intent-to-treat population of 202 FCM subjects and 203 SMC subjects. Achievement of Hb ≥ 120 g/L was comparable in the two groups at 30 days - FCM 9.9% and SMC 6.9% (Fisher's Exact Test $p = 0.29$).

IDA secondary to inflammatory bowel disease

The efficacy of infusions of FCM solutions compared to oral administration of ferrous sulphate in the treatment of IDA secondary to chronic inflammatory bowel disease was examined in a multi-centre, open-label, randomised, 12-week, Phase III study in 200 patients. 4 patients did not receive study drug and were excluded from the analysis. IDA was defined as Hb \leq 110 g/L in combination with TSAT $<$ 20% and/or serum ferritin $<$ 100 μ g/L. Patients were randomised in a 2:1 (FCM: ferrous sulphate) ratio to receive 1 of 2 treatments: FCM intravenous on Day 1 with subsequent doses at 1-week intervals until the patient's calculated cumulative dose had been reached (a maximum dose of 1,000 mg iron per infusion) or oral ferrous sulphate capsules (100 mg iron) twice daily for 12 weeks. Based on the primary response parameter of change in mean Hb from baseline to Week 12 (36.0 g/L FCM group, 32.9 g/L oral iron group), the results of this study demonstrated that FCM was non-inferior to ferrous sulphate. The non-inferiority criterion was lower limit of 95% CI of difference FCM minus ferrous sulphate \geq -5.0 g/L. The non-inferiority criterion was met in both the intent-to-treat and per protocol populations. Furthermore, the mean Week-12 values of serum ferritin (80.2 μ g/L FCM group, 38.6 μ g/L oral iron group) and TSAT (23.1% FCM group, 29.2% oral iron group) demonstrated a successful repletion of the iron stores in patients treated with FCM.

In another study, FCM dosing based on a simplified dosing scheme with four Hb-weight subgroups (see section 4.2 DOSE AND METHOD OF ADMINISTRATION) was compared with Venofer[®] dosing based on the Ganzoni formula. The FCM dose was given in up to three IV infusions on Days 1, 8 and 15 in single doses of up to 1000 mg iron. The Venofer[®] dose was given in up to 11 IV infusions in doses not exceeding 200 mg iron not more than three times per week. The primary endpoint was the percentage of patients achieving a Hb increase \geq 20 g/L at Week 12. The demographic and haematological characteristics of the two groups were similar. About 60% of subjects were female, median age was 39 years (range 18-81), median weight 67 kg (range 39-137), median baseline Hb 104 g/L (range 61-146) and median baseline serum ferritin 7 μ g/L (range 2-299). Subjects in the two treatment groups achieved at least comparable Hb response overall and in the Hb-weight subgroups (see Table 1).

Table 1. Efficacy of FCM (new dosing method) versus Venofer[®] (Ganzoni dose calculation) in iron deficiency anaemia associated with inflammatory bowel diseases - trial FER-IBD-07-COR – patients with 12-week assessment

	FCM n=228	Venofer[®] n=220	Difference [95% CI]
Hb Response (increase \geq 20 g/L) at Week 12	65.8%	53.6%	12.2% [3.1%, 21.0%]
Hb<100 g/L – Wt 35-<70 kg	missing n=7 n=59 86.4%	missing n=8 n=44 75.0%	11.4% [-4.1%, 26.9%]
Hb<100 g/L – Wt \geq 70 kg	n=31 90.3%	n=24 100.0%	-9.7% [-20.1%, 0.7%]
Hb \geq 100 g/L – Wt 35-<70 kg	n=70 75.7%	n=78 71.8%	3.9% [-10.2%, 18.1%]
Hb \geq 100 g/L – Wt \geq 70 kg	n=61 88.5%	n=66 75.8%	12.8% [-0.3%, 25.8%]

IDA secondary to heavy menstrual bleeding

The safety and efficacy of intravenous infusions of FCM solution, compared to oral administration of ferrous sulphate, in improvement of Hb levels in females with IDA secondary to heavy menstrual bleeding was assessed in a multi-centre, randomised, open-label, 6-week, Phase III study. At enrolment, patients had a baseline Hb \leq 114 g/L, TSAT \leq 25%, and serum ferritin \leq 100 μ g/L. Patients were randomised to receive either oral ferrous sulphate tablets (65 mg iron) 3 times daily for 6 weeks or weekly infusions of FCM solution (a

maximum dose of 1,000 mg iron per infusion) until the patient's calculated cumulative dose had been reached, to a maximum of 2,500 mg iron. In a modified intent-to-treat analysis which excluded 18 FCM patients and 6 ferrous sulphate patients, FCM was shown to be superior to oral iron in achieving an increase from baseline in Hb ≥ 20 g/L at any time during the study: 82.0% (187/228) in the FCM group versus 61.8% (139/225) in the oral iron group ($p < 0.001$; 95% CI 12.2, 28.3). The modified intent-to-treat population comprised patients with at least one dose of study medication, baseline Hb ≤ 110 g/L, TSAT $\leq 25\%$, serum ferritin ≤ 100 $\mu\text{g/L}$, at least one post-baseline Hb assessment and confirmed diagnosis of heavy menstrual bleeding.

Post partum IDA

The safety and efficacy of FCM compared to oral ferrous sulphate as treatment for post partum IDA (Hb ≤ 100 g/L or ≤ 105 g/L) was assessed in 3 randomised, open-label, multi-centre trials. In 2 of the studies, patients were randomised 1:1 to receive either oral ferrous sulphate tablets (65 mg iron) 3 times daily for 6 weeks or weekly intravenous FCM at dosages based on the calculated iron deficit. A maximum of 1,000 mg of iron (15 mg iron/kg body weight for pre-pregnancy weight ≤ 66 kg), as intravenous FCM solution, was given at weekly intervals until the individual's calculated cumulative iron dose had been reached or a maximum total iron dose of 2,500 mg had been administered. In the third study, patients were randomised 2:1 to receive either oral ferrous sulphate capsules (100 mg iron) twice daily for 12 weeks or weekly intravenous FCM at dosages based on the calculated iron deficit (to a maximum of 3 infusions and not exceeding a weekly dose of 1,000 mg iron).

In all 3 studies, FCM was shown to be efficacious for the treatment of IDA in post partum subjects. In the first study, the superiority of FCM was demonstrated according to the primary efficacy endpoint (defined as Hb > 120 g/L), with a greater proportion of patients in the FCM group (91.4%, 127/139) versus the oral iron group (66.7%, 98/147) achieving success at any time during the study ($p < 0.0001$; 95% CI 15.20, 34.20). This was based on a modified intent-to-treat population which excluded 4 FCM patients and one ferrous sulfate patient.

In the second study, FCM was demonstrated to be non-inferior to oral iron among subjects who achieved an increase in Hb ≥ 20 g/L: 96.4% (162/168) of the FCM group versus 94.1% (159/169) of the oral iron group (95% CI -2.19, 6.88). The analysis was in a modified intent-to-treat population (6 FCM patients and 9 ferrous sulphate patients excluded) and the non-inferiority margin was 15% based on a 1-sided 97.5% CI of the treatment difference. Statistically significantly greater increases from baseline to highest Hb, TSAT, and serum ferritin values were also observed in the FCM groups compared with the oral iron groups.

In the third study, FCM was shown to be non-inferior to ferrous sulphate for the mean change in Hb from baseline to Week 12 (33.4 g/L in the FCM group ($n=227$) versus 31.8 g/L in the oral iron group ($n=117$)). The non-inferiority criterion was lower limit of 95% CI of difference FCM minus ferrous sulfate ≥ -5.0 g/L. The non-inferiority criterion was met in both the intent-to-treat and per protocol populations.

In another study in patients with iron deficiency anaemia due to heavy menstrual bleeding (HMB) or post-partum, the safety and efficacy of IV injection of FCM solution, 15 mg iron/kg body weight up to 1,000 mg iron administered IV over 15 min, was assessed. The comparator was standard medical care (SMC) as determined by the investigator.

The primary endpoint was the incidence of treatment-emergent serious adverse events from Day 0 to 30 days after the last dose of study drug. The safety population contained 996 FCM subjects and 1,022 SMC subjects. Approximately 60% of the subjects had post-partum anaemia (median Hb 103 g/L) and the other 40% anaemia associated with HMB (median Hb 96 g/L). There were no serious adverse events assessed as related to FCM. Based on overall

incidences and the lack of specific drug-related serious adverse reactions, the safety profiles of FCM and SMC oral iron appeared similar. There was insufficient exposure to SMC IV iron for it to be included in the assessment.

Efficacy was assessed in a modified intent-to-treat population which was approximately 30% less than the randomised population, although still balanced. Achievement of Hb >120 g/L was significantly better with FCM than SMC in the two subgroups at 30 days (see Table 2).

Table 2. Efficacy of FCM in single doses up to 1,000 mg iron versus SMC in iron deficiency anaemia associated with heavy menstrual bleeding and post-partum – trial 1VIT07017 – 30 days follow-up - modified intent-to-treat

	FCM	SMC	Difference p-value ²
Heavy Menstrual Bleeding	n=331	n=329	
Hb >120 g/L ¹	34.4%	15.8%	18.6% p<0.001
Post-Partum	n=342	n=357	
Hb >120 g/L ¹	68.1%	50.7%	17.4% p<0.001

FCM: Ferric Carboxymaltose. SMC: Standard Medical Care as determined by the investigator.

¹ Anytime between baseline and end of study of surgical intervention. ² Fisher's Exact Test.

Pregnancy

In a study in pregnant women in the second and third trimester with iron deficiency anaemia (FER-ASAP-2009-01) randomised to receive either ferric carboxymaltose (maximum permitted total dose 1000 mg for baseline haemoglobin 91-104 g/L or 1500 mg for baseline haemoglobin 80-90 g/L) or oral iron (200 mg orally twice daily). The range of gestation at study entry for the ferric carboxymaltose arm was 16.0 to 33.9 weeks.

Superiority of ferric carboxymaltose for the primary outcome of change in Hb from baseline to week 3 was not shown. The mean total iron dose was 1,028.5 mg (median 1,000 mg) in the ferric carboxymaltose group compared to 11,959.2 mg (median 12,300 mg) in the oral iron group.

Iron deficiency associated with chronic heart failure

In a population with chronic heart failure, a double-blind, placebo-controlled, randomised study demonstrated a statistically significant improvement in both Patient Global Assessment and New York Heart Association functional class at Week 24 (odds ratio for improvement, 2.51 (95% CI 1.75-3.61; p<0.001) and 2.40 (95% CI 1.55-3.71; p<0.001), respectively). The results applied to iron deficient patients with and without anaemia. Superior improvements (p<0.001) were also observed in the 6-minute walk test and patient quality of life (QoL) for patients treated with ferric carboxymaltose.

Study FER-CARS-05 (CONFIRM-HF) in subjects with chronic heart failure and iron deficiency demonstrated the benefit of FCM relative to placebo in improving functional capacity as measured by the change in 6-minute walk test distance from baseline to Week 24, with a difference between treatment groups (least squares mean (\pm standard error)) of 33.2 \pm 10.52 m (p=0.002), thereby confirming the hypothesis of above study. The treatment benefit of FCM in improvement of 6-minute walk test distance was statistically significant from week 24 (p<0.001) and was sustained throughout the study to Week 52 (p<0.001), demonstrating the long-term benefit of iron repletion over a period of 1 year. The improvements in PGA and NYHA functional class were also seen in FCM-treated subjects, with statistical significance for the difference between treatment groups achieved from Week 12 (PGA) or Week 24 (NYHA

functional class) onwards. At Week 52 Endpoint, 54.7% of subjects in the FCM group showed some improvement in PGA score compared to 35.1% in the placebo group, and 18.0% of subjects in the FCM group showed an improvement by 1 NYHA functional class, compared to only 3.3% in the placebo group. Improvements in fatigue score and overall Kansas City cardiomyopathy questionnaire score were also seen, with statistical significance for the difference between treatment groups (in favour of FCM) achieved from Week 12 onwards.

There are no data available regarding the long term use of FERINJECT.

5.2 PHARMACOKINETIC PROPERTIES

After a single 100 mg IV iron dose of FCM solution (n=6) injected over 1 min, serum iron concentration peaked at a mean of 15 min. After 500, 800 or 1,000 mg iron in 250 mL normal saline infused over 15 min (n=6 for each dose), serum iron concentration peaked at means of 20 min, 1 h and 1.2 h, respectively. The mean volume of distribution was approximately 3 L, corresponding to the plasma volume. Mean plasma clearance ranged from 2.6-4.4 mL/min and terminal half life from 7-12 h. Renal elimination was negligible.

Within 8 h of a single radiolabelled 100 mg IV iron dose of FCM to patients with iron deficiency or renal anaemia, most of the radiolabelled iron had cleared the circulation and distributed to the bone marrow, liver and spleen. Within 6-9 days, the radiolabelled iron was incorporated into the red blood cells. After 24 days, iron utilisation was 91-99% in iron deficiency anaemia and 61-84% in renal anaemia.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Ferric carboxymaltose was not genotoxic in assays for gene mutation (in vitro bacterial and mouse lymphoma cell assays) and chromosomal damage (human lymphocytes in vitro and mouse micronucleus test in vivo).

Carcinogenicity

The carcinogenic potential of FERINJECT has not been studied in animals.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium hydroxide (for pH adjustment)

Hydrochloric acid (for pH adjustment)

Water for injections

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

Shelf-life of the product as packaged for sale:

36 months.

Shelf-life after first opening of the container:

From a microbiological point of view, preparations for parenteral administration should be used immediately.

Shelf-life after dilution with sterile 0.9% m/V sodium chloride solution:

To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2-8°C for not more than 12 hours.

Product is for single use in one patient only. Discard any residue.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in the original package. Do not store above 30 °C. Do not freeze, do not refrigerate.

6.5 NATURE AND CONTENTS OF CONTAINER

2 mL of solution in a vial (type I glass) with bromobutyl rubber stopper and aluminium cap in pack sizes of 1 and 5 vials.

10 mL of solution in a vial (type I glass) with bromobutyl rubber stopper and aluminium cap in pack sizes of 1 and 5 vials.

20 mL of solution in a vial (type I glass) with bromobutyl rubber stopper and aluminium cap in pack sizes of 1 vial.

Not all presentations may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waster material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The active substance of FERINJECT is a complex of polynuclear iron(III)-hydroxide with 4(R)-(poly-(1→4)-O-α-D-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate.

The relative molecular weight is approximately 150,000 Da, corresponding to the empirical formula:

$[\text{FeO}_x(\text{OH})_y(\text{H}_2\text{O})_z]_n [\{ (\text{C}_6\text{H}_{10}\text{O}_5)_m (\text{C}_6\text{H}_{12}\text{O}_7) \}_1]_k$, where $n \approx 10^3$, $m \approx 8$, $l \approx 11$, and $k \approx 4$.

CAS number

1461680-64-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4

8 SPONSOR

Vifor Pharma Pty Ltd
 Level 8, 80 Dorcas Street
 South Bank, Melbourne VIC 3006
 Australia
 Tel: 1800 202 674 (Australia)
 Tel: 0800 996 312 (New Zealand)

9 DATE OF FIRST APPROVAL

05 April 2011

10 DATE OF REVISION

13 May 2019

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.2	Maximum weekly dose in pregnancy added. Pregnancy dosing table removed and replaced with text.
4.4	Hypophosphataemia precaution added. Changed “allergic” to “hypersensitivity” and “injection” to “administration”.
4.5	Changed “injection” to “administration”.
4.8	Deletion of “Very Common (≥1/10)” column. Changes to footnotes.
5.1	Heading bolding corrected. Study title added.
8	Addition of NZ phone number.

AUSTRALIAN PRODUCT INFORMATION - FERINJECT® (FERRIC CARBOXYMALTOSE) SOLUTION FOR INJECTION

1 NAME OF THE MEDICINE

Ferric carboxymaltose

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2 mL vial contains 100 mg of iron as ferric carboxymaltose.

Each 10 mL vial contains 500 mg of iron as ferric carboxymaltose.

Each 20 mL vial contains 1000 mg of iron as ferric carboxymaltose.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Solution for intravenous use. FERINJECT is a dark brown, non-transparent, colloidal solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

FERINJECT is indicated for treatment of iron deficiency when oral iron preparations are ineffective or cannot be used.

The diagnosis must be based on laboratory tests.

4.2 DOSE AND METHOD OF ADMINISTRATION

Determination of the cumulative iron dose

The cumulative dose for repletion of iron using FERINJECT is determined based on the patient's body weight and Hb level and must not be exceeded. There are two methods for determining the cumulative dose, the Ganzoni Method and the Simplified Method. Caution is recommended with the Simplified Method since it is based on experience in a single trial in adults with median Hb 104 g/L (range 61-146 g/L) and body weight ≥ 35 kg – see section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials.

Patients should be closely monitored when large single doses of FERINJECT (>200 mg iron) are administered since the safety data are limited.

Post repletion, regular assessments should be done to ensure that iron levels are corrected and maintained.

Ganzoni Method

Cumulative Iron Dose = Body Weight *kg* x (Target Hb – Actual Hb *g/L*) x 0.24 + Iron Stores *mg*

where

Target Hb = 130 g/L for body weight <35 kg and 150 g/L for body weight ≥35 kg

Iron Stores = 15 mg/kg body weight for body weight <35 kg and 500 mg for body weight ≥35 kg.

Round down to nearest 100 mg if body weight ≤66 kg and round up to nearest 100 mg if body weight >66 kg.

Simplified Method (for patients of body weight ≥35 kg)

The cumulative iron dose is determined according to the following table:

Hb g/L	Body weight 35 to <70 kg	Body weight ≥70 kg
<100	1500 mg	2000 mg
≥100	1000 mg	1500 mg

For patients with an Hb value ≥140 g/L, an initial dose of 500 mg iron should be given and iron parameters should be checked prior to repeat dosing.

Intravenous injection

FERINJECT may be administered by intravenous injection using undiluted solution up to a maximum single dose of 1,000 mg iron (up to a maximum of 20 mg iron/kg body weight). For doses greater than 200 and up to 500 mg iron, FERINJECT should be administered at a rate of 100 mg iron/min. For doses greater than 500 and up to 1,000 mg iron, FERINJECT should be administered over 15 minutes. Do not administer more than 1,000 mg of iron per week.

Intravenous infusion

FERINJECT may be administered by intravenous infusion up to a maximum single dose of 1,000 mg iron (up to a maximum of 20 mg iron/kg body weight). Do not administer more than 1,000 mg iron per week.

Haemodialysis-dependent chronic kidney disease

In haemodialysis-dependent chronic kidney disease patients, a single daily injection of FERINJECT should not exceed 200 mg iron.

Pregnancy

It is recommended that the maximum cumulative dose in pregnant patients is restricted to 1,000mg for patients with Hb ≥90 g/L, or 1,500 mg in patients with Hb <90 g/L. Do not administer more than 1,000 mg iron per week.

Method of administration

FERINJECT must be administered only by the intravenous route: by bolus injection, or during a haemodialysis session undiluted directly into the venous limb of the dialyser, or by infusion. In case of infusion FERINJECT must be diluted only in sterile 0.9% m/V sodium chloride solution as follows:

Dilution plan of FERINJECT for intravenous infusion

FERINJECT	Iron	Maximum amount of sterile 0.9% m/V sodium chloride solution	Minimum administration time
2 to 4 mL	100 to 200 mg	50 mL	3 minutes
>4 to 10 mL	>200 to 500 mg	100 mL	6 minutes
>10 to 20 mL	>500 to 1,000 mg	250 mL	15 minutes

Note: For stability reasons, dilutions to concentrations less than 2 mg iron/mL (not including the volume of the ferric carboxymaltose solution) are not permissible.

FERINJECT must not be administered by the subcutaneous or intramuscular route.

Inspect vials visually for sediment and damage before use. Use only those containing sediment-free, homogeneous solution.

Each vial of FERINJECT is intended for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

FERINJECT must only be mixed with sterile 0.9% m/V sodium chloride solution. No other intravenous dilution solutions and therapeutic agents should be used, as there is the potential for precipitation and/or interaction. For dilution instructions, see above.

This medicinal product must not be mixed with other medicinal products than those mentioned above. The compatibility with containers other than polyethylene and glass is not known.

4.3 CONTRAINDICATIONS

The use of FERINJECT is contraindicated in cases of:

- hypersensitivity to ferric carboxymaltose complex, to FERINJECT or to any of its excipients
- anaemia not attributed to iron deficiency, e.g. other microcytic anaemia
- evidence of iron overload or disturbances in utilisation of iron

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**Iron Overload/Haemosiderosis**

Body iron excretion is limited and excess tissue iron can be hazardous causing haemosiderosis. Patients receiving FERINJECT require regular monitoring of red cell indices and serum ferritin to detect iron overload. If there is evidence of iron overload, iron therapy should be withheld.

Patients with Infections

Parenteral iron must be used with caution in case of acute or chronic infection, asthma, eczema or atopic allergies. It is recommended that the administration of FERINJECT is stopped in patients with ongoing bacteraemia. In patients with chronic infection a risk/benefit evaluation has to be performed, taking into account the suppression of erythropoiesis.

Hypersensitivity Reactions

Parenterally administered iron preparations can cause hypersensitivity reactions including anaphylactoid reactions, which may be fatal. Therefore, facilities for cardio-pulmonary

resuscitation must be available. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately. Hypersensitivity reactions have also been reported after previously uneventful doses of any parenteral iron complexes, including ferric carboxymaltose. Each patient should be observed for adverse effects for at least 30 minutes following each FERINJECT administration.

Hypophosphataemia

Parenterally administered iron preparations can cause hypophosphataemia which in most cases is transient and without clinical symptoms. Cases of hypophosphataemia requiring medical attention were reported, mainly in patients with existing risk factors and after prolonged exposure to high-dose IV iron.

Paravenous Leakage

Caution should be exercised to avoid paravenous leakage when administering FERINJECT. Paravenous leakage of FERINJECT at the administration site may lead to potentially long lasting brown discolouration and irritation of the skin. In case of paravenous leakage, the administration of FERINJECT must be stopped immediately.

Sodium Content

One mL of undiluted FERINJECT contains up to 5.5 mg (0.24 mmol) of sodium. This should be considered when prescribing FERINJECT to patients on sodium-controlled diets.

Use in hepatic impairment

In patients with liver dysfunction, parenteral iron should only be administered after careful risk/benefit assessment. Parenteral iron administration should be avoided in patients with hepatic dysfunction where iron overload is a precipitating factor, in particular Porphyria Cutanea Tarda (PCT). Careful monitoring of iron status is recommended to avoid iron overload.

There are no clinical studies performed in patients with hepatic impairment. It is known that ferric carboxymaltose may lead to transient increases in liver enzymes see Section 4.8. A careful benefit/risk evaluation should be made prior to using in patients with hepatic impairment, and if prescribed, close monitoring of liver function is recommended.

Use in the elderly

No data available.

Paediatric use

The use of FERINJECT has not been studied in children and therefore is not recommended in children under 14 years.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

As with all parenteral iron preparations the absorption of oral iron is reduced when administered concomitantly. Therefore, if required, oral iron therapy should not be started for at least 5 days after the last administration of FERINJECT.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Reduced weights of reproductive organs (prostate, seminal vesicle, epididymides, testis or uterus) were seen in rats and dogs at maternally toxic doses following repeated IV dosing with ferric carboxymaltose. There were no effects of ferric carboxymaltose on the fertility or reproductive performance of rats given thrice weekly IV doses of up to 30 mg/kg roughly equal to the maximum weekly clinical dose, based on body surface area (BSA). There are no data on the effect of ferric carboxymaltose on human fertility.

Use in pregnancy (Category B3)

Studies in rats have shown that iron released from ferric carboxymaltose can cross the placental barrier.

In pregnant and iron-replete rabbits and rats, embryotoxicity (decreased placental or litter weights and increased resorptions) and increases in fetal skeletal abnormalities (thickened/kinked ribs in rats and cranial, forepaw and/or limb abnormalities in rabbits) were observed at maternally toxic IV iron doses from 9 or 30 mg/kg/day, respectively given during organogenesis (1-2 times the maximum weekly clinical dose, based on body surface area (BSA)). No effects were observed at IV iron doses up to 4.5 or 9 mg/kg/day, respectively (0.5 times the maximum weekly clinical dose, based on BSA).

There is no efficacy and safety data on the use of FERINJECT in human pregnancy less than 16 weeks' gestation. Iron deficiency occurring in the first trimester of pregnancy can in many cases be treated with oral iron.

There are limited data from the use of FERINJECT in women in pregnancy beyond 16 weeks' gestation. A careful risk/benefit evaluation is required before use during pregnancy and FERINJECT should not be used during pregnancy unless clearly necessary.

If the benefit of FERINJECT treatment is judged to outweigh the potential risk to the fetus, it is recommended that treatment in pregnancy should be confined to women beyond the 16th week of gestation.

Foetal bradycardia may occur following administration of parenteral irons. It is usually transient and a consequence of a hypersensitivity reaction in the mother. The unborn baby should be carefully monitored during intravenous administration of parenteral irons to pregnant women.

Use in lactation

Clinical studies showed that transfer of iron from FERINJECT to human milk was negligible ($\leq 1\%$).

Evidence of delayed postnatal growth and development has been observed in rats exposed to ferric carboxymaltose. Milk transfer of administered iron from ferric carboxymaltose was demonstrated in lactating rats. Caution should be exercised when FERINJECT is used in lactating woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical studies experience

Adverse drug reactions reported in patients treated with ferric carboxymaltose (n=7,391) from completed clinical trials are summarized in the table below.

System Organ Class		Common (≥1/100, <1/10)	Uncommon (≥1/1,000, <1/100)	Rare (≥1/10,000, <1/1,000)
Immune System Disorders		–	Hypersensitivity	Anaphylactoid reactions
Nervous System Disorders		Headache, dizziness	Paraesthesia, dysgeusia	–
Cardiac Disorders		–	Tachycardia	–
Vascular Disorders		Hypertension, flushing	Hypotension	–
Respiratory, Thoracic and Mediastinal Disorders		–	Dyspnoea	–
Gastrointestinal Disorders		Nausea	Vomiting, dyspepsia, flatulence, abdominal pain, constipation, diarrhoea	–
Skin and Subcutaneous Tissue Disorders		–	Pruritus, urticaria, erythema, rash ⁽¹⁾	–
Musculoskeletal and Connective Tissue Disorders		–	Myalgia, back pain, arthralgia, pain in extremity, muscle spasms	–
General Disorders and Administration Site Conditions		Injection/Infusion site reactions ⁽²⁾	Pyrexia, fatigue, chest pain, oedema peripheral, pain, chills	Malaise
Investigations		-	Alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, blood lactate dehydrogenase increased, blood	–

System Organ Class		Common (≥1/100, <1/10)	Uncommon (≥1/1,000, <1/100)	Rare (≥1/10,000, <1/1,000)
			alkaline phosphatase increased	
Metabolism and Nutritional Disorders		Hypophosphataemia [#]	–	–

[#]: based on laboratory findings

1 Includes the following preferred terms: rash (individual ADR frequency determined as uncommon) and rash erythematous, -generalised, -macular, -maculo-papular, -pruritic (all individual ADRs frequencies determined as rare).

2 Includes, but is not limited to the following preferred terms: injection/infusion site -pain, -haematoma, -discolouration, -extravasation, -irritation, reaction, (all individual ADRs frequencies determined as uncommon) and -paraesthesia (individual ADR frequency determined as rare).

Note: ADR = Adverse drug reaction.

The most commonly reported ADR is nausea, occurring in 2.9% of the patients.

Undesirable Effects from Post-marketing Spontaneous Reporting

As part of the continuing post-marketing surveillance of ferric carboxymaltose, the following adverse reactions have been observed:

Post-marketing Spontaneous Reports

System Organ Class	Preferred Terms ⁽¹⁾
Nervous System Disorders	Loss of consciousness and vertigo
Psychiatric Disorders	Anxiety
Cardiovascular Disorders	Syncope, Pre-syncope
Skin and Subcutaneous Tissue Disorders	Angioedema, dermatitis, pallor, and face oedema
Respiratory, Thoracic and Mediastinal Disorders	Bronchospasm
General Disorders and Administration Site Conditions	Influenza like illness

¹ Frequency not known.

Post-marketing Spontaneous Reports in Pregnancy Cases

System Organ Class	Preferred Terms ⁽¹⁾
Immune System Disorders	Hypersensitivity, anaphylactoid reactions
Nervous System Disorders	Headache, dizziness
Vascular Disorders	Hypotension, Blood pressure systolic decreased
Skin and Subcutaneous Tissue Disorders	Rash, urticaria
Respiratory, Thoracic and Mediastinal Disorders	Dyspnoea
General Disorders and Administration Site Conditions	Extravasation, infusion site discolouration, injection site discolouration

¹ Frequency not known.

There have been individual case reports of temporally-related, but not causally-related, events of: antenatal fetal ductus venosus thrombosis, uterine hypertonia or contractions and fetal demise when Ferinject has been used in pregnancy.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Administration of FERINJECT in quantities exceeding the amount needed to correct iron deficit at the time of administration may lead to accumulation of iron in storage sites eventually leading to haemosiderosis. Monitoring of iron parameters such as serum ferritin and transferrin saturation may assist in recognising iron accumulation. If iron accumulation has occurred, the use of an iron chelator may be considered.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Ferric carboxymaltose (FCM) solution for injection/infusion contains iron in a stable ferric state as a complex with a carbohydrate polymer designed to provide iron for the iron transport and storage proteins in the body (transferrin and ferritin). FCM was effective in increasing haemoglobin (Hb) and serum ferritin concentrations in patients with mild to moderate iron-deficiency anaemia. The intravenous (IV) iron dose was 500 mg weekly for up to 4 weeks (n=20) or 1,000 mg weekly for up to 2 weeks (n=26). With the 500 mg iron dose, 37% of patients achieved normal Hb levels within 8 weeks and 75% achieved a ≥ 20 g/L increase in Hb on at least one occasion. With 1,000 mg iron, 48% of patients achieved normal Hb levels within 6 weeks and 73% achieved a ≥ 20 g/L increase in Hb on at least one occasion. The target serum ferritin concentration 100-500 $\mu\text{g/L}$ was reached with both doses and remained within the target range at 2 weeks follow-up (at 6 and 4 weeks respectively for the two dose groups)-data were only available for about half the 500 mg iron dose group.

Clinical trials

Clinical studies showed that the haematological response and the filling of the iron stores was faster after intravenous administration of FCM than with orally administered comparators.

The phase III studies undertaken with FCM included patients with iron deficiency (ID) of different aetiologies, i.e. associated with non-dialysis and dialysis dependent chronic kidney disease (CKD), inflammatory bowel disease, heavy menstrual bleeding, post-partum iron deficiency anaemia (IDA), pregnancy (second and third trimester) or patients with chronic heart failure and iron deficiency.

IDA associated with haemodialysis-dependent chronic kidney disease

The efficacy and safety of FCM compared to Venofer[®] (iron sucrose, intravenous) for the treatment of IDA secondary to chronic renal failure was assessed in a multi-centre, open-label,

randomised, parallel-group, Phase III study in 237 patients on haemodialysis or haemodiafiltration. IDA was defined as Hb \leq 115 g/L in addition to transferrin saturation (TSAT) $<$ 20% and/or serum ferritin $<$ 200 μ g/L. Patients received 200 mg iron 2 or 3 times weekly (depending on the timing of dialysis sessions) until their individual calculated cumulative dose had been reached. The mean duration of treatment was 15.8 days (range 1 to 27) and 16.2 days (range 1 to 43 days) for the FCM and Venofer[®] groups, respectively.

Patients treated with erythropoietin (EPO) should have had received this treatment for at least 8 weeks prior to inclusion in the study and increases in the dose of EPO were not permitted. The primary efficacy endpoint was defined as the percentage of patients reaching an increase in Hb of \geq 10 g/L at 4 weeks. The percentage of responders was 44.1% (52/118) in the FCM group and 35.3% (41/116) in the Venofer[®] group; the difference between groups was not statistically significant ($\chi^2 = 0.2254$). At follow-up 4 weeks after the final dose of medication, secondary efficacy parameters (Hb \geq 110-120 g/L, serum ferritin 200-800 μ g/L, TSAT 20-50%) demonstrated successful increase in iron stores for both treatment groups.

IDA associated with non-dialysis-dependent chronic kidney disease

A multi-centre, randomised, open-label, controlled, 8-week, Phase III study in 255 patients was conducted to compare the safety and efficacy of intravenous infusions of the FCM solution with oral administration of ferrous sulphate, independent of Hb response to EPO, in treating IDA in non-dialysis-dependent chronic kidney disease (ND-CKD). IDA was defined as Hb \leq 110 g/L, TSAT \leq 25%, and serum ferritin \leq 300 μ g/L. Patients treated with EPO should have had received this treatment for at least 8 weeks prior to inclusion in the study and increases in the dose of EPO were not permitted. Patients randomised to FCM treatment received 1 to 3 doses of FCM solution intravenously at 2-4 week intervals: 15 mg iron/kg for weight \leq 66 kg to a maximum of 1,000 mg iron for the initial dose and a maximum of 500 mg iron for subsequent doses. Patients randomised to oral iron treatment received ferrous sulphate tablets (65 mg iron) 3 times daily for 8 weeks.

In a modified intent-to-treat analysis which excluded 8 FCM patients and 2 ferrous sulfate patients, the primary efficacy endpoint, defined as the percentage of patients with an increase in Hb \geq 10 g/L at any time between baseline and end of study, or time of intervention, was reached by 60.4% (87/144) of FCM-treated patients compared to 34.7% (35/101) of oral iron-treated patients ($p < 0.001$; 95% confidence interval (CI) 13.0, 38.5). The modified intent-to-treat population comprised patients with at least one dose of study medication, stable erythropoietin dose, at least one post-baseline Hb assessment and GFR \leq 45 mL/min/1.73 m². FCM was also demonstrated to be superior to oral iron across all secondary ranked efficacy endpoints: Hb change \geq 10 g/L and a serum ferritin change \geq 160 μ g/L at any time during the study (60.4% versus 0.0%, respectively; $p < 0.001$; 95% CI 48.2, 72.6) or a Hb change \geq 10 g/L before Day 42 (54.2% versus 28.7%, respectively; $p < 0.001$; 95% CI 12.8, 38.1).

In a 44-week extension to this study, the efficacy of FCM in the long-term maintenance treatment of anaemia in ND-CKD was evaluated in 140 patients. Clinical success (Hb \geq 110 g/L, serum ferritin 100-800 μ g/L, TSAT 30-50%) was achieved in 51.4% (72/140) of patients, with 10% (14/140) exhibiting sustained clinical success at 50% or more of the assessments.

In the ND-CKD subgroup of another study, the safety and efficacy of IV injection of FCM solution, 15 mg iron/kg body weight up to 1,000 mg iron administered over 15 min. was assessed. The comparator was standard medical care (SMC) as determined by the investigator.

The primary endpoint was the incidence of treatment-emergent serious adverse events from Day 0 to 30 days after the last dose of study drug. The safety population contained 204 FCM subjects and 212 SMC subjects. The majority had mild anaemia (mean Hb 104 g/L in FCM group and

102 g/L in control group). There were no serious adverse events assessed as related to FCM. Based on these limited data and the lack of specific serious drug-related adverse reactions, the safety of single FCM doses of 1,000 mg iron appeared equal to SMC.

Efficacy was assessed in a modified intent-to-treat population of 202 FCM subjects and 203 SMC subjects. Achievement of Hb \geq 120 g/L was comparable in the two groups at 30 days - FCM 9.9% and SMC 6.9% (Fisher's Exact Test $p = 0.29$).

IDA secondary to inflammatory bowel disease

The efficacy of infusions of FCM solutions compared to oral administration of ferrous sulphate in the treatment of IDA secondary to chronic inflammatory bowel disease was examined in a multi-centre, open-label, randomised, 12-week, Phase III study in 200 patients. 4 patients did not receive study drug and were excluded from the analysis. IDA was defined as Hb \leq 110 g/L in combination with TSAT $<$ 20% and/or serum ferritin $<$ 100 μ g/L. Patients were randomised in a 2:1 (FCM: ferrous sulphate) ratio to receive 1 of 2 treatments: FCM intravenous on Day 1 with subsequent doses at 1-week intervals until the patient's calculated cumulative dose had been reached (a maximum dose of 1,000 mg iron per infusion) or oral ferrous sulphate capsules (100 mg iron) twice daily for 12 weeks. Based on the primary response parameter of change in mean Hb from baseline to Week 12 (36.0 g/L FCM group, 32.9 g/L oral iron group), the results of this study demonstrated that FCM was non-inferior to ferrous sulphate. The non-inferiority criterion was lower limit of 95% CI of difference FCM minus ferrous sulphate \geq -5.0 g/L. The non-inferiority criterion was met in both the intent-to-treat and per protocol populations. Furthermore, the mean Week-12 values of serum ferritin (80.2 μ g/L FCM group, 38.6 μ g/L oral iron group) and TSAT (23.1% FCM group, 29.2% oral iron group) demonstrated a successful repletion of the iron stores in patients treated with FCM.

In another study, FCM dosing based on a simplified dosing scheme with four Hb-weight subgroups (see section 4.2 DOSE AND METHOD OF ADMINISTRATION) was compared with Venofer[®] dosing based on the Ganzoni formula. The FCM dose was given in up to three IV infusions on Days 1, 8 and 15 in single doses of up to 1000 mg iron. The Venofer[®] dose was given in up to 11 IV infusions in doses not exceeding 200 mg iron not more than three times per week. The primary endpoint was the percentage of patients achieving a Hb increase \geq 20 g/L at Week 12. The demographic and haematological characteristics of the two groups were similar. About 60% of subjects were female, median age was 39 years (range 18-81), median weight 67 kg (range 39-137), median baseline Hb 104 g/L (range 61-146) and median baseline serum ferritin 7 μ g/L (range 2-299). Subjects in the two treatment groups achieved at least comparable Hb response overall and in the Hb-weight subgroups (see Table 1).

Table 1. Efficacy of FCM (new dosing method) versus Venofer[®] (Ganzoni dose calculation) in iron deficiency anaemia associated with inflammatory bowel diseases - trial FER-IBD-07-COR – patients with 12-week assessment

	FCM n=228	Venofer[®] n=220	Difference [95% CI]
Hb Response (increase \geq 20 g/L) at Week 12	65.8%	53.6%	12.2% [3.1%, 21.0%]
Hb<100 g/L – Wt 35-<70 kg	missing n=7 n=59 86.4%	missing n=8 n=44 75.0%	11.4% [-4.1%, 26.9%]
Hb<100 g/L – Wt \geq 70 kg	n=31 90.3%	n=24 100.0%	-9.7% [-20.1%, 0.7%]
Hb \geq 100 g/L – Wt 35-<70 kg	n=70 75.7%	n=78 71.8%	3.9% [-10.2%, 18.1%]
Hb \geq 100 g/L – Wt \geq 70 kg	n=61 88.5%	n=66 75.8%	12.8% [-0.3%, 25.8%]

IDA secondary to heavy menstrual bleeding

The safety and efficacy of intravenous infusions of FCM solution, compared to oral administration of ferrous sulphate, in improvement of Hb levels in females with IDA secondary to heavy menstrual bleeding was assessed in a multi-centre, randomised, open-label, 6-week, Phase III study. At enrolment, patients had a baseline Hb ≤ 114 g/L, TSAT $\leq 25\%$, and serum ferritin ≤ 100 $\mu\text{g/L}$. Patients were randomised to receive either oral ferrous sulphate tablets (65 mg iron) 3 times daily for 6 weeks or weekly infusions of FCM solution (a maximum dose of 1,000 mg iron per infusion) until the patient's calculated cumulative dose had been reached, to a maximum of 2,500 mg iron. In a modified intent-to-treat analysis which excluded 18 FCM patients and 6 ferrous sulphate patients, FCM was shown to be superior to oral iron in achieving an increase from baseline in Hb ≥ 20 g/L at any time during the study: 82.0% (187/228) in the FCM group versus 61.8% (139/225) in the oral iron group ($p < 0.001$; 95% CI 12.2, 28.3). The modified intent-to-treat population comprised patients with at least one dose of study medication, baseline Hb ≤ 110 g/L, TSAT $\leq 25\%$, serum ferritin ≤ 100 $\mu\text{g/L}$, at least one post-baseline Hb assessment and confirmed diagnosis of heavy menstrual bleeding.

Post partum IDA

The safety and efficacy of FCM compared to oral ferrous sulphate as treatment for post partum IDA (Hb ≤ 100 g/L or ≤ 105 g/L) was assessed in 3 randomised, open-label, multi-centre trials. In 2 of the studies, patients were randomised 1:1 to receive either oral ferrous sulphate tablets (65 mg iron) 3 times daily for 6 weeks or weekly intravenous FCM at dosages based on the calculated iron deficit. A maximum of 1,000 mg of iron (15 mg iron/kg body weight for pre-pregnancy weight ≤ 66 kg), as intravenous FCM solution, was given at weekly intervals until the individual's calculated cumulative iron dose had been reached or a maximum total iron dose of 2,500 mg had been administered. In the third study, patients were randomised 2:1 to receive either oral ferrous sulphate capsules (100 mg iron) twice daily for 12 weeks or weekly intravenous FCM at dosages based on the calculated iron deficit (to a maximum of 3 infusions and not exceeding a weekly dose of 1,000 mg iron).

In all 3 studies, FCM was shown to be efficacious for the treatment of IDA in post partum subjects. In the first study, the superiority of FCM was demonstrated according to the primary efficacy endpoint (defined as Hb > 120 g/L), with a greater proportion of patients in the FCM group (91.4%, 127/139) versus the oral iron group (66.7%, 98/147) achieving success at any time during the study ($p < 0.0001$; 95% CI 15.20, 34.20). This was based on a modified intent-to-treat population which excluded 4 FCM patients and one ferrous sulfate patient.

In the second study, FCM was demonstrated to be non-inferior to oral iron among subjects who achieved an increase in Hb ≥ 20 g/L: 96.4% (162/168) of the FCM group versus 94.1% (159/169) of the oral iron group (95% CI -2.19, 6.88). The analysis was in a modified intent-to-treat population (6 FCM patients and 9 ferrous sulphate patients excluded) and the non-inferiority margin was 15% based on a 1-sided 97.5% CI of the treatment difference. Statistically significantly greater increases from baseline to highest Hb, TSAT, and serum ferritin values were also observed in the FCM groups compared with the oral iron groups.

In the third study, FCM was shown to be non-inferior to ferrous sulphate for the mean change in Hb from baseline to Week 12 (33.4 g/L in the FCM group (n=227) versus 31.8 g/L in the oral iron group (n=117). The non-inferiority criterion was lower limit of 95% CI of difference FCM minus ferrous sulfate ≥ -5.0 g/L. The non-inferiority criterion was met in both the intent-to-treat and per protocol populations.

In another study in patients with iron deficiency anaemia due to heavy menstrual bleeding (HMB) or post-partum, the safety and efficacy of IV injection of FCM solution, 15 mg iron/kg

body weight up to 1,000 mg iron administered IV over 15 min, was assessed. The comparator was standard medical care (SMC) as determined by the investigator.

The primary endpoint was the incidence of treatment-emergent serious adverse events from Day 0 to 30 days after the last dose of study drug. The safety population contained 996 FCM subjects and 1,022 SMC subjects. Approximately 60% of the subjects had post-partum anaemia (median Hb 103 g/L) and the other 40% anaemia associated with HMB (median Hb 96 g/L). There were no serious adverse events assessed as related to FCM. Based on overall incidences and the lack of specific drug-related serious adverse reactions, the safety profiles of FCM and SMC oral iron appeared similar. There was insufficient exposure to SMC IV iron for it to be included in the assessment.

Efficacy was assessed in a modified intent-to-treat population which was approximately 30% less than the randomised population, although still balanced. Achievement of Hb >120 g/L was significantly better with FCM than SMC in the two subgroups at 30 days (see Table 2).

Table 2. Efficacy of FCM in single doses up to 1,000 mg iron versus SMC in iron deficiency anaemia associated with heavy menstrual bleeding and post-partum – trial 1VIT07017 – 30 days follow-up - modified intent-to-treat

	FCM	SMC	Difference p-value ²
Heavy Menstrual Bleeding	n=331	n=329	
Hb >120 g/L ¹	34.4%	15.8%	18.6% p<0.001
Post-Partum	n=342	n=357	
Hb >120 g/L ¹	68.1%	50.7%	17.4% p<0.001

FCM: Ferric Carboxymaltose. SMC: Standard Medical Care as determined by the investigator.

¹ Anytime between baseline and end of study of surgical intervention. ² Fisher's Exact Test.

Pregnancy

In a study in pregnant women in the second and third trimester with iron deficiency anaemia (FER-ASAP-2009-01) randomised to receive either ferric carboxymaltose (maximum permitted total dose 1000 mg for baseline haemoglobin 91-104 g/L or 1500 mg for baseline haemoglobin 80-90 g/L) or oral iron (200 mg orally twice daily). The range of gestation at study entry for the ferric carboxymaltose arm was 16.0 to 33.9 weeks.

Superiority of ferric carboxymaltose for the primary outcome of change in Hb from baseline to week 3 was not shown. The mean total iron dose was 1,028.5 mg (median 1,000 mg) in the ferric carboxymaltose group compared to 11,959.2 mg (median 12,300 mg) in the oral iron group.

Iron deficiency associated with chronic heart failure

In a population with chronic heart failure, a double-blind, placebo-controlled, randomised study demonstrated a statistically significant improvement in both Patient Global Assessment and New York Heart Association functional class at Week 24 (odds ratio for improvement, 2.51 (95% CI 1.75-3.61; p<0.001) and 2.40 (95% CI 1.55-3.71; p<0.001), respectively). The results applied to iron deficient patients with and without anaemia. Superior improvements (p<0.001) were also observed in the 6-minute walk test and patient quality of life (QoL) for patients treated with ferric carboxymaltose.

Study FER-CARS-05 (CONFIRM-HF) in subjects with chronic heart failure and iron deficiency demonstrated the benefit of FCM relative to placebo in improving functional capacity as measured by the change in 6-minute walk test distance from baseline to Week 24, with a

difference between treatment groups (least squares mean (\pm standard error)) of 33.2 ± 10.52 m ($p=0.002$), thereby confirming the hypothesis of above study. The treatment benefit of FCM in improvement of 6-minute walk test distance was statistically significant from week 24 ($p<0.001$) and was sustained throughout the study to Week 52 ($p<0.001$), demonstrating the long-term benefit of iron repletion over a period of 1 year. The improvements in PGA and NYHA functional class were also seen in FCM-treated subjects, with statistical significance for the difference between treatment groups achieved from Week 12 (PGA) or Week 24 (NYHA functional class) onwards. At Week 52 Endpoint, 54.7% of subjects in the FCM group showed some improvement in PGA score compared to 35.1% in the placebo group, and 18.0% of subjects in the FCM group showed an improvement by 1 NYHA functional class, compared to only 3.3% in the placebo group. Improvements in fatigue score and overall Kansas City cardiomyopathy questionnaire score were also seen, with statistical significance for the difference between treatment groups (in favour of FCM) achieved from Week 12 onwards.

There are no data available regarding the long term use of FERINJECT.

5.2 PHARMACOKINETIC PROPERTIES

After a single 100 mg IV iron dose of FCM solution ($n=6$) injected over 1 min, serum iron concentration peaked at a mean of 15 min. After 500, 800 or 1,000 mg iron in 250 mL normal saline infused over 15 min ($n=6$ for each dose), serum iron concentration peaked at means of 20 min, 1 h and 1.2 h, respectively. The mean volume of distribution was approximately 3 L, corresponding to the plasma volume. Mean plasma clearance ranged from 2.6-4.4 mL/min and terminal half life from 7-12 h. Renal elimination was negligible.

Within 8 h of a single radiolabelled 100 mg IV iron dose of FCM to patients with iron deficiency or renal anaemia, most of the radiolabelled iron had cleared the circulation and distributed to the bone marrow, liver and spleen. Within 6-9 days, the radiolabelled iron was incorporated into the red blood cells. After 24 days, iron utilisation was 91-99% in iron deficiency anaemia and 61-84% in renal anaemia.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Ferric carboxymaltose was not genotoxic in assays for gene mutation (in vitro bacterial and mouse lymphoma cell assays) and chromosomal damage (human lymphocytes in vitro and mouse micronucleus test in vivo).

Carcinogenicity

The carcinogenic potential of FERINJECT has not been studied in animals.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium hydroxide (for pH adjustment)

Hydrochloric acid (for pH adjustment)

Water for injections

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

Shelf-life of the product as packaged for sale:

36 months.

Shelf-life after first opening of the container:

From a microbiological point of view, preparations for parenteral administration should be used immediately.

Shelf-life after dilution with sterile 0.9% m/V sodium chloride solution:

To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2-8°C for not more than 12 hours.

Product is for single use in one patient only. Discard any residue.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in the original package. Do not store above 30 °C. Do not freeze, do not refrigerate.

6.5 NATURE AND CONTENTS OF CONTAINER

2 mL of solution in a vial (type I glass) with bromobutyl rubber stopper and aluminium cap in pack sizes of 1 and 5 vials.

10 mL of solution in a vial (type I glass) with bromobutyl rubber stopper and aluminium cap in pack sizes of 1 and 5 vials.

20 mL of solution in a vial (type I glass) with bromobutyl rubber stopper and aluminium cap in pack sizes of 1 vial.

Not all presentations may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waster material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The active substance of FERINJECT is a complex of polynuclear iron(III)-hydroxide with 4(R)-(poly-(1→4)-*O*- α -D-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate.

The relative molecular weight is approximately 150,000 Da, corresponding to the empirical formula:

$[\text{FeO}_x(\text{OH})_y(\text{H}_2\text{O})_z]_n [\{(\text{C}_6\text{H}_{10}\text{O}_5)_m (\text{C}_6\text{H}_{12}\text{O}_7)\}_1]_k$, where $n \approx 10^3$, $m \approx 8$, $l \approx 11$, and $k \approx 4$.

CAS number

1461680-64-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4

8 SPONSOR

Vifor Pharma Pty Ltd
 Level 8, 80 Dorcas Street
 South Bank, Melbourne VIC 3006
 Australia
 Tel: 1800 202 674 (Australia)
 Tel: 0800 996 312 (New Zealand)

9 DATE OF FIRST APPROVAL

05 April 2011

10 DATE OF REVISION

04 May 2020

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	Addition to monitor iron status for use in hepatic impairment and that transient increases in liver enzymes are known.
4.6	Addition that there are no data on the effect of ferric carboxymaltose on human fertility. Addition to include foetal bradycardia warning.

AUSTRALIAN PRODUCT INFORMATION - FERINJECT® (FERRIC CARBOXYMALTOSE) SOLUTION FOR INJECTION

1 NAME OF THE MEDICINE

Ferric carboxymaltose

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2 mL vial contains 100 mg of iron as ferric carboxymaltose.

Each 10 mL vial contains 500 mg of iron as ferric carboxymaltose.

Each 20 mL vial contains 1000 mg of iron as ferric carboxymaltose.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Solution for intravenous use. FERINJECT is a dark brown, non-transparent, colloidal solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

FERINJECT is indicated for treatment of iron deficiency when oral iron preparations are ineffective or cannot be used.

The diagnosis must be based on laboratory tests.

4.2 DOSE AND METHOD OF ADMINISTRATION

Determination of the cumulative iron dose

The cumulative dose for repletion of iron using FERINJECT is determined based on the patient's body weight and Hb level and must not be exceeded. There are two methods for determining the cumulative dose, the Ganzoni Method and the Simplified Method. Caution is recommended with the Simplified Method since it is based on experience in a single trial in adults with median Hb 104 g/L (range 61-146 g/L) and body weight ≥ 35 kg – see section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials.

Patients should be closely monitored when large single doses of FERINJECT (>200 mg iron) are administered since the safety data are limited.

Post repletion, regular assessments should be done to ensure that iron levels are corrected and maintained.

Ganzoni Method

Cumulative Iron Dose = Body Weight *kg* x (Target Hb – Actual Hb *g/L*) x 0.24 + Iron Stores *mg*

where

Target Hb = 130 g/L for body weight <35 kg and 150 g/L for body weight ≥35 kg

Iron Stores = 15 mg/kg body weight for body weight <35 kg and 500 mg for body weight ≥35 kg.

Round down to nearest 100 mg if body weight ≤66 kg and round up to nearest 100 mg if body weight >66 kg.

Simplified Method (for patients of body weight ≥35 kg)

The cumulative iron dose is determined according to the following table:

Hb g/L	Body weight 35 to <70 kg	Body weight ≥70 kg
<100	1500 mg	2000 mg
≥100	1000 mg	1500 mg

For patients with an Hb value ≥140 g/L, an initial dose of 500 mg iron should be given and iron parameters should be checked prior to repeat dosing.

Intravenous injection

FERINJECT may be administered by intravenous injection using undiluted solution up to a maximum single dose of 1,000 mg iron (up to a maximum of 20 mg iron/kg body weight). For doses greater than 200 and up to 500 mg iron, FERINJECT should be administered at a rate of 100 mg iron/min. For doses greater than 500 and up to 1,000 mg iron, FERINJECT should be administered over 15 minutes. Do not administer more than 1,000 mg of iron per week.

Intravenous infusion

FERINJECT may be administered by intravenous infusion up to a maximum single dose of 1,000 mg iron (up to a maximum of 20 mg iron/kg body weight). Do not administer more than 1,000 mg iron per week.

Haemodialysis-dependent chronic kidney disease

In haemodialysis-dependent chronic kidney disease patients, a single daily injection of FERINJECT should not exceed 200 mg iron.

Pregnancy

It is recommended that the maximum cumulative dose in pregnant patients is restricted to 1,000mg for patients with Hb ≥90 g/L, or 1,500 mg in patients with Hb <90 g/L. Do not administer more than 1,000 mg iron per week.

Method of administration

FERINJECT must be administered only by the intravenous route: by bolus injection, or during a haemodialysis session undiluted directly into the venous limb of the dialyser, or by infusion. In case of infusion FERINJECT must be diluted only in sterile 0.9% m/V sodium chloride solution as follows:

Dilution plan of FERINJECT for intravenous infusion

FERINJECT	Iron	Maximum amount of sterile 0.9% m/V sodium chloride solution	Minimum administration time
2 to 4 mL	100 to 200 mg	50 mL	3 minutes
>4 to 10 mL	>200 to 500 mg	100 mL	6 minutes
>10 to 20 mL	>500 to 1,000 mg	250 mL	15 minutes

Note: For stability reasons, dilutions to concentrations less than 2 mg iron/mL (not including the volume of the ferric carboxymaltose solution) are not permissible.

FERINJECT must not be administered by the subcutaneous or intramuscular route.

Inspect vials visually for sediment and damage before use. Use only those containing sediment-free, homogeneous solution.

Each vial of FERINJECT is intended for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

FERINJECT must only be mixed with sterile 0.9% m/V sodium chloride solution. No other intravenous dilution solutions and therapeutic agents should be used, as there is the potential for precipitation and/or interaction. For dilution instructions, see above.

This medicinal product must not be mixed with other medicinal products than those mentioned above. The compatibility with containers other than polyethylene and glass is not known.

4.3 CONTRAINDICATIONS

The use of FERINJECT is contraindicated in cases of:

- hypersensitivity to ferric carboxymaltose complex, to FERINJECT or to any of its excipients
- anaemia not attributed to iron deficiency, e.g. other microcytic anaemia
- evidence of iron overload or disturbances in utilisation of iron

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**Iron Overload/Haemosiderosis**

Body iron excretion is limited and excess tissue iron can be hazardous causing haemosiderosis. Patients receiving FERINJECT require regular monitoring of red cell indices and serum ferritin to detect iron overload. If there is evidence of iron overload, iron therapy should be withheld.

Patients with Infections

Parenteral iron must be used with caution in case of acute or chronic infection, asthma, eczema or atopic allergies. It is recommended that the administration of FERINJECT is stopped in patients with ongoing bacteraemia. In patients with chronic infection a risk/benefit evaluation has to be performed, taking into account the suppression of erythropoiesis.

Hypersensitivity Reactions

Parenterally administered iron preparations can cause hypersensitivity reactions including anaphylactoid reactions, which may be fatal. There have been reports of hypersensitivity

reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction). Therefore, facilities for cardio-pulmonary resuscitation must be available. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately. Hypersensitivity reactions have also been reported after previously uneventful doses of any parenteral iron complexes, including ferric carboxymaltose. Each patient should be observed for adverse effects for at least 30 minutes following each FERINJECT administration.

Hypophosphataemia

Parenterally administered iron preparations can cause hypophosphataemia which in most cases is transient and without clinical symptoms. Cases of hypophosphataemia requiring medical attention were reported, mainly in patients with existing risk factors and after prolonged exposure to high-dose IV iron.

Paravenous Leakage

Caution should be exercised to avoid paravenous leakage when administering FERINJECT. Paravenous leakage of FERINJECT at the administration site may lead to potentially long lasting brown discolouration and irritation of the skin. In case of paravenous leakage, the administration of FERINJECT must be stopped immediately.

Sodium Content

One mL of undiluted FERINJECT contains up to 5.5 mg (0.24 mmol) of sodium. This should be considered when prescribing FERINJECT to patients on sodium-controlled diets.

Use in hepatic impairment

In patients with liver dysfunction, parenteral iron should only be administered after careful risk/benefit assessment. Parenteral iron administration should be avoided in patients with hepatic dysfunction where iron overload is a precipitating factor, in particular Porphyria Cutanea Tarda (PCT). Careful monitoring of iron status is recommended to avoid iron overload.

There are no clinical studies performed in patients with hepatic impairment. It is known that ferric carboxymaltose may lead to transient increases in liver enzymes see Section 4.8. A careful benefit/risk evaluation should be made prior to using in patients with hepatic impairment, and if prescribed, close monitoring of liver function is recommended.

Use in the elderly

No data available.

Paediatric use

The use of FERINJECT has not been studied in children and therefore is not recommended in children under 14 years.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

As with all parenteral iron preparations the absorption of oral iron is reduced when administered concomitantly. Therefore, if required, oral iron therapy should not be started for at least 5 days after the last administration of FERINJECT.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Reduced weights of reproductive organs (prostate, seminal vesicle, epididymides, testis or uterus) were seen in rats and dogs at maternally toxic doses following repeated IV dosing with ferric carboxymaltose. There were no effects of ferric carboxymaltose on the fertility or reproductive performance of rats given thrice weekly IV doses of up to 30 mg/kg roughly equal to the maximum weekly clinical dose, based on body surface area (BSA). There are no data on the effect of ferric carboxymaltose on human fertility.

Use in pregnancy (Category B3)

Studies in rats have shown that iron released from ferric carboxymaltose can cross the placental barrier.

In pregnant and iron-replete rabbits and rats, embryotoxicity (decreased placental or litter weights and increased resorptions) and increases in fetal skeletal abnormalities (thickened/kinked ribs in rats and cranial, forepaw and/or limb abnormalities in rabbits) were observed at maternally toxic IV iron doses from 9 or 30 mg/kg/day, respectively given during organogenesis (1-2 times the maximum weekly clinical dose, based on body surface area (BSA)). No effects were observed at IV iron doses up to 4.5 or 9 mg/kg/day, respectively (0.5 times the maximum weekly clinical dose, based on BSA).

There is no efficacy and safety data on the use of FERINJECT in human pregnancy less than 16 weeks' gestation. Iron deficiency occurring in the first trimester of pregnancy can in many cases be treated with oral iron.

There are limited data from the use of FERINJECT in women in pregnancy beyond 16 weeks' gestation. A careful risk/benefit evaluation is required before use during pregnancy and FERINJECT should not be used during pregnancy unless clearly necessary.

If the benefit of FERINJECT treatment is judged to outweigh the potential risk to the fetus, it is recommended that treatment in pregnancy should be confined to women beyond the 16th week of gestation.

Foetal bradycardia may occur following administration of parenteral irons. It is usually transient and a consequence of a hypersensitivity reaction in the mother. The unborn baby should be carefully monitored during intravenous administration of parenteral irons to pregnant women.

Use in lactation

Clinical studies showed that transfer of iron from FERINJECT to human milk was negligible ($\leq 1\%$).

Evidence of delayed postnatal growth and development has been observed in rats exposed to ferric carboxymaltose. Milk transfer of administered iron from ferric carboxymaltose was demonstrated in lactating rats. Caution should be exercised when FERINJECT is used in lactating woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical studies experience

Adverse drug reactions reported in patients treated with ferric carboxymaltose (n=7,391) from completed clinical trials are summarized in the table below.

System Organ Class		Common (≥1/100, <1/10)	Uncommon (≥1/1,000, <1/100)	Rare (≥1/10,000, <1/1,000)
Immune System Disorders		–	Hypersensitivity	Anaphylactoid reactions
Nervous System Disorders		Headache, dizziness	Paraesthesia, dysgeusia	–
Cardiac Disorders		–	Tachycardia	–
Vascular Disorders		Hypertension, flushing	Hypotension	–
Respiratory, Thoracic and Mediastinal Disorders		–	Dyspnoea	–
Gastrointestinal Disorders		Nausea	Vomiting, dyspepsia, flatulence, abdominal pain, constipation, diarrhoea	–
Skin and Subcutaneous Tissue Disorders		–	Pruritus, urticaria, erythema, rash ⁽¹⁾	–
Musculoskeletal and Connective Tissue Disorders		–	Myalgia, back pain, arthralgia, pain in extremity, muscle spasms	–
General Disorders and Administration Site Conditions		Injection/Infusion site reactions ⁽²⁾	Pyrexia, fatigue, chest pain, oedema peripheral, pain, chills	Malaise
Investigations		-	Alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, blood lactate dehydrogenase increased, blood	–

System Organ Class		Common (≥1/100, <1/10)	Uncommon (≥1/1,000, <1/100)	Rare (≥1/10,000, <1/1,000)
			alkaline phosphatase increased	
Metabolism and Nutritional Disorders		Hypophosphataemia [#]	–	–

[#]: based on laboratory findings

1 Includes the following preferred terms: rash (individual ADR frequency determined as uncommon) and rash erythematous, -generalised, -macular, -maculo-papular, -pruritic (all individual ADRs frequencies determined as rare).

2 Includes, but is not limited to the following preferred terms: injection/infusion site -pain, -haematoma, -discolouration, -extravasation, -irritation, reaction, (all individual ADRs frequencies determined as uncommon) and -paraesthesia (individual ADR frequency determined as rare).

Note: ADR = Adverse drug reaction.

The most commonly reported ADR is nausea, occurring in 2.9% of the patients.

Undesirable Effects from Post-marketing Spontaneous Reporting

As part of the continuing post-marketing surveillance of ferric carboxymaltose, the following adverse reactions have been observed:

Post-marketing Spontaneous Reports

System Organ Class	Preferred Terms ⁽¹⁾
Nervous System Disorders	Loss of consciousness and vertigo
Psychiatric Disorders	Anxiety
Cardiovascular Disorders	Syncope, Pre-syncope
Skin and Subcutaneous Tissue Disorders	Angioedema, dermatitis, pallor, and face oedema
Respiratory, Thoracic and Mediastinal Disorders	Bronchospasm
General Disorders and Administration Site Conditions	Influenza like illness

¹ Frequency not known.

Post-marketing Spontaneous Reports in Pregnancy Cases

System Organ Class	Preferred Terms ⁽¹⁾
Immune System Disorders	Hypersensitivity, anaphylactoid reactions
Nervous System Disorders	Headache, dizziness
Vascular Disorders	Hypotension, Blood pressure systolic decreased
Skin and Subcutaneous Tissue Disorders	Rash, urticaria
Respiratory, Thoracic and Mediastinal Disorders	Dyspnoea
General Disorders and Administration Site Conditions	Extravasation, infusion site discolouration, injection site discolouration

¹ Frequency not known.

There have been individual case reports of temporally-related, but not causally-related, events of: antenatal fetal ductus venosus thrombosis, uterine hypertonia or contractions and fetal demise when Ferinject has been used in pregnancy.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Administration of FERINJECT in quantities exceeding the amount needed to correct iron deficit at the time of administration may lead to accumulation of iron in storage sites eventually leading to haemosiderosis. Monitoring of iron parameters such as serum ferritin and transferrin saturation may assist in recognising iron accumulation. If iron accumulation has occurred, the use of an iron chelator may be considered.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Ferric carboxymaltose (FCM) solution for injection/infusion contains iron in a stable ferric state as a complex with a carbohydrate polymer designed to provide iron for the iron transport and storage proteins in the body (transferrin and ferritin). FCM was effective in increasing haemoglobin (Hb) and serum ferritin concentrations in patients with mild to moderate iron-deficiency anaemia. The intravenous (IV) iron dose was 500 mg weekly for up to 4 weeks (n=20) or 1,000 mg weekly for up to 2 weeks (n=26). With the 500 mg iron dose, 37% of patients achieved normal Hb levels within 8 weeks and 75% achieved a ≥ 20 g/L increase in Hb on at least one occasion. With 1,000 mg iron, 48% of patients achieved normal Hb levels within 6 weeks and 73% achieved a ≥ 20 g/L increase in Hb on at least one occasion. The target serum ferritin concentration 100-500 $\mu\text{g/L}$ was reached with both doses and remained within the target range at 2 weeks follow-up (at 6 and 4 weeks respectively for the two dose groups)-data were only available for about half the 500 mg iron dose group.

Clinical trials

Clinical studies showed that the haematological response and the filling of the iron stores was faster after intravenous administration of FCM than with orally administered comparators.

The phase III studies undertaken with FCM included patients with iron deficiency (ID) of different aetiologies, i.e. associated with non-dialysis and dialysis dependent chronic kidney disease (CKD), inflammatory bowel disease, heavy menstrual bleeding, post-partum iron deficiency anaemia (IDA), pregnancy (second and third trimester) or patients with chronic heart failure and iron deficiency.

IDA associated with haemodialysis-dependent chronic kidney disease

The efficacy and safety of FCM compared to Venofer[®] (iron sucrose, intravenous) for the treatment of IDA secondary to chronic renal failure was assessed in a multi-centre, open-label,

randomised, parallel-group, Phase III study in 237 patients on haemodialysis or haemodiafiltration. IDA was defined as Hb \leq 115 g/L in addition to transferrin saturation (TSAT) $<$ 20% and/or serum ferritin $<$ 200 μ g/L. Patients received 200 mg iron 2 or 3 times weekly (depending on the timing of dialysis sessions) until their individual calculated cumulative dose had been reached. The mean duration of treatment was 15.8 days (range 1 to 27) and 16.2 days (range 1 to 43 days) for the FCM and Venofer[®] groups, respectively.

Patients treated with erythropoietin (EPO) should have had received this treatment for at least 8 weeks prior to inclusion in the study and increases in the dose of EPO were not permitted. The primary efficacy endpoint was defined as the percentage of patients reaching an increase in Hb of \geq 10 g/L at 4 weeks. The percentage of responders was 44.1% (52/118) in the FCM group and 35.3% (41/116) in the Venofer[®] group; the difference between groups was not statistically significant ($\chi^2 = 0.2254$). At follow-up 4 weeks after the final dose of medication, secondary efficacy parameters (Hb \geq 110-120 g/L, serum ferritin 200-800 μ g/L, TSAT 20-50%) demonstrated successful increase in iron stores for both treatment groups.

IDA associated with non-dialysis-dependent chronic kidney disease

A multi-centre, randomised, open-label, controlled, 8-week, Phase III study in 255 patients was conducted to compare the safety and efficacy of intravenous infusions of the FCM solution with oral administration of ferrous sulphate, independent of Hb response to EPO, in treating IDA in non-dialysis-dependent chronic kidney disease (ND-CKD). IDA was defined as Hb \leq 110 g/L, TSAT \leq 25%, and serum ferritin \leq 300 μ g/L. Patients treated with EPO should have had received this treatment for at least 8 weeks prior to inclusion in the study and increases in the dose of EPO were not permitted. Patients randomised to FCM treatment received 1 to 3 doses of FCM solution intravenously at 2-4 week intervals: 15 mg iron/kg for weight \leq 66 kg to a maximum of 1,000 mg iron for the initial dose and a maximum of 500 mg iron for subsequent doses. Patients randomised to oral iron treatment received ferrous sulphate tablets (65 mg iron) 3 times daily for 8 weeks.

In a modified intent-to-treat analysis which excluded 8 FCM patients and 2 ferrous sulfate patients, the primary efficacy endpoint, defined as the percentage of patients with an increase in Hb \geq 10 g/L at any time between baseline and end of study, or time of intervention, was reached by 60.4% (87/144) of FCM-treated patients compared to 34.7% (35/101) of oral iron-treated patients ($p < 0.001$; 95% confidence interval (CI) 13.0, 38.5). The modified intent-to-treat population comprised patients with at least one dose of study medication, stable erythropoietin dose, at least one post-baseline Hb assessment and GFR \leq 45 mL/min/1.73 m². FCM was also demonstrated to be superior to oral iron across all secondary ranked efficacy endpoints: Hb change \geq 10 g/L and a serum ferritin change \geq 160 μ g/L at any time during the study (60.4% versus 0.0%, respectively; $p < 0.001$; 95% CI 48.2, 72.6) or a Hb change \geq 10 g/L before Day 42 (54.2% versus 28.7%, respectively; $p < 0.001$; 95% CI 12.8, 38.1).

In a 44-week extension to this study, the efficacy of FCM in the long-term maintenance treatment of anaemia in ND-CKD was evaluated in 140 patients. Clinical success (Hb \geq 110 g/L, serum ferritin 100-800 μ g/L, TSAT 30-50%) was achieved in 51.4% (72/140) of patients, with 10% (14/140) exhibiting sustained clinical success at 50% or more of the assessments.

In the ND-CKD subgroup of another study, the safety and efficacy of IV injection of FCM solution, 15 mg iron/kg body weight up to 1,000 mg iron administered over 15 min. was assessed. The comparator was standard medical care (SMC) as determined by the investigator.

The primary endpoint was the incidence of treatment-emergent serious adverse events from Day 0 to 30 days after the last dose of study drug. The safety population contained 204 FCM subjects and 212 SMC subjects. The majority had mild anaemia (mean Hb 104 g/L in FCM group and

102 g/L in control group). There were no serious adverse events assessed as related to FCM. Based on these limited data and the lack of specific serious drug-related adverse reactions, the safety of single FCM doses of 1,000 mg iron appeared equal to SMC.

Efficacy was assessed in a modified intent-to-treat population of 202 FCM subjects and 203 SMC subjects. Achievement of Hb \geq 120 g/L was comparable in the two groups at 30 days - FCM 9.9% and SMC 6.9% (Fisher's Exact Test $p = 0.29$).

IDA secondary to inflammatory bowel disease

The efficacy of infusions of FCM solutions compared to oral administration of ferrous sulphate in the treatment of IDA secondary to chronic inflammatory bowel disease was examined in a multi-centre, open-label, randomised, 12-week, Phase III study in 200 patients. 4 patients did not receive study drug and were excluded from the analysis. IDA was defined as Hb \leq 110 g/L in combination with TSAT $<$ 20% and/or serum ferritin $<$ 100 μ g/L. Patients were randomised in a 2:1 (FCM: ferrous sulphate) ratio to receive 1 of 2 treatments: FCM intravenous on Day 1 with subsequent doses at 1-week intervals until the patient's calculated cumulative dose had been reached (a maximum dose of 1,000 mg iron per infusion) or oral ferrous sulphate capsules (100 mg iron) twice daily for 12 weeks. Based on the primary response parameter of change in mean Hb from baseline to Week 12 (36.0 g/L FCM group, 32.9 g/L oral iron group), the results of this study demonstrated that FCM was non-inferior to ferrous sulphate. The non-inferiority criterion was lower limit of 95% CI of difference FCM minus ferrous sulphate \geq -5.0 g/L. The non-inferiority criterion was met in both the intent-to-treat and per protocol populations. Furthermore, the mean Week-12 values of serum ferritin (80.2 μ g/L FCM group, 38.6 μ g/L oral iron group) and TSAT (23.1% FCM group, 29.2% oral iron group) demonstrated a successful repletion of the iron stores in patients treated with FCM.

In another study, FCM dosing based on a simplified dosing scheme with four Hb-weight subgroups (see section 4.2 DOSE AND METHOD OF ADMINISTRATION) was compared with Venofer[®] dosing based on the Ganzoni formula. The FCM dose was given in up to three IV infusions on Days 1, 8 and 15 in single doses of up to 1000 mg iron. The Venofer[®] dose was given in up to 11 IV infusions in doses not exceeding 200 mg iron not more than three times per week. The primary endpoint was the percentage of patients achieving a Hb increase \geq 20 g/L at Week 12. The demographic and haematological characteristics of the two groups were similar. About 60% of subjects were female, median age was 39 years (range 18-81), median weight 67 kg (range 39-137), median baseline Hb 104 g/L (range 61-146) and median baseline serum ferritin 7 μ g/L (range 2-299). Subjects in the two treatment groups achieved at least comparable Hb response overall and in the Hb-weight subgroups (see Table 1).

Table 1. Efficacy of FCM (new dosing method) versus Venofer[®] (Ganzoni dose calculation) in iron deficiency anaemia associated with inflammatory bowel diseases - trial FER-IBD-07-COR – patients with 12-week assessment

	FCM n=228	Venofer[®] n=220	Difference [95% CI]
Hb Response (increase \geq 20 g/L) at Week 12	65.8%	53.6%	12.2% [3.1%, 21.0%]
Hb<100 g/L – Wt 35-<70 kg	missing n=7 n=59 86.4%	missing n=8 n=44 75.0%	11.4% [-4.1%, 26.9%]
Hb<100 g/L – Wt \geq 70 kg	n=31 90.3%	n=24 100.0%	-9.7% [-20.1%, 0.7%]
Hb \geq 100 g/L – Wt 35-<70 kg	n=70 75.7%	n=78 71.8%	3.9% [-10.2%, 18.1%]
Hb \geq 100 g/L – Wt \geq 70 kg	n=61 88.5%	n=66 75.8%	12.8% [-0.3%, 25.8%]

IDA secondary to heavy menstrual bleeding

The safety and efficacy of intravenous infusions of FCM solution, compared to oral administration of ferrous sulphate, in improvement of Hb levels in females with IDA secondary to heavy menstrual bleeding was assessed in a multi-centre, randomised, open-label, 6-week, Phase III study. At enrolment, patients had a baseline Hb ≤ 114 g/L, TSAT $\leq 25\%$, and serum ferritin ≤ 100 $\mu\text{g/L}$. Patients were randomised to receive either oral ferrous sulphate tablets (65 mg iron) 3 times daily for 6 weeks or weekly infusions of FCM solution (a maximum dose of 1,000 mg iron per infusion) until the patient's calculated cumulative dose had been reached, to a maximum of 2,500 mg iron. In a modified intent-to-treat analysis which excluded 18 FCM patients and 6 ferrous sulphate patients, FCM was shown to be superior to oral iron in achieving an increase from baseline in Hb ≥ 20 g/L at any time during the study: 82.0% (187/228) in the FCM group versus 61.8% (139/225) in the oral iron group ($p < 0.001$; 95% CI 12.2, 28.3). The modified intent-to-treat population comprised patients with at least one dose of study medication, baseline Hb ≤ 110 g/L, TSAT $\leq 25\%$, serum ferritin ≤ 100 $\mu\text{g/L}$, at least one post-baseline Hb assessment and confirmed diagnosis of heavy menstrual bleeding.

Post partum IDA

The safety and efficacy of FCM compared to oral ferrous sulphate as treatment for post partum IDA (Hb ≤ 100 g/L or ≤ 105 g/L) was assessed in 3 randomised, open-label, multi-centre trials. In 2 of the studies, patients were randomised 1:1 to receive either oral ferrous sulphate tablets (65 mg iron) 3 times daily for 6 weeks or weekly intravenous FCM at dosages based on the calculated iron deficit. A maximum of 1,000 mg of iron (15 mg iron/kg body weight for pre-pregnancy weight ≤ 66 kg), as intravenous FCM solution, was given at weekly intervals until the individual's calculated cumulative iron dose had been reached or a maximum total iron dose of 2,500 mg had been administered. In the third study, patients were randomised 2:1 to receive either oral ferrous sulphate capsules (100 mg iron) twice daily for 12 weeks or weekly intravenous FCM at dosages based on the calculated iron deficit (to a maximum of 3 infusions and not exceeding a weekly dose of 1,000 mg iron).

In all 3 studies, FCM was shown to be efficacious for the treatment of IDA in post partum subjects. In the first study, the superiority of FCM was demonstrated according to the primary efficacy endpoint (defined as Hb > 120 g/L), with a greater proportion of patients in the FCM group (91.4%, 127/139) versus the oral iron group (66.7%, 98/147) achieving success at any time during the study ($p < 0.0001$; 95% CI 15.20, 34.20). This was based on a modified intent-to-treat population which excluded 4 FCM patients and one ferrous sulfate patient.

In the second study, FCM was demonstrated to be non-inferior to oral iron among subjects who achieved an increase in Hb ≥ 20 g/L: 96.4% (162/168) of the FCM group versus 94.1% (159/169) of the oral iron group (95% CI -2.19, 6.88). The analysis was in a modified intent-to-treat population (6 FCM patients and 9 ferrous sulphate patients excluded) and the non-inferiority margin was 15% based on a 1-sided 97.5% CI of the treatment difference. Statistically significantly greater increases from baseline to highest Hb, TSAT, and serum ferritin values were also observed in the FCM groups compared with the oral iron groups.

In the third study, FCM was shown to be non-inferior to ferrous sulphate for the mean change in Hb from baseline to Week 12 (33.4 g/L in the FCM group (n=227) versus 31.8 g/L in the oral iron group (n=117). The non-inferiority criterion was lower limit of 95% CI of difference FCM minus ferrous sulfate ≥ -5.0 g/L. The non-inferiority criterion was met in both the intent-to-treat and per protocol populations.

In another study in patients with iron deficiency anaemia due to heavy menstrual bleeding (HMB) or post-partum, the safety and efficacy of IV injection of FCM solution, 15 mg iron/kg

body weight up to 1,000 mg iron administered IV over 15 min, was assessed. The comparator was standard medical care (SMC) as determined by the investigator.

The primary endpoint was the incidence of treatment-emergent serious adverse events from Day 0 to 30 days after the last dose of study drug. The safety population contained 996 FCM subjects and 1,022 SMC subjects. Approximately 60% of the subjects had post-partum anaemia (median Hb 103 g/L) and the other 40% anaemia associated with HMB (median Hb 96 g/L). There were no serious adverse events assessed as related to FCM. Based on overall incidences and the lack of specific drug-related serious adverse reactions, the safety profiles of FCM and SMC oral iron appeared similar. There was insufficient exposure to SMC IV iron for it to be included in the assessment.

Efficacy was assessed in a modified intent-to-treat population which was approximately 30% less than the randomised population, although still balanced. Achievement of Hb >120 g/L was significantly better with FCM than SMC in the two subgroups at 30 days (see Table 2).

Table 2. Efficacy of FCM in single doses up to 1,000 mg iron versus SMC in iron deficiency anaemia associated with heavy menstrual bleeding and post-partum – trial 1VIT07017 – 30 days follow-up - modified intent-to-treat

	FCM	SMC	Difference p-value ²
Heavy Menstrual Bleeding	n=331	n=329	
Hb >120 g/L ¹	34.4%	15.8%	18.6% p<0.001
Post-Partum	n=342	n=357	
Hb >120 g/L ¹	68.1%	50.7%	17.4% p<0.001

FCM: Ferric Carboxymaltose. SMC: Standard Medical Care as determined by the investigator.

¹ Anytime between baseline and end of study of surgical intervention. ² Fisher's Exact Test.

Pregnancy

In a study in pregnant women in the second and third trimester with iron deficiency anaemia (FER-ASAP-2009-01) randomised to receive either ferric carboxymaltose (maximum permitted total dose 1000 mg for baseline haemoglobin 91-104 g/L or 1500 mg for baseline haemoglobin 80-90 g/L) or oral iron (200 mg orally twice daily). The range of gestation at study entry for the ferric carboxymaltose arm was 16.0 to 33.9 weeks.

Superiority of ferric carboxymaltose for the primary outcome of change in Hb from baseline to week 3 was not shown. The mean total iron dose was 1,028.5 mg (median 1,000 mg) in the ferric carboxymaltose group compared to 11,959.2 mg (median 12,300 mg) in the oral iron group.

Iron deficiency associated with chronic heart failure

In a population with chronic heart failure, a double-blind, placebo-controlled, randomised study demonstrated a statistically significant improvement in both Patient Global Assessment and New York Heart Association functional class at Week 24 (odds ratio for improvement, 2.51 (95% CI 1.75-3.61; p<0.001) and 2.40 (95% CI 1.55-3.71; p<0.001), respectively). The results applied to iron deficient patients with and without anaemia. Superior improvements (p<0.001) were also observed in the 6-minute walk test and patient quality of life (QoL) for patients treated with ferric carboxymaltose.

Study FER-CARS-05 (CONFIRM-HF) in subjects with chronic heart failure and iron deficiency demonstrated the benefit of FCM relative to placebo in improving functional capacity as measured by the change in 6-minute walk test distance from baseline to Week 24, with a

difference between treatment groups (least squares mean (\pm standard error)) of 33.2 ± 10.52 m ($p=0.002$), thereby confirming the hypothesis of above study. The treatment benefit of FCM in improvement of 6-minute walk test distance was statistically significant from week 24 ($p<0.001$) and was sustained throughout the study to Week 52 ($p<0.001$), demonstrating the long-term benefit of iron repletion over a period of 1 year. The improvements in PGA and NYHA functional class were also seen in FCM-treated subjects, with statistical significance for the difference between treatment groups achieved from Week 12 (PGA) or Week 24 (NYHA functional class) onwards. At Week 52 Endpoint, 54.7% of subjects in the FCM group showed some improvement in PGA score compared to 35.1% in the placebo group, and 18.0% of subjects in the FCM group showed an improvement by 1 NYHA functional class, compared to only 3.3% in the placebo group. Improvements in fatigue score and overall Kansas City cardiomyopathy questionnaire score were also seen, with statistical significance for the difference between treatment groups (in favour of FCM) achieved from Week 12 onwards.

There are no data available regarding the long term use of FERINJECT.

5.2 PHARMACOKINETIC PROPERTIES

After a single 100 mg IV iron dose of FCM solution ($n=6$) injected over 1 min, serum iron concentration peaked at a mean of 15 min. After 500, 800 or 1,000 mg iron in 250 mL normal saline infused over 15 min ($n=6$ for each dose), serum iron concentration peaked at means of 20 min, 1 h and 1.2 h, respectively. The mean volume of distribution was approximately 3 L, corresponding to the plasma volume. Mean plasma clearance ranged from 2.6-4.4 mL/min and terminal half life from 7-12 h. Renal elimination was negligible.

Within 8 h of a single radiolabelled 100 mg IV iron dose of FCM to patients with iron deficiency or renal anaemia, most of the radiolabelled iron had cleared the circulation and distributed to the bone marrow, liver and spleen. Within 6-9 days, the radiolabelled iron was incorporated into the red blood cells. After 24 days, iron utilisation was 91-99% in iron deficiency anaemia and 61-84% in renal anaemia.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Ferric carboxymaltose was not genotoxic in assays for gene mutation (in vitro bacterial and mouse lymphoma cell assays) and chromosomal damage (human lymphocytes in vitro and mouse micronucleus test in vivo).

Carcinogenicity

The carcinogenic potential of FERINJECT has not been studied in animals.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium hydroxide (for pH adjustment)

Hydrochloric acid (for pH adjustment)

Water for injections

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

Shelf-life of the product as packaged for sale:

36 months.

Shelf-life after first opening of the container:

From a microbiological point of view, preparations for parenteral administration should be used immediately.

Shelf-life after dilution with sterile 0.9% m/V sodium chloride solution:

To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2-8°C for not more than 12 hours.

Product is for single use in one patient only. Discard any residue.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in the original package. Do not store above 30 °C. Do not freeze, do not refrigerate.

6.5 NATURE AND CONTENTS OF CONTAINER

2 mL of solution in a vial (type I glass) with bromobutyl rubber stopper and aluminium cap in pack sizes of 1 and 5 vials.

10 mL of solution in a vial (type I glass) with bromobutyl rubber stopper and aluminium cap in pack sizes of 1 and 5 vials.

20 mL of solution in a vial (type I glass) with bromobutyl rubber stopper and aluminium cap in pack sizes of 1 vial.

Not all presentations may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waster material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The active substance of FERINJECT is a complex of polynuclear iron(III)-hydroxide with 4(R)-(poly-(1→4)-O-α-D-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate.

The relative molecular weight is approximately 150,000 Da, corresponding to the empirical formula:

$[\text{FeO}_x(\text{OH})_y(\text{H}_2\text{O})_z]_n [\{ (\text{C}_6\text{H}_{10}\text{O}_5)_m (\text{C}_6\text{H}_{12}\text{O}_7) \}_1]_k$, where $n \approx 10^3$, $m \approx 8$, $l \approx 11$, and $k \approx 4$.

CAS number

1461680-64-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4

8 SPONSOR

Vifor Pharma Pty Ltd
 Level 8, 80 Dorcas Street
 South Bank, Melbourne VIC 3006
 Australia
 Tel: 1800 202 674 (Australia)
 Tel: 0800 996 312 (New Zealand)

9 DATE OF FIRST APPROVAL

05 April 2011

10 DATE OF REVISION

27 July 2020

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	Addition of information on Kounis syndrome

AUSTRALIAN PRODUCT INFORMATION - FERINJECT® (FERRIC CARBOXYMALTOSE) SOLUTION FOR INJECTION

1 NAME OF THE MEDICINE

Ferric carboxymaltose

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2 mL vial contains 100 mg of iron as ferric carboxymaltose.

Each 10 mL vial contains 500 mg of iron as ferric carboxymaltose.

Each 20 mL vial contains 1000 mg of iron as ferric carboxymaltose.

Excipient(s) with known effect:

Sodium hydroxide (for pH adjustment).

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Solution for intravenous use. FERINJECT is a dark brown, non-transparent, colloidal solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

FERINJECT is indicated for the treatment of iron deficiency when:

- oral iron preparations are ineffective
- oral iron preparations cannot be used
- there is a clinical need to deliver iron rapidly

The diagnosis must be based on laboratory tests.

4.2 DOSE AND METHOD OF ADMINISTRATION

Determination of the cumulative iron dose

The cumulative dose for repletion of iron using FERINJECT is determined based on the patient's body weight and Hb level and must not be exceeded. There are two methods for determining the cumulative dose, the Ganzoni Method and the Simplified Method. Caution is recommended with the Simplified Method since it is based on experience in a single trial in adults with median Hb 104 g/L (range 61-146 g/L) and body weight ≥ 35 kg – see section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials.

Patients should be closely monitored when large single doses of FERINJECT (>200 mg iron) are administered since the safety data are limited.

Post repletion, regular assessments should be done to ensure that iron levels are corrected and maintained.

Ganzoni Method

Cumulative Iron Dose = Body Weight kg x (Target Hb – Actual Hb g/L) x 0.24 + Iron Stores mg

where

Target Hb = 130 g/L for body weight <35 kg and 150 g/L for body weight ≥35 kg

Iron Stores = 15 mg/kg body weight for body weight <35 kg and 500 mg for body weight ≥35 kg.

Round down to nearest 100 mg if body weight ≤66 kg and round up to nearest 100 mg if body weight >66 kg.

Simplified Method (for patients of body weight ≥35 kg)

The cumulative iron dose is determined according to the following table.

Table 1 Determination of the Iron Need

Hb g/L	Patient Body Weight	
	35 kg to <70 kg	70 kg and above
<100	1,500 mg	2,000 mg
100 to < 140	1,000 mg	1,500 mg
≥140	500 mg	500 mg

For patients with an Hb value ≥140 g/L, an initial dose of 500 mg iron should be given and iron parameters should be checked prior to repeat dosing.

Iron deficiency must be confirmed by laboratory tests as stated in section 4.1 THERAPEUTIC INDICATIONS.

Calculation and administration of the maximum individual iron dose(s)

Based on the iron need determined above the appropriate dose(s) of FERINJECT should be administered taking into consideration the following:

A single FERINJECT administration should not exceed:

- 20 mg iron/kg body weight
- 1,000 mg of iron (20 mL ferric carboxymaltose)

The maximum recommended cumulative dose of FERINJECT is 1,000 mg of iron (20 mL ferric carboxymaltose) per week.

Post-iron repletion assessments

Re-assessment should be performed by the clinician based on the individual patient's condition. The Hb level should be re-assessed no earlier than 4 weeks post final FERINJECT administration to allow adequate time for erythropoiesis and iron utilisation. In the event the patient requires further iron repletion, the iron need should be recalculated using either Ganzoni method or simplified method described above (see section 5.1 PHARMACODYNAMIC PROPERTIES).

Renal Impairment

A single maximum daily dose of 200 mg iron as FERINJECT should not be exceeded in haemodialysis-dependent chronic kidney disease patients.

Pregnancy

It is recommended that the maximum cumulative dose in pregnant patients is restricted to 1,000 mg for patients with Hb \geq 90 g/L, or 1,500 mg in patients with Hb $<$ 90 g/L. Do not administer more than 1,000 mg iron per week.

Method of Administration

FERINJECT must be administered only by the intravenous route:

- By injection, or
- By infusion, or
- During a haemodialysis session undiluted directly into the venous limb of the dialyser.

FERINJECT must not be administered by the subcutaneous or intramuscular route.

Intravenous injection

FERINJECT may be administered by intravenous injection using undiluted solution. The maximum single dose is 20 mg iron/kg body weight but should not exceed 1,000 mg of iron per week. The administration rates are shown in Table 2:

Table 2 Administration Rates for Intravenous Injection of FERINJECT

Volume of FERINJECT Required	Equivalent of Iron Dose	Administration Rate/Minimum Administration time
2 to 4 mL	100 to 200 mg	No minimal prescribed time
>4 to 10 mL	>200 to 500 mg	100 mg iron/min
>10 to 20 mL	>500 to 1,000 mg	15 minutes

Intravenous infusion

FERINJECT may be administered by intravenous infusion, in which case it needs to be diluted. The maximum single dose is 20 mg iron/kg body weight but should not exceed more than 1,000 mg iron per week.

For infusion, FERINJECT must only be diluted in sterile 0.9% m/V sodium chloride solution as shown in Table 3. Note: for stability reasons, FERINJECT should not be diluted to

concentrations less than 2 mg iron/mL (not including the volume of the ferric carboxymaltose solution).

Table 3: Dilution Plan of FERINJECT for intravenous infusion

FERINJECT	Equivalent of Iron Dose	Maximum Amount of Sterile 0.9% m/V Sodium Chloride Solution	Minimum Administration Time
2 to 4 mL	100 to 200 mg	50 mL	3 minutes
>4 to 10 mL	>200 to 500 mg	100 mL	6 minutes
>10 to 20 mL	>500 to 1,000 mg	250 mL	15 minutes

Note: For stability reasons, dilutions to concentrations less than 2 mg iron/mL (not including the volume of the ferric carboxymaltose solution) are not permissible.

Inspect vials visually for sediment and damage before use. Use only those containing sediment-free, homogeneous solution.

Each vial of FERINJECT is intended for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

FERINJECT must only be mixed with sterile 0.9% m/V sodium chloride solution. No other intravenous dilution solutions and therapeutic agents should be used, as there is the potential for precipitation and/or interaction. For dilution instructions, see above.

This medicinal product must not be mixed with other medicinal products than those mentioned above. The compatibility with containers other than polyethylene and glass is not known.

4.3 CONTRAINDICATIONS

The use of FERINJECT is contraindicated in cases of:

- hypersensitivity to ferric carboxymaltose complex, to FERINJECT or to any of its excipients
- anaemia not attributed to iron deficiency, e.g. other microcytic anaemia
- evidence of iron overload or disturbances in utilisation of iron

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Iron Overload/Haemosiderosis

Body iron excretion is limited and excess tissue iron can be hazardous causing haemosiderosis. Patients receiving FERINJECT require regular monitoring of red cell indices and serum ferritin to detect iron overload. If there is evidence of iron overload, iron therapy should be withheld.

Patients with Infections

Parenteral iron must be used with caution in case of acute or chronic infection, asthma, eczema or atopic allergies. It is recommended that the administration of FERINJECT is stopped in patients with ongoing bacteraemia. In patients with chronic infection a risk/benefit evaluation has to be performed, taking into account the suppression of erythropoiesis.

Hypersensitivity Reactions

Parenterally administered iron preparations can cause hypersensitivity reactions including anaphylactoid reactions, which may be fatal. There have been reports of hypersensitivity reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction). Therefore, facilities for cardio-pulmonary resuscitation must be available. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately. Hypersensitivity reactions have also been reported after previously uneventful doses of any parenteral iron complexes, including ferric carboxymaltose. Each patient should be observed for adverse effects for at least 30 minutes following each FERINJECT administration.

Hypophosphataemia and Hypophosphataemic Osteomalacia

Parenterally administered iron preparations can cause hypophosphataemia which in most cases is transient and without clinical symptoms. Cases of hypophosphataemia requiring medical attention were reported, mainly in patients with existing risk factors and after prolonged exposure to high-dose IV iron.

Cases of hypophosphataemia leading to hypophosphataemic osteomalacia and fractures which required clinical intervention including surgery were reported in the post marketing setting. Patients should be asked to seek medical advice if they experience arthralgia or bone pain.

Patients who receive multiple higher doses for a long-term treatment and with underlying risk factors (such as Vitamin D deficiency, calcium and phosphate malabsorption, secondary hyperparathyroidism, hereditary haemorrhagic telangiectasia, inflammatory bowel disease, and osteoporosis) should be monitored for hypophosphataemic osteomalacia. In case of persisting hypophosphataemia, treatment with ferric carboxymaltose should be re-evaluated.

Paravenous Leakage

Caution should be exercised to avoid paravenous leakage when administering FERINJECT. Paravenous leakage of FERINJECT at the administration site may lead to potentially long lasting brown discolouration and irritation of the skin. In case of paravenous leakage, the administration of FERINJECT must be stopped immediately.

Sodium Content

This medicinal product contains up to 5.5 mg (0.24 mmol) sodium per mL of undiluted solution, equivalent to 0.3% of the WHO recommended maximum daily intake of 2 g sodium for an adult. This should be considered when prescribing FERINJECT to patients on sodium-controlled diets.

Use in hepatic impairment

In patients with liver dysfunction, parenteral iron should only be administered after careful risk/benefit assessment. Parenteral iron administration should be avoided in patients with hepatic dysfunction where iron overload is a precipitating factor, in particular Porphyria Cutanea Tarda (PCT). Careful monitoring of iron status is recommended to avoid iron overload.

There are no clinical studies performed in patients with hepatic impairment. It is known that ferric carboxymaltose may lead to transient increases in liver enzymes see Section 4.8. A careful benefit/risk evaluation should be made prior to using in patients with hepatic impairment, and if prescribed, close monitoring of liver function is recommended.

Use in the elderly

No data available.

Paediatric use

The use of FERINJECT has not been studied in children and therefore is not recommended in children under 14 years.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

As with all parenteral iron preparations the absorption of oral iron is reduced when administered concomitantly. Therefore, if required, oral iron therapy should not be started for at least 5 days after the last administration of FERINJECT.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Reduced weights of reproductive organs (prostate, seminal vesicle, epididymis, testis or uterus) were seen in rats and dogs at maternally toxic doses following repeated IV dosing with ferric carboxymaltose. There were no effects of ferric carboxymaltose on the fertility or reproductive performance of rats given thrice weekly IV doses of up to 30 mg/kg roughly equal to the maximum weekly clinical dose, based on body surface area (BSA). There are no data on the effect of ferric carboxymaltose on human fertility.

Use in pregnancy (Category B3)

Studies in rats have shown that iron released from ferric carboxymaltose can cross the placental barrier.

In pregnant and iron-replete rabbits and rats, embryotoxicity (decreased placental or litter weights and increased resorptions) and increases in fetal skeletal abnormalities (thickened/kinked ribs in rats and cranial, forepaw and/or limb abnormalities in rabbits) were observed at maternally toxic IV iron doses from 9 or 30 mg/kg/day, respectively given during organogenesis (1-2 times the maximum weekly clinical dose, based on body surface area (BSA)). No effects were observed at IV iron doses up to 4.5 or 9 mg/kg/day, respectively (0.5 times the maximum weekly clinical dose, based on BSA).

There is no efficacy and safety data on the use of FERINJECT in human pregnancy less than 16 weeks' gestation. Iron deficiency occurring in the first trimester of pregnancy can in many cases be treated with oral iron.

There are limited data from the use of FERINJECT in women in pregnancy beyond 16 weeks' gestation. A careful risk/benefit evaluation is required before use during pregnancy and FERINJECT should not be used during pregnancy unless clearly necessary.

If the benefit of FERINJECT treatment is judged to outweigh the potential risk to the fetus, it is recommended that treatment in pregnancy should be confined to women beyond the 16th week of gestation.

Foetal bradycardia may occur following administration of parenteral irons. It is usually transient and a consequence of a hypersensitivity reaction in the mother. The unborn baby should be carefully monitored during intravenous administration of parenteral irons to pregnant women.

Use in lactation

Clinical studies showed that transfer of iron from FERINJECT to human milk was negligible ($\leq 1\%$).

Evidence of delayed postnatal growth and development has been observed in rats exposed to ferric carboxymaltose. Milk transfer of administered iron from ferric carboxymaltose was demonstrated in lactating rats. Caution should be exercised when FERINJECT is used in lactating woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The most commonly reported ADR is nausea (occurring in 2.9% of the subjects), followed by injection/infusion site reactions, hypophosphataemia, headache, flushing, dizziness and hypertension. Injection/infusion site reactions comprise several ADRs which individually are either uncommon or rare. The most serious ADR is anaphylactoid reaction (rare). See section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE for further details. In pregnancy, foetal bradycardia associated to hypersensitivity in the mother may occur with parenteral iron preparations (see section 4.6 FERTILITY, PREGNANCY AND LACTATION).

Clinical studies experience

Adverse drug reactions reported in patients treated with ferric carboxymaltose (n=8,245) from completed clinical trials are summarized in the table below.

For subjects in clinical trials that showed a decrease in serum phosphorous, the minimum values were obtained after approximately 2 weeks, and in most cases returned to baseline values by 12 weeks following ferric carboxymaltose treatment.

System Organ Class	Common (≥1/100, <1/10)	Uncommon (≥1/1,000, <1/100)	Rare (≥1/10,000, <1/1,000)
Immune System Disorders	–	Hypersensitivity	Anaphylactoid reactions
Nervous System Disorders	Headache, dizziness	Paraesthesia, dysgeusia	–
Cardiac Disorders	–	Tachycardia	–
Vascular Disorders	Hypertension, flushing	Hypotension	–
Respiratory, Thoracic and Mediastinal Disorders	–	Dyspnoea	–
Gastrointestinal Disorders	Nausea	Vomiting, dyspepsia, flatulence, abdominal pain, constipation, diarrhoea	–
Skin and Subcutaneous Tissue Disorders	–	Pruritus, urticaria, erythema, rash ⁽¹⁾ .	–
Musculoskeletal and Connective Tissue Disorders	–	Myalgia, back pain, arthralgia, pain in extremity, muscle spasms	–
General Disorders and Administration Site Conditions	Injection/Infusion site reactions ⁽²⁾	Pyrexia, fatigue, chest pain, oedema peripheral, pain, chills	Malaise
Investigations	-	Alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, blood lactate dehydrogenase increased, blood alkaline phosphatase increased	–
Metabolism and Nutritional Disorders	Hypophosphataemia [#]	–	–

#: Based on laboratory findings

1 Includes the following preferred terms: rash (individual ADR frequency determined as uncommon) and rash erythematous, -generalised, -macular, -maculo-papular, -pruritic (all individual ADRs frequencies determined as rare).

2 Includes, but is not limited to the following preferred terms: injection/infusion site -pain, -haematoma, -discolouration, -extravasation, -irritation, reaction, (all individual ADRs frequencies determined as uncommon) and -paraesthesia (individual ADR frequency determined as rare).

Note: ADR = Adverse drug reaction.

Undesirable Effects from Post-marketing Spontaneous Reporting

As part of the continuing post-marketing surveillance of ferric carboxymaltose, the following adverse reactions have been observed:

System Organ Class	Common (≥1/100, <1/10)	Uncommon (≥1/1,000, <1/100)	Rare (≥1/10,000, <1/1,000)	Frequency not known
Nervous System Disorders	-	-	Vertigo	Loss of consciousness ²
Cardiac Disorders	-	-	Syncope, pre syncope ³	Kounis syndrome
Respiratory, Thoracic and Mediastinal Disorders	-	-	Bronchospasm ³	
Skin and Subcutaneous Tissue Disorders	-	-	Angioedema and pallor, distant skin discolouration ³	Face oedema ² Dermatitis ²
General Disorders and Administration Site Conditions	-	-	Influenza like illness ¹	
Psychiatric Disorders	-	-	Anxiety ³	
Musculoskeletal and Connective Tissue Disorders				Hypophosphataemic osteomalacia ²

¹ whose onset may vary from a few hours to several days.

² ADRs exclusively reported in the post marketing setting ; estimated as rare

³ ADRs reported in the post-marketing setting which are also observed in the clinical setting.

Post-marketing Spontaneous Reports in Pregnancy Cases

System Organ Class	Preferred Terms ⁽¹⁾
Immune System Disorders	Hypersensitivity, anaphylactoid reactions
Nervous System Disorders	Headache, dizziness
Vascular Disorders	Hypotension, Blood pressure systolic decreased
Skin and Subcutaneous Tissue Disorders	Rash, urticaria
Respiratory, Thoracic and Mediastinal Disorders	Dyspnoea
General Disorders and Administration Site Conditions	Extravasation, infusion site discolouration, injection site discolouration

¹ Frequency not known.

There have been individual case reports of temporally-related, but not causally-related, events of: antenatal foetal ductus venosus thrombosis, uterine hypertonia or contractions and foetal demise when Ferinject has been used in pregnancy.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Ferinject has a low toxicity and is well tolerated. The risk for accidental overdosing is minimal.

Administration of FERINJECT in quantities exceeding the amount needed to correct iron deficit at the time of administration may lead to accumulation of iron in storage sites eventually leading to haemosiderosis. Monitoring of iron parameters such as serum ferritin and transferrin saturation (TSAT) may assist in recognising iron accumulation. If iron accumulation has occurred, the use of an iron chelator may be considered.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Ferric carboxymaltose (FCM) solution for injection/infusion contains iron in a stable ferric state as a complex with a carbohydrate polymer designed to provide iron for the iron transport and storage proteins in the body (transferrin and ferritin). FCM was effective in increasing haemoglobin (Hb) and serum ferritin concentrations in patients with mild to moderate iron-deficiency anaemia. The intravenous (IV) iron dose was 500 mg weekly for up to 4 weeks (n=20) or 1,000 mg weekly for up to 2 weeks (n=26). With the 500 mg iron dose, 37% of patients achieved normal Hb levels within 8 weeks and 75% achieved a ≥ 20 g/L increase in Hb on at least one occasion. With 1,000 mg iron, 48% of patients achieved normal Hb levels within 6 weeks and 73% achieved a ≥ 20 g/L increase in Hb on at least one occasion. The target serum ferritin concentration 100-500 $\mu\text{g/L}$ was reached with both doses and remained within the target range at 2 weeks follow-up (at 6 and 4 weeks respectively for the two dose groups)-data were only available for about half the 500 mg iron dose group.

Clinical trials

Clinical studies showed that the haematological response and the filling of the iron stores was faster after intravenous administration of FCM than with orally administered comparators.

The phase III studies undertaken with FCM included patients with iron deficiency of different aetiologies, i.e. associated with non-dialysis and dialysis dependent chronic kidney disease (CKD), inflammatory bowel disease, heavy menstrual bleeding, post-partum iron deficiency anaemia (IDA), pregnancy (second and third trimester) or patients with chronic heart failure and iron deficiency.

Additionally, there are limited data available with FCM in patients with iron deficiency associated with chemotherapy related anaemia and gastric bypass.

IDA associated with haemodialysis-dependent chronic kidney disease

The efficacy and safety of FCM compared to Venofer[®] (iron sucrose, intravenous) for the treatment of IDA secondary to chronic renal failure was assessed in a multi-centre, open-label, randomised, parallel-group, Phase III study (VIT-IV-CL-015) in 237 patients on haemodialysis or haemodiafiltration. IDA was defined as Hb ≤ 115 g/L in addition to transferrin saturation

(TSAT) <20% and/or serum ferritin <200 µg/L. Patients received 200 mg iron 2 or 3 times weekly (depending on the timing of dialysis sessions) until their individual calculated cumulative dose had been reached. The mean duration of treatment was 15.8 days (range 1 to 27) and 16.2 days (range 1 to 43 days) for the FCM and Venofer® groups, respectively.

Patients treated with erythropoietin (EPO) should have had received this treatment for at least 8 weeks prior to inclusion in the study and increases in the dose of EPO were not permitted. The primary efficacy endpoint was defined as the percentage of patients reaching an increase in Hb of ≥10 g/L at 4 weeks. The percentage of responders was 44.1% (52/118) in the FCM group and 35.3% (41/116) in the Venofer® group; the difference between groups was not statistically significant ($\chi^2 = 0.2254$). At follow-up 4 weeks after the final dose of medication, secondary efficacy parameters (Hb ≥110-120 g/L, serum ferritin 200-800 µg/L, TSAT 20-50%) demonstrated successful increase in iron stores for both treatment groups.

IDA associated with non-dialysis-dependent chronic kidney disease

A multi-centre, randomised, open-label, controlled, 8-week, Phase III study (1VIT04004) in 255 patients was conducted to compare the safety and efficacy of intravenous infusions of the FCM solution with oral administration of ferrous sulphate, independent of Hb response to EPO, in treating IDA in non-dialysis-dependent chronic kidney disease (ND-CKD). IDA was defined as Hb ≤110 g/L, TSAT ≤25%, and serum ferritin ≤300 µg/L. Patients treated with EPO should have had received this treatment for at least 8 weeks prior to inclusion in the study and increases in the dose of EPO were not permitted. Patients randomised to FCM treatment received 1 to 3 doses of FCM solution intravenously at 2-4 week intervals: 15 mg iron/kg for weight ≤66 kg to a maximum of 1,000 mg iron for the initial dose and a maximum of 500 mg iron for subsequent doses. Patients randomised to oral iron treatment received ferrous sulphate tablets (65 mg iron) 3 times daily for 8 weeks.

In a modified intent-to-treat analysis which excluded 8 FCM patients and 2 ferrous sulfate patients, the primary efficacy endpoint, defined as the percentage of patients with an increase in Hb ≥10 g/L at any time between baseline and end of study, or time of intervention, was reached by 60.4% (87/144) of FCM-treated patients compared to 34.7% (35/101) of oral iron-treated patients ($p < 0.001$; 95% confidence interval (CI) 13.0, 38.5). The modified intent-to-treat population comprised patients with at least one dose of study medication, stable erythropoietin dose, at least one post-baseline Hb assessment and GFR ≤45 mL/min/1.73 m². FCM was also demonstrated to be superior to oral iron across all secondary ranked efficacy endpoints: Hb change ≥10 g/L and a serum ferritin change ≥160 µg/L at any time during the study (60.4% versus 0.0%, respectively; $p < 0.001$; 95% CI 48.2, 72.6) or a Hb change ≥10 g/L before Day 42 (54.2% versus 28.7%, respectively; $p < 0.001$; 95% CI 12.8, 38.1).

In a 44-week extension to this study (1VIT05005), the efficacy of FCM in the long-term maintenance treatment of anaemia in ND-CKD was evaluated in 140 patients. Clinical success (Hb ≥110 g/L, serum ferritin 100-800 µg/L, TSAT 30-50%) was achieved in 51.4% (72/140) of patients, with 10% (14/140) exhibiting sustained clinical success at 50% or more of the assessments.

In the ND-CKD subgroup of another study (1VIT07018), the safety and efficacy of IV injection of FCM solution, 15 mg iron/kg body weight up to 1,000 mg iron administered over 15 min. was assessed. The comparator was standard medical care (SMC) as determined by the investigator.

The primary endpoint was the incidence of treatment-emergent serious adverse events from Day 0 to 30 days after the last dose of study drug. The safety population contained 204 FCM subjects and 212 SMC subjects. The majority had mild anaemia (mean Hb 104 g/L in FCM group and

102 g/L in control group). There were no serious adverse events assessed as related to FCM. Based on these limited data and the lack of specific serious drug-related adverse reactions, the safety of single FCM doses of 1,000 mg iron appeared equal to SMC.

Efficacy was assessed in a modified intent-to-treat population of 202 FCM subjects and 203 SMC subjects. Achievement of Hb \geq 120 g/L was comparable in the two groups at 30 days - FCM 9.9% and SMC 6.9% (Fisher's Exact Test $p = 0.29$).

IDA secondary to inflammatory bowel disease

The efficacy of infusions of FCM solutions compared to oral administration of ferrous sulphate in the treatment of IDA secondary to chronic inflammatory bowel disease was examined in a multi-centre, open-label, randomised, 12-week, Phase III study (VIT-IV-CL-008) in 200 patients. 4 patients did not receive study drug and were excluded from the analysis. IDA was defined as Hb \leq 110 g/L in combination with TSAT $<$ 20% and/or serum ferritin $<$ 100 μ g/L. Patients were randomised in a 2:1 (FCM: ferrous sulphate) ratio to receive 1 of 2 treatments: FCM intravenous on Day 1 with subsequent doses at 1-week intervals until the patient's calculated cumulative dose had been reached (a maximum dose of 1,000 mg iron per infusion) or oral ferrous sulphate capsules (100 mg iron) twice daily for 12 weeks. Based on the primary response parameter of change in mean Hb from baseline to Week 12 (36.0 g/L FCM group, 32.9 g/L oral iron group), the results of this study demonstrated that FCM was non-inferior to ferrous sulphate. The non-inferiority criterion was lower limit of 95% CI of difference FCM minus ferrous sulphate \geq -5.0 g/L. The non-inferiority criterion was met in both the intent-to-treat and per protocol populations. Furthermore, the mean Week-12 values of serum ferritin (80.2 μ g/L FCM group, 38.6 μ g/L oral iron group) and TSAT (23.1% FCM group, 29.2% oral iron group) demonstrated a successful repletion of the iron stores in patients treated with FCM.

In another study (FER-IBD-07-COR), FCM dosing based on a simplified dosing scheme with four Hb-weight subgroups (see section 4.2 DOSE AND METHOD OF ADMINISTRATION) was compared with Venofer[®] dosing based on the Ganzoni formula. The FCM dose was given in up to three IV infusions on Days 1, 8 and 15 in single doses of up to 1000 mg iron. The Venofer[®] dose was given in up to 11 IV infusions in doses not exceeding 200 mg iron not more than three times per week. The primary endpoint was the percentage of patients achieving a Hb increase \geq 20 g/L at Week 12. The demographic and haematological characteristics of the two groups were similar. About 60% of subjects were female, median age was 39 years (range 18-81), median weight 67 kg (range 39-137), median baseline Hb 104 g/L (range 61-146) and median baseline serum ferritin 7 μ g/L (range 2-299). Subjects in the two treatment groups achieved at least comparable Hb response overall and in the Hb-weight subgroups (see Table 4).

Table 4. Efficacy of FCM (new dosing method) versus Venofer[®] (Ganzoni dose calculation) in iron deficiency anaemia associated with inflammatory bowel diseases - trial FER-IBD-07-COR – patients with 12-week assessment

	FCM n=228	Venofer[®] n=220	Difference [95% CI]
Hb Response (increase \geq 20 g/L) at Week 12	65.8%	53.6%	12.2% [3.1%, 21.0%]
Hb<100 g/L – Wt 35-<70 kg	missing n=7 n=59 86.4%	missing n=8 n=44 75.0%	11.4% [-4.1%, 26.9%]
Hb<100 g/L – Wt \geq 70 kg	n=31 90.3%	n=24 100.0%	-9.7% [-20.1%, 0.7%]
Hb \geq 100 g/L – Wt 35-<70 kg	n=70 75.7%	n=78 71.8%	3.9% [-10.2%, 18.1%]
Hb \geq 100 g/L – Wt \geq 70 kg	n=61 88.5%	n=66 75.8%	12.8% [-0.3%, 25.8%]

IDA secondary to heavy menstrual bleeding

The safety and efficacy of intravenous infusions of FCM solution, compared to oral administration of ferrous sulphate, in improvement of Hb levels in females with IDA secondary to heavy menstrual bleeding was assessed in a multi-centre, randomised, open-label, 6-week, Phase III study (1VIT04002/1VIT04003). At enrolment, patients had a baseline Hb \leq 114 g/L, TSAT \leq 25%, and serum ferritin \leq 100 μ g/L. Patients were randomised to receive either oral ferrous sulphate tablets (65 mg iron) 3 times daily for 6 weeks or weekly infusions of FCM solution (a maximum dose of 1,000 mg iron per infusion) until the patient's calculated cumulative dose had been reached, to a maximum of 2,500 mg iron. In a modified intent-to-treat analysis which excluded 18 FCM patients and 6 ferrous sulphate patients, FCM was shown to be superior to oral iron in achieving an increase from baseline in Hb \geq 20 g/L at any time during the study: 82.0% (187/228) in the FCM group versus 61.8% (139/225) in the oral iron group ($p < 0.001$; 95% CI 12.2, 28.3). The modified intent-to-treat population comprised patients with at least one dose of study medication, baseline Hb \leq 110 g/L, TSAT \leq 25%, serum ferritin \leq 100 μ g/L, at least one post-baseline Hb assessment and confirmed diagnosis of heavy menstrual bleeding.

Post partum IDA

The safety and efficacy of FCM compared to oral ferrous sulphate as treatment for post partum IDA (Hb \leq 100 g/L or \leq 105 g/L) was assessed in 3 randomised, open-label, multi-centre trials. In 2 of the studies, patients were randomised 1:1 to receive either oral ferrous sulphate tablets (65 mg iron) 3 times daily for 6 weeks or weekly intravenous FCM at dosages based on the calculated iron deficit. A maximum of 1,000 mg of iron (15 mg iron/kg body weight for pre-pregnancy weight \leq 66 kg), as intravenous FCM solution, was given at weekly intervals until the individual's calculated cumulative iron dose had been reached or a maximum total iron dose of 2,500 mg had been administered. In the third study, patients were randomised 2:1 to receive either oral ferrous sulphate capsules (100 mg iron) twice daily for 12 weeks or weekly intravenous FCM at dosages based on the calculated iron deficit (to a maximum of 3 infusions and not exceeding a weekly dose of 1,000 mg iron).

In all 3 studies, FCM was shown to be efficacious for the treatment of IDA in post partum subjects. In the first study (1VIT06011), the superiority of FCM was demonstrated according to the primary efficacy endpoint (defined as Hb $>$ 120 g/L), with a greater proportion of patients in the FCM group (91.4%, 127/139) versus the oral iron group (66.7%, 98/147) achieving success at any time during the study ($p < 0.0001$; 95% CI 15.20, 34.20). This was based on a modified intent-to-treat population which excluded 4 FCM patients and one ferrous sulfate patient.

In the second study (1VIT03001), FCM was demonstrated to be non-inferior to oral iron among subjects who achieved an increase in Hb \geq 20 g/L: 96.4% (162/168) of the FCM group versus 94.1% (159/169) of the oral iron group (95% CI -2.19, 6.88). The analysis was in a modified intent-to-treat population (6 FCM patients and 9 ferrous sulphate patients excluded) and the non-inferiority margin was 15% based on a 1-sided 97.5% CI of the treatment difference. Statistically significantly greater increases from baseline to highest Hb, TSAT, and serum ferritin values were also observed in the FCM groups compared with the oral iron groups.

In the third study (VIT-IV-CL-009), FCM was shown to be non-inferior to ferrous sulphate for the mean change in Hb from baseline to Week 12 (33.4 g/L in the FCM group (n=227) versus 31.8 g/L in the oral iron group (n=117)). The non-inferiority criterion was lower limit of 95% CI of difference FCM minus ferrous sulfate \geq -5.0 g/L. The non-inferiority criterion was met in both the intent-to-treat and per protocol populations.

In another study (1VIT07017) in patients with iron deficiency anaemia due to heavy menstrual bleeding (HMB) or post-partum, the safety and efficacy of IV injection of FCM solution, 15 mg iron/kg body weight up to 1,000 mg iron administered IV over 15 min, was assessed. The comparator was standard medical care (SMC) as determined by the investigator.

The primary endpoint was the incidence of treatment-emergent serious adverse events from Day 0 to 30 days after the last dose of study drug. The safety population contained 996 FCM subjects and 1,022 SMC subjects. Approximately 60% of the subjects had post-partum anaemia (median Hb 103 g/L) and the other 40% anaemia associated with HMB (median Hb 96 g/L). There were no serious adverse events assessed as related to FCM. Based on overall incidences and the lack of specific drug-related serious adverse reactions, the safety profiles of FCM and SMC oral iron appeared similar. There was insufficient exposure to SMC IV iron for it to be included in the assessment.

Efficacy was assessed in a modified intent-to-treat population which was approximately 30% less than the randomised population, although still balanced. Achievement of Hb >120 g/L was significantly better with FCM than SMC in the two subgroups at 30 days (see Table 5).

Table 5. Efficacy of FCM in single doses up to 1,000 mg iron versus SMC in iron deficiency anaemia associated with heavy menstrual bleeding and post-partum – trial 1VIT07017 – 30 days follow-up - modified intent-to-treat

	FCM	SMC	Difference p-value ²
Heavy Menstrual Bleeding	n=331	n=329	
Hb >120 g/L ¹	34.4%	15.8%	18.6% p<0.001
Post-Partum	n=342	n=357	
Hb >120 g/L ¹	68.1%	50.7%	17.4% p<0.001

FCM: Ferric Carboxymaltose. SMC: Standard Medical Care as determined by the investigator.

¹ Anytime between baseline and end of study of surgical intervention. ² Fisher's Exact Test.

Pregnancy

In a study in pregnant women in the second and third trimester with iron deficiency anaemia (FER-ASAP-2009-01) randomised to receive either ferric carboxymaltose (maximum permitted total dose 1000 mg for baseline haemoglobin 91-104 g/L or 1500 mg for baseline haemoglobin 80-90 g/L) or oral iron (200 mg orally twice daily). The range of gestation at study entry for the ferric carboxymaltose arm was 16.0 to 33.9 weeks.

Superiority of ferric carboxymaltose for the primary outcome of change in Hb from baseline to week 3 was not shown. The mean total iron dose was 1,028.5 mg (median 1,000 mg) in the ferric carboxymaltose group compared to 11,959.2 mg (median 12,300 mg) in the oral iron group.

Iron deficiency associated with chronic heart failure

In a population with chronic heart failure, a double-blind, placebo-controlled, randomised study (FER-CARS-02 FAIR-HF) demonstrated a statistically significant improvement in both Patient Global Assessment and New York Heart Association functional class at Week 24 (odds ratio for improvement, 2.51 (95% CI 1.75-3.61; p<0.001) and 2.40 (95% CI 1.55-3.71; p<0.001), respectively). The results applied to iron deficient patients with and without anaemia. Superior improvements (p<0.001) were also observed in the 6-minute walk test and patient quality of life (QoL) for patients treated with ferric carboxymaltose.

Study FER-CARS-05 (CONFIRM-HF) in subjects with chronic heart failure and iron deficiency demonstrated the benefit of ferric carboxymaltose relative to placebo in improving functional capacity as measured by the change in 6-minute walk test distance from baseline to Week 24, with a difference between treatment groups (least squares mean (\pm standard error)) of 33.2 ± 10.52 m ($p=0.002$), thereby confirming the hypothesis of study FER_CARS_02. The treatment benefit of ferric carboxymaltose in improvement of 6-minute walk test distance was statistically significant from week 24 ($p<0.001$) and was sustained throughout the study to Week 52 ($p<0.001$), demonstrating the long-term benefit of iron repletion over a period of 1 year. The improvements in PGA and NYHA functional class were also seen in ferric carboxymaltose - treated subjects, with statistical significance for the difference between treatment groups achieved from Week 12 (PGA) or Week 24 (NYHA functional class) onwards. At Week 52 Endpoint, 54.7% of subjects in the ferric carboxymaltose group showed some improvement in PGA score compared to 35.1% in the placebo group, and 18.0% of subjects in the ferric carboxymaltose group showed an improvement by 1 NYHA functional class, compared to only 3.3% in the placebo group. Improvements in fatigue score and overall Kansas City cardiomyopathy questionnaire score were also seen, with statistical significance for the difference between treatment groups (in favour of ferric carboxymaltose) achieved from Week 12 onwards.

Study FER-CARS-04 (EFFECT-HF) was an open-label (with blinded endpoint evaluation), randomised, 2-arm study comparing ferric carboxymaltose ($n=86$) versus standard of care ($n=86$) of which 29 patients received at least 1 dose of oral iron during the study) in subjects with chronic heart failure and iron deficiency for a treatment period of 24 weeks. At Day 1 and Week 6 (correction phase), subjects received either ferric carboxymaltose according to a simplified dosing grid using baseline Hb and body weight at screening (see section 4.2 DOSE AND METHOD OF ADMINISTRATION) or standard of care. At Week 12, (maintenance phase) subjects received ferric carboxymaltose (500 mg iron) or standard of care if serum ferritin <100 ng/mL or 100 to 300 ng/mL and TSAT $<20\%$. For the primary efficacy endpoint, the treatment difference (ferric carboxymaltose – standard of care) in LS mean change in peak VO_2 from baseline to Week 24 was 1.04 mL/kg/min [95% CI: 0.164, 1.909; $p = 0.0202$] An individual patient data meta-analysis of four double-blind, randomised studies in subjects with chronic heart failure and iron deficiency receiving ferric carboxymaltose versus placebo (studies FER-CARS-01 [12 weeks], FER-CARS-02 FAIR-HF [26 weeks], FER-CARS-03 EFFICACY-HF [26 weeks] and FER-CARS-05 CONFIRM-HF [52 weeks]) compared the efficacy and safety of ferric carboxymaltose ($n=504$) versus placebo ($n=335$) for up to 52 weeks. Ferric carboxymaltose and placebo were administered according to the dosing regimen of the individual studies. The treatment of ferric carboxymaltose versus placebo resulted in a reduction of recurrent cardiovascular hospitalisations and cardiovascular mortality (relative risk (95% CI) of 0.59 (0.40–0.88); $p=0.009$); hospitalisations and mortality as exploratory endpoints in individual studies).

There are no data available regarding the long term use of FERINJECT.

Ferritin Monitoring After Replacement Therapy

There is limited data from study VIT-IV-CL-008, which demonstrates that ferritin levels decrease rapidly 2-4 weeks following replacement and more slowly thereafter. The mean ferritin levels did not drop to levels where retreatment might be considered during the 12 weeks of study follow up. Thus, the available data does not clearly indicate an optimal time for ferritin retesting although assessing ferritin levels earlier than 4 weeks after replacement therapy appears premature. Thus, it is recommended that further re-assessment of ferritin should be made by the clinician based on the individual patient's condition.

5.2 PHARMACOKINETIC PROPERTIES

After a single 100 mg IV iron dose of FCM solution (n=6) injected over 1 min, serum iron concentration peaked at a mean of 15 min. After 500, 800 or 1,000 mg iron in 250 mL normal saline infused over 15 min (n=6 for each dose), serum iron concentration peaked at means of 20 min, 1 h and 1.2 h, respectively. The mean volume of distribution was approximately 3 L, corresponding to the plasma volume. Mean plasma clearance ranged from 2.6-4.4 mL/min and terminal half life from 7-12 h. Renal elimination was negligible.

Within 8 h of a single radiolabelled 100 mg IV iron dose of FCM to patients with iron deficiency or renal anaemia, most of the radiolabelled iron had cleared the circulation and distributed to the bone marrow, liver and spleen. Within 6-9 days, the radiolabelled iron was incorporated into the red blood cells. After 24 days, iron utilisation was 91-99% in iron deficiency anaemia and 61-84% in renal anaemia.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Ferric carboxymaltose was not genotoxic in assays for gene mutation (in vitro bacterial and mouse lymphoma cell assays) and chromosomal damage (human lymphocytes in vitro and mouse micronucleus test in vivo).

Carcinogenicity

The carcinogenic potential of FERINJECT has not been studied in animals.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
Water for injections

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

Shelf-life of the product as packaged for sale:

36 months.

Shelf-life after first opening of the container:

From a microbiological point of view, preparations for parenteral administration should be used immediately.

Shelf-life after dilution with sterile 0.9% m/V sodium chloride solution:

To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2-8°C for not more than 12 hours.

Product is for single use in one patient only. Discard any residue.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in the original package. Do not store above 30 °C. Do not freeze, do not refrigerate.

6.5 NATURE AND CONTENTS OF CONTAINER

2 mL of solution in a vial (type I glass) with bromobutyl rubber stopper and aluminium cap in pack sizes of 1 and 5 vials.

10 mL of solution in a vial (type I glass) with bromobutyl rubber stopper and aluminium cap in pack sizes of 1 and 5 vials.

20 mL of solution in a vial (type I glass) with bromobutyl rubber stopper and aluminium cap in pack sizes of 1 vial.

Not all presentations may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES**Chemical structure**

The active substance of FERINJECT is a complex of polynuclear iron(III)-hydroxide with 4(R)-(poly-(1→4)-*O*-α-D-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate.

The relative molecular weight is approximately 150,000 Da, corresponding to the empirical formula:

$[\text{FeO}_x(\text{OH})_y(\text{H}_2\text{O})_z]_n [\{ (\text{C}_6\text{H}_{10}\text{O}_5)_m (\text{C}_6\text{H}_{12}\text{O}_7) \}_1]_k$, where $n \approx 10^3$, $m \approx 8$, $l \approx 11$, and $k \approx 4$.

CAS number

1461680-64-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4

8 SPONSOR

Vifor Pharma Pty Ltd
Level 8, 80 Dorcas Street
South Bank, Melbourne VIC 3006
Australia
Tel: 1800 202 674 (Australia)
Tel: 0800 996 312 (New Zealand)

9 DATE OF FIRST APPROVAL

05 April 2011

10 DATE OF REVISION

18 May 2021

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.8	Addition of information on foetal bradycardia & Kounis syndrome

AUSTRALIAN PRODUCT INFORMATION - FERINJECT® (FERRIC CARBOXYMALTOSE) SOLUTION FOR INJECTION

1 NAME OF THE MEDICINE

Ferric carboxymaltose

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2 mL vial contains 100 mg of iron as ferric carboxymaltose.

Each 10 mL vial contains 500 mg of iron as ferric carboxymaltose.

Each 20 mL vial contains 1000 mg of iron as ferric carboxymaltose.

Excipient(s) with known effect:

Sodium hydroxide (for pH adjustment).

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Solution for intravenous use. FERINJECT is a dark brown, non-transparent, colloidal solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

FERINJECT is indicated for the treatment of iron deficiency when:

- oral iron preparations are ineffective
- oral iron preparations cannot be used
- there is a clinical need to deliver iron rapidly

The diagnosis must be based on laboratory tests.

4.2 DOSE AND METHOD OF ADMINISTRATION

Determination of the cumulative iron dose

The cumulative dose for repletion of iron using FERINJECT is determined based on the patient's body weight and Hb level and must not be exceeded. There are two methods for determining the cumulative dose, the Ganzoni Method and the Simplified Method. Caution is recommended with the Simplified Method since it is based on experience in a single trial in adults with median Hb 104 g/L (range 61-146 g/L) and body weight ≥ 35 kg – see section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials.

Patients should be closely monitored when large single doses of FERINJECT (>200 mg iron) are administered since the safety data are limited.

Post repletion, regular assessments should be done to ensure that iron levels are corrected and maintained.

Ganzoni Method

Cumulative Iron Dose = Body Weight kg x (Target Hb – Actual Hb g/L) x 0.24 + Iron Stores mg

where

Target Hb = 130 g/L for body weight <35 kg and 150 g/L for body weight ≥35 kg

Iron Stores = 15 mg/kg body weight for body weight <35 kg and 500 mg for body weight ≥35 kg.

Round down to nearest 100 mg if body weight ≤66 kg and round up to nearest 100 mg if body weight >66 kg.

Simplified Method (for patients of body weight ≥35 kg)

The cumulative iron dose is determined according to the following table.

Table 1 Determination of the Iron Need

Hb g/L	Patient Body Weight	
	35 kg to <70 kg	70 kg and above
<100	1,500 mg	2,000 mg
100 to < 140	1,000 mg	1,500 mg
≥140	500 mg	500 mg

For patients with an Hb value ≥140 g/L, an initial dose of 500 mg iron should be given and iron parameters should be checked prior to repeat dosing.

Iron deficiency must be confirmed by laboratory tests as stated in section 4.1 THERAPEUTIC INDICATIONS.

Calculation and administration of the maximum individual iron dose(s)

Based on the iron need determined above the appropriate dose(s) of FERINJECT should be administered taking into consideration the following:

A single FERINJECT administration should not exceed:

- 20 mg iron/kg body weight
- 1,000 mg of iron (20 mL ferric carboxymaltose)

The maximum recommended cumulative dose of FERINJECT is 1,000 mg of iron (20 mL ferric carboxymaltose) per week.

Post-iron repletion assessments

Re-assessment should be performed by the clinician based on the individual patient's condition. The Hb level should be re-assessed no earlier than 4 weeks post final FERINJECT administration to allow adequate time for erythropoiesis and iron utilisation. In the event the patient requires further iron repletion, the iron need should be recalculated using either Ganzoni method or simplified method described above (see section 5.1 PHARMACODYNAMIC PROPERTIES).

Renal Impairment

A single maximum daily dose of 200 mg iron as FERINJECT should not be exceeded in haemodialysis-dependent chronic kidney disease patients.

Pregnancy

It is recommended that the maximum cumulative dose in pregnant patients is restricted to 1,000 mg for patients with Hb \geq 90 g/L, or 1,500 mg in patients with Hb $<$ 90 g/L. Do not administer more than 1,000 mg iron per week.

Method of Administration

FERINJECT must be administered only by the intravenous route:

- By injection, or
- By infusion, or
- During a haemodialysis session undiluted directly into the venous limb of the dialyser.

FERINJECT must not be administered by the subcutaneous or intramuscular route.

Intravenous injection

FERINJECT may be administered by intravenous injection using undiluted solution. The maximum single dose is 20 mg iron/kg body weight but should not exceed 1,000 mg of iron per week. The administration rates are shown in Table 2:

Table 2 Administration Rates for Intravenous Injection of FERINJECT

Volume of FERINJECT Required	Equivalent of Iron Dose	Administration Rate/Minimum Administration time
2 to 4 mL	100 to 200 mg	No minimal prescribed time
>4 to 10 mL	>200 to 500 mg	100 mg iron/min
>10 to 20 mL	>500 to 1,000 mg	15 minutes

Intravenous infusion

FERINJECT may be administered by intravenous infusion, in which case it needs to be diluted. The maximum single dose is 20 mg iron/kg body weight but should not exceed more than 1,000 mg iron per week.

For infusion, FERINJECT must only be diluted in sterile 0.9% m/V sodium chloride solution as shown in Table 3. Note: for stability reasons, FERINJECT should not be diluted to

concentrations less than 2 mg iron/mL (not including the volume of the ferric carboxymaltose solution).

Table 3: Dilution Plan of FERINJECT for intravenous infusion

FERINJECT	Equivalent of Iron Dose	Maximum Amount of Sterile 0.9% m/V Sodium Chloride Solution	Minimum Administration Time
2 to 4 mL	100 to 200 mg	50 mL	3 minutes
>4 to 10 mL	>200 to 500 mg	100 mL	6 minutes
>10 to 20 mL	>500 to 1,000 mg	250 mL	15 minutes

Note: For stability reasons, dilutions to concentrations less than 2 mg iron/mL (not including the volume of the ferric carboxymaltose solution) are not permissible.

Inspect vials visually for sediment and damage before use. Use only those containing sediment-free, homogeneous solution.

Each vial of FERINJECT is intended for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

FERINJECT must only be mixed with sterile 0.9% m/V sodium chloride solution. No other intravenous dilution solutions and therapeutic agents should be used, as there is the potential for precipitation and/or interaction. For dilution instructions, see above.

This medicinal product must not be mixed with other medicinal products than those mentioned above. The compatibility with containers other than polyethylene and glass is not known.

4.3 CONTRAINDICATIONS

The use of FERINJECT is contraindicated in cases of:

- hypersensitivity to ferric carboxymaltose complex, to FERINJECT or to any of its excipients
- anaemia not attributed to iron deficiency, e.g. other microcytic anaemia
- evidence of iron overload or disturbances in utilisation of iron

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Iron Overload/Haemosiderosis

Body iron excretion is limited and excess tissue iron can be hazardous causing haemosiderosis. Patients receiving FERINJECT require regular monitoring of red cell indices and serum ferritin to detect iron overload. If there is evidence of iron overload, iron therapy should be withheld.

Patients with Infections

Parenteral iron must be used with caution in case of acute or chronic infection, asthma, eczema or atopic allergies. It is recommended that the administration of FERINJECT is stopped in patients with ongoing bacteraemia. In patients with chronic infection a risk/benefit evaluation has to be performed, taking into account the suppression of erythropoiesis.

Hypersensitivity Reactions

Parenterally administered iron preparations can cause hypersensitivity reactions including anaphylactoid reactions, which may be fatal. There have been reports of hypersensitivity reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction). Therefore, facilities for cardio-pulmonary resuscitation must be available. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately. Hypersensitivity reactions have also been reported after previously uneventful doses of any parenteral iron complexes, including ferric carboxymaltose. Each patient should be observed for adverse effects for at least 30 minutes following each FERINJECT administration.

Hypophosphataemia and Hypophosphataemic Osteomalacia

Parenterally administered iron preparations can cause hypophosphataemia which in most cases is transient and without clinical symptoms. Cases of hypophosphataemia requiring medical attention were reported, mainly in patients with existing risk factors and after prolonged exposure to high-dose IV iron.

Cases of hypophosphataemia leading to hypophosphataemic osteomalacia and fractures which required clinical intervention including surgery were reported in the post marketing setting. Patients should be asked to seek medical advice if they experience arthralgia or bone pain.

Patients who receive multiple higher doses for a long-term treatment and with underlying risk factors (such as Vitamin D deficiency, calcium and phosphate malabsorption, secondary hyperparathyroidism, hereditary haemorrhagic telangiectasia, inflammatory bowel disease, and osteoporosis) should be monitored for hypophosphataemic osteomalacia. In case of persisting hypophosphataemia, treatment with ferric carboxymaltose should be re-evaluated.

Paravenous Leakage

Caution should be exercised to avoid paravenous leakage when administering FERINJECT. Paravenous leakage of FERINJECT at the administration site may lead to potentially long lasting brown discolouration and irritation of the skin. In case of paravenous leakage, the administration of FERINJECT must be stopped immediately.

Sodium Content

This medicinal product contains up to 5.5 mg (0.24 mmol) sodium per mL of undiluted solution, equivalent to 0.3% of the WHO recommended maximum daily intake of 2 g sodium for an adult. This should be considered when prescribing FERINJECT to patients on sodium-controlled diets.

Use in hepatic impairment

In patients with liver dysfunction, parenteral iron should only be administered after careful risk/benefit assessment. Parenteral iron administration should be avoided in patients with hepatic dysfunction where iron overload is a precipitating factor, in particular Porphyria Cutanea Tarda (PCT). Careful monitoring of iron status is recommended to avoid iron overload.

There are no clinical studies performed in patients with hepatic impairment. It is known that ferric carboxymaltose may lead to transient increases in liver enzymes see Section 4.8. A careful benefit/risk evaluation should be made prior to using in patients with hepatic impairment, and if prescribed, close monitoring of liver function is recommended.

Use in the elderly

No data available.

Paediatric use

The use of FERINJECT has not been studied in children and therefore is not recommended in children under 14 years.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

As with all parenteral iron preparations the absorption of oral iron is reduced when administered concomitantly. Therefore, if required, oral iron therapy should not be started for at least 5 days after the last administration of FERINJECT.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Reduced weights of reproductive organs (prostate, seminal vesicle, epididymis, testis or uterus) were seen in rats and dogs at maternally toxic doses following repeated IV dosing with ferric carboxymaltose. There were no effects of ferric carboxymaltose on the fertility or reproductive performance of rats given thrice weekly IV doses of up to 30 mg/kg roughly equal to the maximum weekly clinical dose, based on body surface area (BSA). There are no data on the effect of ferric carboxymaltose on human fertility.

Use in pregnancy (Category B3)

Studies in rats have shown that iron released from ferric carboxymaltose can cross the placental barrier.

In pregnant and iron-replete rabbits and rats, embryotoxicity (decreased placental or litter weights and increased resorptions) and increases in fetal skeletal abnormalities (thickened/kinked ribs in rats and cranial, forepaw and/or limb abnormalities in rabbits) were observed at maternally toxic IV iron doses from 9 or 30 mg/kg/day, respectively given during organogenesis (1-2 times the maximum weekly clinical dose, based on body surface area (BSA)). No effects were observed at IV iron doses up to 4.5 or 9 mg/kg/day, respectively (0.5 times the maximum weekly clinical dose, based on BSA).

There is no efficacy and safety data on the use of FERINJECT in human pregnancy less than 16 weeks' gestation. Iron deficiency occurring in the first trimester of pregnancy can in many cases be treated with oral iron.

There are limited data from the use of FERINJECT in women in pregnancy beyond 16 weeks' gestation. A careful risk/benefit evaluation is required before use during pregnancy and FERINJECT should not be used during pregnancy unless clearly necessary.

If the benefit of FERINJECT treatment is judged to outweigh the potential risk to the fetus, it is recommended that treatment in pregnancy should be confined to women beyond the 16th week of gestation.

Foetal bradycardia may occur following administration of parenteral irons. It is usually transient and a consequence of a hypersensitivity reaction in the mother. The unborn baby should be carefully monitored during intravenous administration of parenteral irons to pregnant women.

Use in lactation

Clinical studies showed that transfer of iron from FERINJECT to human milk was negligible ($\leq 1\%$).

Evidence of delayed postnatal growth and development has been observed in rats exposed to ferric carboxymaltose. Milk transfer of administered iron from ferric carboxymaltose was demonstrated in lactating rats. Caution should be exercised when FERINJECT is used in lactating woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The most commonly reported ADR is nausea (occurring in 2.9% of the subjects), followed by injection/infusion site reactions, hypophosphataemia, headache, flushing, dizziness and hypertension. Injection/infusion site reactions comprise several ADRs which individually are either uncommon or rare. The most serious ADR is anaphylactoid reaction (rare). See section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE for further details. In pregnancy, foetal bradycardia associated to hypersensitivity in the mother may occur with parenteral iron preparations (see section 4.6 FERTILITY, PREGNANCY AND LACTATION).

Clinical studies experience

Adverse drug reactions reported in patients treated with ferric carboxymaltose (n=8,245) from completed clinical trials are summarized in the table below.

For subjects in clinical trials that showed a decrease in serum phosphorous, the minimum values were obtained after approximately 2 weeks, and in most cases returned to baseline values by 12 weeks following ferric carboxymaltose treatment.

System Organ Class	Common (≥1/100, <1/10)	Uncommon (≥1/1,000, <1/100)	Rare (≥1/10,000, <1/1,000)
Immune System Disorders	–	Hypersensitivity	Anaphylactoid reactions
Nervous System Disorders	Headache, dizziness	Paraesthesia, dysgeusia	–
Cardiac Disorders	–	Tachycardia	–
Vascular Disorders	Hypertension, flushing	Hypotension	–
Respiratory, Thoracic and Mediastinal Disorders	–	Dyspnoea	–
Gastrointestinal Disorders	Nausea	Vomiting, dyspepsia, flatulence, abdominal pain, constipation, diarrhoea	–
Skin and Subcutaneous Tissue Disorders	–	Pruritus, urticaria, erythema, rash ⁽¹⁾ .	–
Musculoskeletal and Connective Tissue Disorders	–	Myalgia, back pain, arthralgia, pain in extremity, muscle spasms	–
General Disorders and Administration Site Conditions	Injection/Infusion site reactions ⁽²⁾	Pyrexia, fatigue, chest pain, oedema peripheral, pain, chills	Malaise
Investigations	-	Alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, blood lactate dehydrogenase increased, blood alkaline phosphatase increased	–
Metabolism and Nutritional Disorders	Hypophosphataemia [#]	–	–

#: Based on laboratory findings

1 Includes the following preferred terms: rash (individual ADR frequency determined as uncommon) and rash erythematous, -generalised, -macular, -maculo-papular, -pruritic (all individual ADRs frequencies determined as rare).

2 Includes, but is not limited to the following preferred terms: injection/infusion site -pain, -haematoma, -discolouration, -extravasation, -irritation, reaction, (all individual ADRs frequencies determined as uncommon) and -paraesthesia (individual ADR frequency determined as rare).

Note: ADR = Adverse drug reaction.

Undesirable Effects from Post-marketing Spontaneous Reporting

As part of the continuing post-marketing surveillance of ferric carboxymaltose, the following adverse reactions have been observed:

System Organ Class	Common (≥1/100, <1/10)	Uncommon (≥1/1,000, <1/100)	Rare (≥1/10,000, <1/1,000)	Frequency not known
Nervous System Disorders	-	-	Vertigo	Loss of consciousness ²
Cardiac Disorders	-	-	Syncope, pre syncope ³	Kounis syndrome
Respiratory, Thoracic and Mediastinal Disorders	-	-	Bronchospasm ³	
Skin and Subcutaneous Tissue Disorders	-	-	Angioedema and pallor, distant skin discolouration ³	Face oedema ² Dermatitis ²
General Disorders and Administration Site Conditions	-	-	Influenza like illness ¹	
Psychiatric Disorders	-	-	Anxiety ³	
Musculoskeletal and Connective Tissue Disorders				Hypophosphataemic osteomalacia ²

¹ whose onset may vary from a few hours to several days.

² ADRs exclusively reported in the post marketing setting ; estimated as rare

³ ADRs reported in the post-marketing setting which are also observed in the clinical setting.

Post-marketing Spontaneous Reports in Pregnancy Cases

System Organ Class	Preferred Terms ⁽¹⁾
Immune System Disorders	Hypersensitivity, anaphylactoid reactions
Nervous System Disorders	Headache, dizziness
Vascular Disorders	Hypotension, Blood pressure systolic decreased
Skin and Subcutaneous Tissue Disorders	Rash, urticaria
Respiratory, Thoracic and Mediastinal Disorders	Dyspnoea
General Disorders and Administration Site Conditions	Extravasation, infusion site discolouration, injection site discolouration

¹ Frequency not known.

There have been individual case reports of temporally-related, but not causally-related, events of: antenatal foetal ductus venosus thrombosis, uterine hypertonia or contractions and foetal demise when Ferinject has been used in pregnancy.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Ferinject has a low toxicity and is well tolerated. The risk for accidental overdosing is minimal.

Administration of FERINJECT in quantities exceeding the amount needed to correct iron deficit at the time of administration may lead to accumulation of iron in storage sites eventually leading to haemosiderosis. Monitoring of iron parameters such as serum ferritin and transferrin saturation (TSAT) may assist in recognising iron accumulation. If iron accumulation has occurred, the use of an iron chelator may be considered.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Ferric carboxymaltose (FCM) solution for injection/infusion contains iron in a stable ferric state as a complex with a carbohydrate polymer designed to provide iron for the iron transport and storage proteins in the body (transferrin and ferritin). FCM was effective in increasing haemoglobin (Hb) and serum ferritin concentrations in patients with mild to moderate iron-deficiency anaemia. The intravenous (IV) iron dose was 500 mg weekly for up to 4 weeks (n=20) or 1,000 mg weekly for up to 2 weeks (n=26). With the 500 mg iron dose, 37% of patients achieved normal Hb levels within 8 weeks and 75% achieved a ≥ 20 g/L increase in Hb on at least one occasion. With 1,000 mg iron, 48% of patients achieved normal Hb levels within 6 weeks and 73% achieved a ≥ 20 g/L increase in Hb on at least one occasion. The target serum ferritin concentration 100-500 $\mu\text{g/L}$ was reached with both doses and remained within the target range at 2 weeks follow-up (at 6 and 4 weeks respectively for the two dose groups)-data were only available for about half the 500 mg iron dose group.

Clinical trials

Clinical studies showed that the haematological response and the filling of the iron stores was faster after intravenous administration of FCM than with orally administered comparators.

The phase III studies undertaken with FCM included patients with iron deficiency of different aetiologies, i.e. associated with non-dialysis and dialysis dependent chronic kidney disease (CKD), inflammatory bowel disease, heavy menstrual bleeding, post-partum iron deficiency anaemia (IDA), pregnancy (second and third trimester) or patients with chronic heart failure and iron deficiency.

Additionally, there are limited data available with FCM in patients with iron deficiency associated with chemotherapy related anaemia and gastric bypass.

IDA associated with haemodialysis-dependent chronic kidney disease

The efficacy and safety of FCM compared to Venofer[®] (iron sucrose, intravenous) for the treatment of IDA secondary to chronic renal failure was assessed in a multi-centre, open-label, randomised, parallel-group, Phase III study (VIT-IV-CL-015) in 237 patients on haemodialysis or haemodiafiltration. IDA was defined as Hb ≤ 115 g/L in addition to transferrin saturation

(TSAT) <20% and/or serum ferritin <200 µg/L. Patients received 200 mg iron 2 or 3 times weekly (depending on the timing of dialysis sessions) until their individual calculated cumulative dose had been reached. The mean duration of treatment was 15.8 days (range 1 to 27) and 16.2 days (range 1 to 43 days) for the FCM and Venofer[®] groups, respectively.

Patients treated with erythropoietin (EPO) should have had received this treatment for at least 8 weeks prior to inclusion in the study and increases in the dose of EPO were not permitted. The primary efficacy endpoint was defined as the percentage of patients reaching an increase in Hb of ≥10 g/L at 4 weeks. The percentage of responders was 44.1% (52/118) in the FCM group and 35.3% (41/116) in the Venofer[®] group; the difference between groups was not statistically significant ($\chi^2 = 0.2254$). At follow-up 4 weeks after the final dose of medication, secondary efficacy parameters (Hb ≥110-120 g/L, serum ferritin 200-800 µg/L, TSAT 20-50%) demonstrated successful increase in iron stores for both treatment groups.

IDA associated with non-dialysis-dependent chronic kidney disease

A multi-centre, randomised, open-label, controlled, 8-week, Phase III study (1VIT04004) in 255 patients was conducted to compare the safety and efficacy of intravenous infusions of the FCM solution with oral administration of ferrous sulphate, independent of Hb response to EPO, in treating IDA in non-dialysis-dependent chronic kidney disease (ND-CKD). IDA was defined as Hb ≤110 g/L, TSAT ≤25%, and serum ferritin ≤300 µg/L. Patients treated with EPO should have had received this treatment for at least 8 weeks prior to inclusion in the study and increases in the dose of EPO were not permitted. Patients randomised to FCM treatment received 1 to 3 doses of FCM solution intravenously at 2-4 week intervals: 15 mg iron/kg for weight ≤66 kg to a maximum of 1,000 mg iron for the initial dose and a maximum of 500 mg iron for subsequent doses. Patients randomised to oral iron treatment received ferrous sulphate tablets (65 mg iron) 3 times daily for 8 weeks.

In a modified intent-to-treat analysis which excluded 8 FCM patients and 2 ferrous sulfate patients, the primary efficacy endpoint, defined as the percentage of patients with an increase in Hb ≥10 g/L at any time between baseline and end of study, or time of intervention, was reached by 60.4% (87/144) of FCM-treated patients compared to 34.7% (35/101) of oral iron-treated patients ($p < 0.001$; 95% confidence interval (CI) 13.0, 38.5). The modified intent-to-treat population comprised patients with at least one dose of study medication, stable erythropoietin dose, at least one post-baseline Hb assessment and GFR ≤45 mL/min/1.73 m². FCM was also demonstrated to be superior to oral iron across all secondary ranked efficacy endpoints: Hb change ≥10 g/L and a serum ferritin change ≥160 µg/L at any time during the study (60.4% versus 0.0%, respectively; $p < 0.001$; 95% CI 48.2, 72.6) or a Hb change ≥10 g/L before Day 42 (54.2% versus 28.7%, respectively; $p < 0.001$; 95% CI 12.8, 38.1).

In a 44-week extension to this study (1VIT05005), the efficacy of FCM in the long-term maintenance treatment of anaemia in ND-CKD was evaluated in 140 patients. Clinical success (Hb ≥110 g/L, serum ferritin 100-800 µg/L, TSAT 30-50%) was achieved in 51.4% (72/140) of patients, with 10% (14/140) exhibiting sustained clinical success at 50% or more of the assessments.

In the ND-CKD subgroup of another study (1VIT07018), the safety and efficacy of IV injection of FCM solution, 15 mg iron/kg body weight up to 1,000 mg iron administered over 15 min. was assessed. The comparator was standard medical care (SMC) as determined by the investigator.

The primary endpoint was the incidence of treatment-emergent serious adverse events from Day 0 to 30 days after the last dose of study drug. The safety population contained 204 FCM subjects and 212 SMC subjects. The majority had mild anaemia (mean Hb 104 g/L in FCM group and

102 g/L in control group). There were no serious adverse events assessed as related to FCM. Based on these limited data and the lack of specific serious drug-related adverse reactions, the safety of single FCM doses of 1,000 mg iron appeared equal to SMC.

Efficacy was assessed in a modified intent-to-treat population of 202 FCM subjects and 203 SMC subjects. Achievement of Hb \geq 120 g/L was comparable in the two groups at 30 days - FCM 9.9% and SMC 6.9% (Fisher's Exact Test p = 0.29).

IDA secondary to inflammatory bowel disease

The efficacy of infusions of FCM solutions compared to oral administration of ferrous sulphate in the treatment of IDA secondary to chronic inflammatory bowel disease was examined in a multi-centre, open-label, randomised, 12-week, Phase III study (VIT-IV-CL-008) in 200 patients. 4 patients did not receive study drug and were excluded from the analysis. IDA was defined as Hb \leq 110 g/L in combination with TSAT $<$ 20% and/or serum ferritin $<$ 100 μ g/L. Patients were randomised in a 2:1 (FCM: ferrous sulphate) ratio to receive 1 of 2 treatments: FCM intravenous on Day 1 with subsequent doses at 1-week intervals until the patient's calculated cumulative dose had been reached (a maximum dose of 1,000 mg iron per infusion) or oral ferrous sulphate capsules (100 mg iron) twice daily for 12 weeks. Based on the primary response parameter of change in mean Hb from baseline to Week 12 (36.0 g/L FCM group, 32.9 g/L oral iron group), the results of this study demonstrated that FCM was non-inferior to ferrous sulphate. The non-inferiority criterion was lower limit of 95% CI of difference FCM minus ferrous sulphate \geq -5.0 g/L. The non-inferiority criterion was met in both the intent-to-treat and per protocol populations. Furthermore, the mean Week-12 values of serum ferritin (80.2 μ g/L FCM group, 38.6 μ g/L oral iron group) and TSAT (23.1% FCM group, 29.2% oral iron group) demonstrated a successful repletion of the iron stores in patients treated with FCM.

In another study (FER-IBD-07-COR), FCM dosing based on a simplified dosing scheme with four Hb-weight subgroups (see section 4.2 DOSE AND METHOD OF ADMINISTRATION) was compared with Venofer[®] dosing based on the Ganzoni formula. The FCM dose was given in up to three IV infusions on Days 1, 8 and 15 in single doses of up to 1000 mg iron. The Venofer[®] dose was given in up to 11 IV infusions in doses not exceeding 200 mg iron not more than three times per week. The primary endpoint was the percentage of patients achieving a Hb increase \geq 20 g/L at Week 12. The demographic and haematological characteristics of the two groups were similar. About 60% of subjects were female, median age was 39 years (range 18-81), median weight 67 kg (range 39-137), median baseline Hb 104 g/L (range 61-146) and median baseline serum ferritin 7 μ g/L (range 2-299). Subjects in the two treatment groups achieved at least comparable Hb response overall and in the Hb-weight subgroups (see Table 4).

Table 4. Efficacy of FCM (new dosing method) versus Venofer[®] (Ganzoni dose calculation) in iron deficiency anaemia associated with inflammatory bowel diseases - trial FER-IBD-07-COR – patients with 12-week assessment

	FCM n=228	Venofer[®] n=220	Difference [95% CI]
Hb Response (increase \geq 20 g/L) at Week 12	65.8%	53.6%	12.2% [3.1%, 21.0%]
Hb<100 g/L – Wt 35-<70 kg	missing n=7 n=59 86.4%	missing n=8 n=44 75.0%	11.4% [-4.1%, 26.9%]
Hb<100 g/L – Wt \geq 70 kg	n=31 90.3%	n=24 100.0%	-9.7% [-20.1%, 0.7%]
Hb \geq 100 g/L – Wt 35-<70 kg	n=70 75.7%	n=78 71.8%	3.9% [-10.2%, 18.1%]
Hb \geq 100 g/L – Wt \geq 70 kg	n=61 88.5%	n=66 75.8%	12.8% [-0.3%, 25.8%]

IDA secondary to heavy menstrual bleeding

The safety and efficacy of intravenous infusions of FCM solution, compared to oral administration of ferrous sulphate, in improvement of Hb levels in females with IDA secondary to heavy menstrual bleeding was assessed in a multi-centre, randomised, open-label, 6-week, Phase III study (1VIT04002/1VIT04003). At enrolment, patients had a baseline Hb \leq 114 g/L, TSAT \leq 25%, and serum ferritin \leq 100 μ g/L. Patients were randomised to receive either oral ferrous sulphate tablets (65 mg iron) 3 times daily for 6 weeks or weekly infusions of FCM solution (a maximum dose of 1,000 mg iron per infusion) until the patient's calculated cumulative dose had been reached, to a maximum of 2,500 mg iron. In a modified intent-to-treat analysis which excluded 18 FCM patients and 6 ferrous sulphate patients, FCM was shown to be superior to oral iron in achieving an increase from baseline in Hb \geq 20 g/L at any time during the study: 82.0% (187/228) in the FCM group versus 61.8% (139/225) in the oral iron group (p <0.001; 95% CI 12.2, 28.3). The modified intent-to-treat population comprised patients with at least one dose of study medication, baseline Hb \leq 110 g/L, TSAT \leq 25%, serum ferritin \leq 100 μ g/L, at least one post-baseline Hb assessment and confirmed diagnosis of heavy menstrual bleeding.

Post partum IDA

The safety and efficacy of FCM compared to oral ferrous sulphate as treatment for post partum IDA (Hb \leq 100 g/L or \leq 105 g/L) was assessed in 3 randomised, open-label, multi-centre trials. In 2 of the studies, patients were randomised 1:1 to receive either oral ferrous sulphate tablets (65 mg iron) 3 times daily for 6 weeks or weekly intravenous FCM at dosages based on the calculated iron deficit. A maximum of 1,000 mg of iron (15 mg iron/kg body weight for pre-pregnancy weight \leq 66 kg), as intravenous FCM solution, was given at weekly intervals until the individual's calculated cumulative iron dose had been reached or a maximum total iron dose of 2,500 mg had been administered. In the third study, patients were randomised 2:1 to receive either oral ferrous sulphate capsules (100 mg iron) twice daily for 12 weeks or weekly intravenous FCM at dosages based on the calculated iron deficit (to a maximum of 3 infusions and not exceeding a weekly dose of 1,000 mg iron).

In all 3 studies, FCM was shown to be efficacious for the treatment of IDA in post partum subjects. In the first study (1VIT06011), the superiority of FCM was demonstrated according to the primary efficacy endpoint (defined as Hb >120 g/L), with a greater proportion of patients in the FCM group (91.4%, 127/139) versus the oral iron group (66.7%, 98/147) achieving success at any time during the study (p <0.0001; 95% CI 15.20, 34.20). This was based on a modified intent-to-treat population which excluded 4 FCM patients and one ferrous sulfate patient.

In the second study (1VIT03001), FCM was demonstrated to be non-inferior to oral iron among subjects who achieved an increase in Hb \geq 20 g/L: 96.4% (162/168) of the FCM group versus 94.1% (159/169) of the oral iron group (95% CI -2.19, 6.88). The analysis was in a modified intent-to-treat population (6 FCM patients and 9 ferrous sulphate patients excluded) and the non-inferiority margin was 15% based on a 1-sided 97.5% CI of the treatment difference. Statistically significantly greater increases from baseline to highest Hb, TSAT, and serum ferritin values were also observed in the FCM groups compared with the oral iron groups.

In the third study (VIT-IV-CL-009), FCM was shown to be non-inferior to ferrous sulphate for the mean change in Hb from baseline to Week 12 (33.4 g/L in the FCM group (n=227) versus 31.8 g/L in the oral iron group (n=117)). The non-inferiority criterion was lower limit of 95% CI of difference FCM minus ferrous sulfate \geq -5.0 g/L. The non-inferiority criterion was met in both the intent-to-treat and per protocol populations.

In another study (1VIT07017) in patients with iron deficiency anaemia due to heavy menstrual bleeding (HMB) or post-partum, the safety and efficacy of IV injection of FCM solution, 15 mg iron/kg body weight up to 1,000 mg iron administered IV over 15 min, was assessed. The comparator was standard medical care (SMC) as determined by the investigator.

The primary endpoint was the incidence of treatment-emergent serious adverse events from Day 0 to 30 days after the last dose of study drug. The safety population contained 996 FCM subjects and 1,022 SMC subjects. Approximately 60% of the subjects had post-partum anaemia (median Hb 103 g/L) and the other 40% anaemia associated with HMB (median Hb 96 g/L). There were no serious adverse events assessed as related to FCM. Based on overall incidences and the lack of specific drug-related serious adverse reactions, the safety profiles of FCM and SMC oral iron appeared similar. There was insufficient exposure to SMC IV iron for it to be included in the assessment.

Efficacy was assessed in a modified intent-to-treat population which was approximately 30% less than the randomised population, although still balanced. Achievement of Hb >120 g/L was significantly better with FCM than SMC in the two subgroups at 30 days (see Table 5).

Table 5. Efficacy of FCM in single doses up to 1,000 mg iron versus SMC in iron deficiency anaemia associated with heavy menstrual bleeding and post-partum – trial 1VIT07017 – 30 days follow-up - modified intent-to-treat

	FCM	SMC	Difference p-value ²
Heavy Menstrual Bleeding	n=331	n=329	
Hb >120 g/L ¹	34.4%	15.8%	18.6% p<0.001
Post-Partum	n=342	n=357	
Hb >120 g/L ¹	68.1%	50.7%	17.4% p<0.001

FCM: Ferric Carboxymaltose. SMC: Standard Medical Care as determined by the investigator.

¹ Anytime between baseline and end of study of surgical intervention. ² Fisher's Exact Test.

Pregnancy

In a study in pregnant women in the second and third trimester with iron deficiency anaemia (FER-ASAP-2009-01) randomised to receive either ferric carboxymaltose (maximum permitted total dose 1000 mg for baseline haemoglobin 91-104 g/L or 1500 mg for baseline haemoglobin 80-90 g/L) or oral iron (200 mg orally twice daily). The range of gestation at study entry for the ferric carboxymaltose arm was 16.0 to 33.9 weeks.

Superiority of ferric carboxymaltose for the primary outcome of change in Hb from baseline to week 3 was not shown. The mean total iron dose was 1,028.5 mg (median 1,000 mg) in the ferric carboxymaltose group compared to 11,959.2 mg (median 12,300 mg) in the oral iron group.

Iron deficiency associated with chronic heart failure

In a population with chronic heart failure, a double-blind, placebo-controlled, randomised study (FER-CARS-02 FAIR-HF) demonstrated a statistically significant improvement in both Patient Global Assessment and New York Heart Association functional class at Week 24 (odds ratio for improvement, 2.51 (95% CI 1.75-3.61; p<0.001) and 2.40 (95% CI 1.55-3.71; p<0.001), respectively). The results applied to iron deficient patients with and without anaemia. Superior improvements (p<0.001) were also observed in the 6-minute walk test and patient quality of life (QoL) for patients treated with ferric carboxymaltose.

Study FER-CARS-05 (CONFIRM-HF) in subjects with chronic heart failure and iron deficiency demonstrated the benefit of ferric carboxymaltose relative to placebo in improving functional capacity as measured by the change in 6-minute walk test distance from baseline to Week 24, with a difference between treatment groups (least squares mean (\pm standard error)) of 33.2 ± 10.52 m ($p=0.002$), thereby confirming the hypothesis of study FER_CARS_02. The treatment benefit of ferric carboxymaltose in improvement of 6-minute walk test distance was statistically significant from week 24 ($p<0.001$) and was sustained throughout the study to Week 52 ($p<0.001$), demonstrating the long-term benefit of iron repletion over a period of 1 year. The improvements in PGA and NYHA functional class were also seen in ferric carboxymaltose - treated subjects, with statistical significance for the difference between treatment groups achieved from Week 12 (PGA) or Week 24 (NYHA functional class) onwards. At Week 52 Endpoint, 54.7% of subjects in the ferric carboxymaltose group showed some improvement in PGA score compared to 35.1% in the placebo group, and 18.0% of subjects in the ferric carboxymaltose group showed an improvement by 1 NYHA functional class, compared to only 3.3% in the placebo group. Improvements in fatigue score and overall Kansas City cardiomyopathy questionnaire score were also seen, with statistical significance for the difference between treatment groups (in favour of ferric carboxymaltose) achieved from Week 12 onwards.

Study FER-CARS-04 (EFFECT-HF) was an open-label (with blinded endpoint evaluation), randomised, 2-arm study comparing ferric carboxymaltose ($n=86$) versus standard of care ($n=86$) of which 29 patients received at least 1 dose of oral iron during the study) in subjects with chronic heart failure and iron deficiency for a treatment period of 24 weeks. At Day 1 and Week 6 (correction phase), subjects received either ferric carboxymaltose according to a simplified dosing grid using baseline Hb and body weight at screening (see section 4.2 DOSE AND METHOD OF ADMINISTRATION) or standard of care. At Week 12, (maintenance phase) subjects received ferric carboxymaltose (500 mg iron) or standard of care if serum ferritin <100 ng/mL or 100 to 300 ng/mL and TSAT $<20\%$. For the primary efficacy endpoint, the treatment difference (ferric carboxymaltose – standard of care) in LS mean change in peak VO_2 from baseline to Week 24 was 1.04 mL/kg/min [95% CI: 0.164, 1.909; $p = 0.0202$] An individual patient data meta-analysis of four double-blind, randomised studies in subjects with chronic heart failure and iron deficiency receiving ferric carboxymaltose versus placebo (studies FER-CARS-01 [12 weeks], FER-CARS-02 FAIR-HF [26 weeks], FER-CARS-03 EFFICACY-HF [26 weeks] and FER-CARS-05 CONFIRM-HF [52 weeks]) compared the efficacy and safety of ferric carboxymaltose ($n=504$) versus placebo ($n=335$) for up to 52 weeks. Ferric carboxymaltose and placebo were administered according to the dosing regimen of the individual studies. The treatment of ferric carboxymaltose versus placebo resulted in a reduction of recurrent cardiovascular hospitalisations and cardiovascular mortality (relative risk (95% CI) of 0.59 (0.40–0.88); $p=0.009$); hospitalisations and mortality as exploratory endpoints in individual studies).

There are no data available regarding the long term use of FERINJECT.

Ferritin Monitoring After Replacement Therapy

There is limited data from study VIT-IV-CL-008, which demonstrates that ferritin levels decrease rapidly 2-4 weeks following replacement and more slowly thereafter. The mean ferritin levels did not drop to levels where retreatment might be considered during the 12 weeks of study follow up. Thus, the available data does not clearly indicate an optimal time for ferritin retesting although assessing ferritin levels earlier than 4 weeks after replacement therapy appears premature. Thus, it is recommended that further re-assessment of ferritin should be made by the clinician based on the individual patient's condition.

5.2 PHARMACOKINETIC PROPERTIES

After a single 100 mg IV iron dose of FCM solution (n=6) injected over 1 min, serum iron concentration peaked at a mean of 15 min. After 500, 800 or 1,000 mg iron in 250 mL normal saline infused over 15 min (n=6 for each dose), serum iron concentration peaked at means of 20 min, 1 h and 1.2 h, respectively. The mean volume of distribution was approximately 3 L, corresponding to the plasma volume. Mean plasma clearance ranged from 2.6-4.4 mL/min and terminal half life from 7-12 h. Renal elimination was negligible.

Within 8 h of a single radiolabelled 100 mg IV iron dose of FCM to patients with iron deficiency or renal anaemia, most of the radiolabelled iron had cleared the circulation and distributed to the bone marrow, liver and spleen. Within 6-9 days, the radiolabelled iron was incorporated into the red blood cells. After 24 days, iron utilisation was 91-99% in iron deficiency anaemia and 61-84% in renal anaemia.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Ferric carboxymaltose was not genotoxic in assays for gene mutation (in vitro bacterial and mouse lymphoma cell assays) and chromosomal damage (human lymphocytes in vitro and mouse micronucleus test in vivo).

Carcinogenicity

The carcinogenic potential of FERINJECT has not been studied in animals.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
Water for injections

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

Shelf-life of the product as packaged for sale:

36 months.

Shelf-life after first opening of the container:

From a microbiological point of view, preparations for parenteral administration should be used immediately.

Shelf-life after dilution with sterile 0.9% m/V sodium chloride solution:

To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2-8°C for not more than 12 hours.

Product is for single use in one patient only. Discard any residue.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in the original package. Do not store above 30 °C. Do not freeze, do not refrigerate.

6.5 NATURE AND CONTENTS OF CONTAINER

2 mL of solution in a vial (type I glass) with bromobutyl rubber stopper and aluminium cap in pack sizes of 1 and 5 vials.

10 mL of solution in a vial (type I glass) with bromobutyl rubber stopper and aluminium cap in pack sizes of 1 and 5 vials.

20 mL of solution in a vial (type I glass) with bromobutyl rubber stopper and aluminium cap in pack sizes of 1 vial.

Not all presentations may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES**Chemical structure**

The active substance of FERINJECT is a complex of polynuclear iron(III)-hydroxide with 4(R)-(poly-(1→4)-*O*-α-D-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate.

The relative molecular weight is approximately 150,000 Da, corresponding to the empirical formula:

$[\text{FeO}_x(\text{OH})_y(\text{H}_2\text{O})_z]_n [\{ (\text{C}_6\text{H}_{10}\text{O}_5)_m (\text{C}_6\text{H}_{12}\text{O}_7) \}_1]_k$, where $n \approx 10^3$, $m \approx 8$, $l \approx 11$, and $k \approx 4$.

CAS number

1461680-64-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4

8 SPONSOR

Vifor Pharma Pty Ltd
 Level 8, 80 Dorcas Street
 South Bank, Melbourne VIC 3006
 Australia
 Tel: 1800 202 674 (Australia)
 Tel: 0800 996 312 (New Zealand)

9 DATE OF FIRST APPROVAL

05 April 2011

10 DATE OF REVISION

28 May 2021

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
2	Sodium hydroxide added as an excipient with known effect.
4.1	Indications amended to include when there is a clinical need to deliver iron rapidly.
4.2	Dosage and administration details clarified. Post-iron repletion assessments added.
4.4	Sodium content details clarified. Warming added relating to chronic heart failure in renal failure patients.
4.8	Most commonly reported ADRs listed. Number of patients updated. Format of spontaneous reports updated to reflect frequency of cases.
4.9	Additional statement added re risk of accidental dosing.
5.1	List of aetiologies updated. Study names/numbers added. Clinical studies updated for iron deficiency associated with chronic heart failure and ferritin monitoring after replacement therapy.

AUSTRALIAN PRODUCT INFORMATION - FERINJECT® (FERRIC CARBOXYMALTOSE) SOLUTION FOR INJECTION

1 NAME OF THE MEDICINE

Ferric carboxymaltose

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2 mL vial contains 100 mg of iron as ferric carboxymaltose.

Each 10 mL vial contains 500 mg of iron as ferric carboxymaltose.

Each 20 mL vial contains 1000 mg of iron as ferric carboxymaltose.

Excipient(s) with known effect:

Sodium hydroxide (for pH adjustment).

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Solution for intravenous use. FERINJECT is a dark brown, non-transparent, colloidal solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

FERINJECT is indicated for the treatment of iron deficiency when:

- oral iron preparations are ineffective
- oral iron preparations cannot be used
- there is a clinical need to deliver iron rapidly

The diagnosis must be based on laboratory tests.

4.2 DOSE AND METHOD OF ADMINISTRATION

Determination of the cumulative iron dose

The cumulative dose for repletion of iron using FERINJECT is determined based on the patient's body weight and Hb level and must not be exceeded. There are two methods for determining the cumulative dose, the Ganzoni Method and the Simplified Method. Caution is recommended with the Simplified Method since it is based on experience in a single trial in adults with median Hb 104 g/L (range 61-146 g/L) and body weight ≥ 35 kg – see section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials.

Patients should be closely monitored when large single doses of FERINJECT (>200 mg iron) are administered since the safety data are limited.

Post repletion, regular assessments should be done to ensure that iron levels are corrected and maintained.

Ganzoni Method

Cumulative Iron Dose = Body Weight kg x (Target Hb – Actual Hb g/L) x 0.24 + Iron Stores mg

where

Target Hb = 130 g/L for body weight <35 kg and 150 g/L for body weight ≥35 kg

Iron Stores = 15 mg/kg body weight for body weight <35 kg and 500 mg for body weight ≥35 kg.

Round down to nearest 100 mg if body weight ≤66 kg and round up to nearest 100 mg if body weight >66 kg.

Simplified Method (for patients of body weight ≥35 kg)

The cumulative iron dose is determined according to the following table.

Table 1 Determination of the Iron Need

Hb g/L	Patient Body Weight	
	35 kg to <70 kg	70 kg and above
<100	1,500 mg	2,000 mg
100 to < 140	1,000 mg	1,500 mg
≥140	500 mg	500 mg

For patients with an Hb value ≥140 g/L, an initial dose of 500 mg iron should be given and iron parameters should be checked prior to repeat dosing.

Iron deficiency must be confirmed by laboratory tests as stated in section 4.1 THERAPEUTIC INDICATIONS.

Calculation and administration of the maximum individual iron dose(s)

Based on the iron need determined above the appropriate dose(s) of FERINJECT should be administered taking into consideration the following:

A single FERINJECT administration should not exceed:

- 20 mg iron/kg body weight
- 1,000 mg of iron (20 mL ferric carboxymaltose)

The maximum recommended cumulative dose of FERINJECT is 1,000 mg of iron (20 mL ferric carboxymaltose) per week.

Post-iron repletion assessments

Re-assessment should be performed by the clinician based on the individual patient's condition. The Hb level should be re-assessed no earlier than 4 weeks post final FERINJECT administration to allow adequate time for erythropoiesis and iron utilisation. In the event the patient requires further iron repletion, the iron need should be recalculated using either Ganzoni method or simplified method described above (see section 5.1 PHARMACODYNAMIC PROPERTIES).

Renal Impairment

A single maximum daily dose of 200 mg iron as FERINJECT should not be exceeded in haemodialysis-dependent chronic kidney disease patients.

Pregnancy

It is recommended that the maximum cumulative dose in pregnant patients is restricted to 1,000 mg for patients with Hb \geq 90 g/L, or 1,500 mg in patients with Hb $<$ 90 g/L. Do not administer more than 1,000 mg iron per week.

Method of Administration

FERINJECT must be administered only by the intravenous route:

- By injection, or
- By infusion, or
- During a haemodialysis session undiluted directly into the venous limb of the dialyser.

FERINJECT must not be administered by the subcutaneous or intramuscular route.

Intravenous injection

FERINJECT may be administered by intravenous injection using undiluted solution. The maximum single dose is 20 mg iron/kg body weight but should not exceed 1,000 mg of iron per week. The administration rates are shown in Table 2:

Table 2 Administration Rates for Intravenous Injection of FERINJECT

Volume of FERINJECT Required	Equivalent of Iron Dose	Administration Rate/Minimum Administration time
2 to 4 mL	100 to 200 mg	No minimal prescribed time
>4 to 10 mL	>200 to 500 mg	100 mg iron/min
>10 to 20 mL	>500 to 1,000 mg	15 minutes

Intravenous infusion

FERINJECT may be administered by intravenous infusion, in which case it needs to be diluted. The maximum single dose is 20 mg iron/kg body weight but should not exceed more than 1,000 mg iron per week.

For infusion, FERINJECT must only be diluted in sterile 0.9% m/V sodium chloride solution as shown in Table 3. Note: for stability reasons, FERINJECT should not be diluted to

concentrations less than 2 mg iron/mL (not including the volume of the ferric carboxymaltose solution).

Table 3: Dilution Plan of FERINJECT for intravenous infusion

FERINJECT	Equivalent of Iron Dose	Maximum Amount of Sterile 0.9% m/V Sodium Chloride Solution	Minimum Administration Time
2 to 4 mL	100 to 200 mg	50 mL	3 minutes
>4 to 10 mL	>200 to 500 mg	100 mL	6 minutes
>10 to 20 mL	>500 to 1,000 mg	250 mL	15 minutes

Note: For stability reasons, dilutions to concentrations less than 2 mg iron/mL (not including the volume of the ferric carboxymaltose solution) are not permissible.

Inspect vials visually for sediment and damage before use. Use only those containing sediment-free, homogeneous solution.

Each vial of FERINJECT is intended for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

FERINJECT must only be mixed with sterile 0.9% m/V sodium chloride solution. No other intravenous dilution solutions and therapeutic agents should be used, as there is the potential for precipitation and/or interaction. For dilution instructions, see above.

This medicinal product must not be mixed with other medicinal products than those mentioned above. The compatibility with containers other than polyethylene and glass is not known.

4.3 CONTRAINDICATIONS

The use of FERINJECT is contraindicated in cases of:

- hypersensitivity to ferric carboxymaltose complex, to FERINJECT or to any of its excipients
- anaemia not attributed to iron deficiency, e.g. other microcytic anaemia
- evidence of iron overload or disturbances in utilisation of iron

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Iron Overload/Haemosiderosis

Body iron excretion is limited and excess tissue iron can be hazardous causing haemosiderosis. Patients receiving FERINJECT require regular monitoring of red cell indices and serum ferritin to detect iron overload. If there is evidence of iron overload, iron therapy should be withheld.

Patients with Infections

Parenteral iron must be used with caution in case of acute or chronic infection, asthma, eczema or atopic allergies. It is recommended that the administration of FERINJECT is stopped in patients with ongoing bacteraemia. In patients with chronic infection a risk/benefit evaluation has to be performed, taking into account the suppression of erythropoiesis.

Hypersensitivity Reactions

Parenterally administered iron preparations can cause hypersensitivity reactions including anaphylactoid reactions, which may be fatal. There have been reports of hypersensitivity reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction). Therefore, facilities for cardio-pulmonary resuscitation must be available. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately. Hypersensitivity reactions have also been reported after previously uneventful doses of any parenteral iron complexes, including ferric carboxymaltose. Each patient should be observed for adverse effects for at least 30 minutes following each FERINJECT administration.

Hypophosphataemia and Hypophosphataemic Osteomalacia

Parenterally administered iron preparations can cause hypophosphataemia which in most cases is transient and without clinical symptoms. Cases of hypophosphataemia requiring medical attention were reported, mainly in patients with existing risk factors and after prolonged exposure to high-dose IV iron.

Cases of hypophosphataemia leading to hypophosphataemic osteomalacia and fractures which required clinical intervention including surgery were reported in the post marketing setting. Patients should be asked to seek medical advice if they experience arthralgia or bone pain.

Patients who receive multiple higher doses for a long-term treatment and with underlying risk factors (such as Vitamin D deficiency, calcium and phosphate malabsorption, secondary hyperparathyroidism, hereditary haemorrhagic telangiectasia, inflammatory bowel disease, and osteoporosis) should be monitored for hypophosphataemic osteomalacia. In case of persisting hypophosphataemia, treatment with ferric carboxymaltose should be re-evaluated.

Paravenous Leakage

Caution should be exercised to avoid paravenous leakage when administering FERINJECT. Paravenous leakage of FERINJECT at the administration site may lead to potentially long lasting brown discolouration and irritation of the skin. In case of paravenous leakage, the administration of FERINJECT must be stopped immediately.

Sodium Content

This medicinal product contains up to 5.5 mg (0.24 mmol) sodium per mL of undiluted solution, equivalent to 0.3% of the WHO recommended maximum daily intake of 2 g sodium for an adult. This should be considered when prescribing FERINJECT to patients on sodium-controlled diets.

Use in hepatic impairment

In patients with liver dysfunction, parenteral iron should only be administered after careful risk/benefit assessment. Parenteral iron administration should be avoided in patients with hepatic dysfunction where iron overload is a precipitating factor, in particular Porphyria Cutanea Tarda (PCT). Careful monitoring of iron status is recommended to avoid iron overload.

There are no clinical studies performed in patients with hepatic impairment. It is known that ferric carboxymaltose may lead to transient increases in liver enzymes see Section 4.8. A careful benefit/risk evaluation should be made prior to using in patients with hepatic impairment, and if prescribed, close monitoring of liver function is recommended.

Use in the elderly

No data available.

Paediatric use

The use of FERINJECT has not been studied in children and therefore is not recommended in children under 14 years.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

As with all parenteral iron preparations the absorption of oral iron is reduced when administered concomitantly. Therefore, if required, oral iron therapy should not be started for at least 5 days after the last administration of FERINJECT.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Reduced weights of reproductive organs (prostate, seminal vesicle, epididymis, testis or uterus) were seen in rats and dogs at maternally toxic doses following repeated IV dosing with ferric carboxymaltose. There were no effects of ferric carboxymaltose on the fertility or reproductive performance of rats given thrice weekly IV doses of up to 30 mg/kg roughly equal to the maximum weekly clinical dose, based on body surface area (BSA). There are no data on the effect of ferric carboxymaltose on human fertility.

Use in pregnancy (Category B3)

Studies in rats have shown that iron released from ferric carboxymaltose can cross the placental barrier.

In pregnant and iron-replete rabbits and rats, embryotoxicity (decreased placental or litter weights and increased resorptions) and increases in fetal skeletal abnormalities (thickened/kinked ribs in rats and cranial, forepaw and/or limb abnormalities in rabbits) were observed at maternally toxic IV iron doses from 9 or 30 mg/kg/day, respectively given during organogenesis (1-2 times the maximum weekly clinical dose, based on body surface area (BSA)). No effects were observed at IV iron doses up to 4.5 or 9 mg/kg/day, respectively (0.5 times the maximum weekly clinical dose, based on BSA).

There is no efficacy and safety data on the use of FERINJECT in human pregnancy less than 16 weeks' gestation. Iron deficiency occurring in the first trimester of pregnancy can in many cases be treated with oral iron.

There are limited data from the use of FERINJECT in women in pregnancy beyond 16 weeks' gestation. A careful risk/benefit evaluation is required before use during pregnancy and FERINJECT should not be used during pregnancy unless clearly necessary.

If the benefit of FERINJECT treatment is judged to outweigh the potential risk to the fetus, it is recommended that treatment in pregnancy should be confined to women beyond the 16th week of gestation.

Foetal bradycardia may occur following administration of parenteral irons. It is usually transient and a consequence of a hypersensitivity reaction in the mother. The unborn baby should be carefully monitored during intravenous administration of parenteral irons to pregnant women.

Use in lactation

Clinical studies showed that transfer of iron from FERINJECT to human milk was negligible ($\leq 1\%$).

Evidence of delayed postnatal growth and development has been observed in rats exposed to ferric carboxymaltose. Milk transfer of administered iron from ferric carboxymaltose was demonstrated in lactating rats. Caution should be exercised when FERINJECT is used in lactating woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The most commonly reported ADR is nausea (occurring in 2.9% of the subjects), followed by injection/infusion site reactions, hypophosphataemia, headache, flushing, dizziness and hypertension. Injection/infusion site reactions comprise several ADRs which individually are either uncommon or rare. The most serious ADR is anaphylactoid reaction (rare). See section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE for further details. In pregnancy, foetal bradycardia associated to hypersensitivity in the mother may occur with parenteral iron preparations (see section 4.6 FERTILITY, PREGNANCY AND LACTATION).

Clinical studies experience

Adverse drug reactions reported in patients treated with ferric carboxymaltose (n=8,245) from completed clinical trials are summarized in the table below.

For subjects in clinical trials that showed a decrease in serum phosphorous, the minimum values were obtained after approximately 2 weeks, and in most cases returned to baseline values by 12 weeks following ferric carboxymaltose treatment.

System Organ Class	Common (≥1/100, <1/10)	Uncommon (≥1/1,000, <1/100)	Rare (≥1/10,000, <1/1,000)
Immune System Disorders	–	Hypersensitivity	Anaphylactoid reactions
Nervous System Disorders	Headache, dizziness	Paraesthesia, dysgeusia	–
Cardiac Disorders	–	Tachycardia	–
Vascular Disorders	Hypertension, flushing	Hypotension	–
Respiratory, Thoracic and Mediastinal Disorders	–	Dyspnoea	–
Gastrointestinal Disorders	Nausea	Vomiting, dyspepsia, flatulence, abdominal pain, constipation, diarrhoea	–
Skin and Subcutaneous Tissue Disorders	–	Pruritus, urticaria, erythema, rash ⁽¹⁾ .	–
Musculoskeletal and Connective Tissue Disorders	–	Myalgia, back pain, arthralgia, pain in extremity, muscle spasms	–
General Disorders and Administration Site Conditions	Injection/Infusion site reactions ⁽²⁾	Pyrexia, fatigue, chest pain, oedema peripheral, pain, chills	Malaise
Investigations	-	Alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, blood lactate dehydrogenase increased, blood alkaline phosphatase increased	–
Metabolism and Nutritional Disorders	Hypophosphataemia [#]	–	–

#: Based on laboratory findings

1 Includes the following preferred terms: rash (individual ADR frequency determined as uncommon) and rash erythematous, -generalised, -macular, -maculo-papular, -pruritic (all individual ADRs frequencies determined as rare).

2 Includes, but is not limited to the following preferred terms: injection/infusion site -pain, -haematoma, -discolouration, -extravasation, -irritation, reaction, (all individual ADRs frequencies determined as uncommon) and -paraesthesia (individual ADR frequency determined as rare).

Note: ADR = Adverse drug reaction.

Undesirable Effects from Post-marketing Spontaneous Reporting

As part of the continuing post-marketing surveillance of ferric carboxymaltose, the following adverse reactions have been observed:

System Organ Class	Common (≥1/100, <1/10)	Uncommon (≥1/1,000, <1/100)	Rare (≥1/10,000, <1/1,000)	Frequency not known
Nervous System Disorders	-	-	Vertigo	Loss of consciousness ²
Cardiac Disorders	-	-	Syncope, pre syncope ³	Kounis syndrome
Respiratory, Thoracic and Mediastinal Disorders	-	-	Bronchospasm ³	
Skin and Subcutaneous Tissue Disorders	-	-	Angioedema and pallor, distant skin discolouration ³	Face oedema ² Dermatitis ²
General Disorders and Administration Site Conditions	-	-	Influenza like illness ¹	
Psychiatric Disorders	-	-	Anxiety ³	
Musculoskeletal and Connective Tissue Disorders				Hypophosphataemic osteomalacia ²

¹ whose onset may vary from a few hours to several days.

² ADRs exclusively reported in the post marketing setting ; estimated as rare

³ ADRs reported in the post-marketing setting which are also observed in the clinical setting.

Post-marketing Spontaneous Reports in Pregnancy Cases

System Organ Class	Preferred Terms ⁽¹⁾
Immune System Disorders	Hypersensitivity, anaphylactoid reactions
Nervous System Disorders	Headache, dizziness
Vascular Disorders	Hypotension, Blood pressure systolic decreased
Skin and Subcutaneous Tissue Disorders	Rash, urticaria
Respiratory, Thoracic and Mediastinal Disorders	Dyspnoea
General Disorders and Administration Site Conditions	Extravasation, infusion site discolouration, injection site discolouration

¹ Frequency not known.

There have been individual case reports of temporally-related, but not causally-related, events of: antenatal foetall ductus venosus thrombosis, uterine hypertonia or contractions and foetal demise when Ferinject has been used in pregnancy.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Ferinject has a low toxicity and is well tolerated. The risk for accidental overdosing is minimal.

Administration of FERINJECT in quantities exceeding the amount needed to correct iron deficit at the time of administration may lead to accumulation of iron in storage sites eventually leading to haemosiderosis. Monitoring of iron parameters such as serum ferritin and transferrin saturation (TSAT) may assist in recognising iron accumulation. If iron accumulation has occurred, the use of an iron chelator may be considered.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Ferric carboxymaltose (FCM) solution for injection/infusion contains iron in a stable ferric state as a complex with a carbohydrate polymer designed to provide iron for the iron transport and storage proteins in the body (transferrin and ferritin). FCM was effective in increasing haemoglobin (Hb) and serum ferritin concentrations in patients with mild to moderate iron-deficiency anaemia. The intravenous (IV) iron dose was 500 mg weekly for up to 4 weeks (n=20) or 1,000 mg weekly for up to 2 weeks (n=26). With the 500 mg iron dose, 37% of patients achieved normal Hb levels within 8 weeks and 75% achieved a ≥ 20 g/L increase in Hb on at least one occasion. With 1,000 mg iron, 48% of patients achieved normal Hb levels within 6 weeks and 73% achieved a ≥ 20 g/L increase in Hb on at least one occasion. The target serum ferritin concentration 100-500 $\mu\text{g/L}$ was reached with both doses and remained within the target range at 2 weeks follow-up (at 6 and 4 weeks respectively for the two dose groups)-data were only available for about half the 500 mg iron dose group.

Clinical trials

Clinical studies showed that the haematological response and the filling of the iron stores was faster after intravenous administration of FCM than with orally administered comparators.

The phase III studies undertaken with FCM included patients with iron deficiency of different aetiologies, i.e. associated with non-dialysis and dialysis dependent chronic kidney disease (CKD), inflammatory bowel disease, heavy menstrual bleeding, post-partum iron deficiency anaemia (IDA), pregnancy (second and third trimester) or patients with chronic heart failure and iron deficiency.

Additionally, there are limited data available with FCM in patients with iron deficiency associated with chemotherapy related anaemia and gastric bypass.

IDA associated with haemodialysis-dependent chronic kidney disease

The efficacy and safety of FCM compared to Venofer[®] (iron sucrose, intravenous) for the treatment of IDA secondary to chronic renal failure was assessed in a multi-centre, open-label, randomised, parallel-group, Phase III study (VIT-IV-CL-015) in 237 patients on haemodialysis or haemodiafiltration. IDA was defined as Hb ≤ 115 g/L in addition to transferrin saturation

(TSAT) <20% and/or serum ferritin <200 µg/L. Patients received 200 mg iron 2 or 3 times weekly (depending on the timing of dialysis sessions) until their individual calculated cumulative dose had been reached. The mean duration of treatment was 15.8 days (range 1 to 27) and 16.2 days (range 1 to 43 days) for the FCM and Venofer[®] groups, respectively.

Patients treated with erythropoietin (EPO) should have had received this treatment for at least 8 weeks prior to inclusion in the study and increases in the dose of EPO were not permitted. The primary efficacy endpoint was defined as the percentage of patients reaching an increase in Hb of ≥10 g/L at 4 weeks. The percentage of responders was 44.1% (52/118) in the FCM group and 35.3% (41/116) in the Venofer[®] group; the difference between groups was not statistically significant ($\chi^2 = 0.2254$). At follow-up 4 weeks after the final dose of medication, secondary efficacy parameters (Hb ≥110-120 g/L, serum ferritin 200-800 µg/L, TSAT 20-50%) demonstrated successful increase in iron stores for both treatment groups.

IDA associated with non-dialysis-dependent chronic kidney disease

A multi-centre, randomised, open-label, controlled, 8-week, Phase III study (1VIT04004) in 255 patients was conducted to compare the safety and efficacy of intravenous infusions of the FCM solution with oral administration of ferrous sulphate, independent of Hb response to EPO, in treating IDA in non-dialysis-dependent chronic kidney disease (ND-CKD). IDA was defined as Hb ≤110 g/L, TSAT ≤25%, and serum ferritin ≤300 µg/L. Patients treated with EPO should have had received this treatment for at least 8 weeks prior to inclusion in the study and increases in the dose of EPO were not permitted. Patients randomised to FCM treatment received 1 to 3 doses of FCM solution intravenously at 2-4 week intervals: 15 mg iron/kg for weight ≤66 kg to a maximum of 1,000 mg iron for the initial dose and a maximum of 500 mg iron for subsequent doses. Patients randomised to oral iron treatment received ferrous sulphate tablets (65 mg iron) 3 times daily for 8 weeks.

In a modified intent-to-treat analysis which excluded 8 FCM patients and 2 ferrous sulfate patients, the primary efficacy endpoint, defined as the percentage of patients with an increase in Hb ≥10 g/L at any time between baseline and end of study, or time of intervention, was reached by 60.4% (87/144) of FCM-treated patients compared to 34.7% (35/101) of oral iron-treated patients ($p < 0.001$; 95% confidence interval (CI) 13.0, 38.5). The modified intent-to-treat population comprised patients with at least one dose of study medication, stable erythropoietin dose, at least one post-baseline Hb assessment and GFR ≤45 mL/min/1.73 m². FCM was also demonstrated to be superior to oral iron across all secondary ranked efficacy endpoints: Hb change ≥10 g/L and a serum ferritin change ≥160 µg/L at any time during the study (60.4% versus 0.0%, respectively; $p < 0.001$; 95% CI 48.2, 72.6) or a Hb change ≥10 g/L before Day 42 (54.2% versus 28.7%, respectively; $p < 0.001$; 95% CI 12.8, 38.1).

In a 44-week extension to this study (1VIT05005), the efficacy of FCM in the long-term maintenance treatment of anaemia in ND-CKD was evaluated in 140 patients. Clinical success (Hb ≥110 g/L, serum ferritin 100-800 µg/L, TSAT 30-50%) was achieved in 51.4% (72/140) of patients, with 10% (14/140) exhibiting sustained clinical success at 50% or more of the assessments.

In the ND-CKD subgroup of another study (1VIT07018), the safety and efficacy of IV injection of FCM solution, 15 mg iron/kg body weight up to 1,000 mg iron administered over 15 min. was assessed. The comparator was standard medical care (SMC) as determined by the investigator.

The primary endpoint was the incidence of treatment-emergent serious adverse events from Day 0 to 30 days after the last dose of study drug. The safety population contained 204 FCM subjects and 212 SMC subjects. The majority had mild anaemia (mean Hb 104 g/L in FCM group and

102 g/L in control group). There were no serious adverse events assessed as related to FCM. Based on these limited data and the lack of specific serious drug-related adverse reactions, the safety of single FCM doses of 1,000 mg iron appeared equal to SMC.

Efficacy was assessed in a modified intent-to-treat population of 202 FCM subjects and 203 SMC subjects. Achievement of Hb \geq 120 g/L was comparable in the two groups at 30 days - FCM 9.9% and SMC 6.9% (Fisher's Exact Test p = 0.29).

IDA secondary to inflammatory bowel disease

The efficacy of infusions of FCM solutions compared to oral administration of ferrous sulphate in the treatment of IDA secondary to chronic inflammatory bowel disease was examined in a multi-centre, open-label, randomised, 12-week, Phase III study (VIT-IV-CL-008) in 200 patients. 4 patients did not receive study drug and were excluded from the analysis. IDA was defined as Hb \leq 110 g/L in combination with TSAT $<$ 20% and/or serum ferritin $<$ 100 μ g/L. Patients were randomised in a 2:1 (FCM: ferrous sulphate) ratio to receive 1 of 2 treatments: FCM intravenous on Day 1 with subsequent doses at 1-week intervals until the patient's calculated cumulative dose had been reached (a maximum dose of 1,000 mg iron per infusion) or oral ferrous sulphate capsules (100 mg iron) twice daily for 12 weeks. Based on the primary response parameter of change in mean Hb from baseline to Week 12 (36.0 g/L FCM group, 32.9 g/L oral iron group), the results of this study demonstrated that FCM was non-inferior to ferrous sulphate. The non-inferiority criterion was lower limit of 95% CI of difference FCM minus ferrous sulphate \geq -5.0 g/L. The non-inferiority criterion was met in both the intent-to-treat and per protocol populations. Furthermore, the mean Week-12 values of serum ferritin (80.2 μ g/L FCM group, 38.6 μ g/L oral iron group) and TSAT (23.1% FCM group, 29.2% oral iron group) demonstrated a successful repletion of the iron stores in patients treated with FCM.

In another study (FER-IBD-07-COR), FCM dosing based on a simplified dosing scheme with four Hb-weight subgroups (see section 4.2 DOSE AND METHOD OF ADMINISTRATION) was compared with Venofer[®] dosing based on the Ganzoni formula. The FCM dose was given in up to three IV infusions on Days 1, 8 and 15 in single doses of up to 1000 mg iron. The Venofer[®] dose was given in up to 11 IV infusions in doses not exceeding 200 mg iron not more than three times per week. The primary endpoint was the percentage of patients achieving a Hb increase \geq 20 g/L at Week 12. The demographic and haematological characteristics of the two groups were similar. About 60% of subjects were female, median age was 39 years (range 18-81), median weight 67 kg (range 39-137), median baseline Hb 104 g/L (range 61-146) and median baseline serum ferritin 7 μ g/L (range 2-299). Subjects in the two treatment groups achieved at least comparable Hb response overall and in the Hb-weight subgroups (see Table 4).

Table 4. Efficacy of FCM (new dosing method) versus Venofer[®] (Ganzoni dose calculation) in iron deficiency anaemia associated with inflammatory bowel diseases - trial FER-IBD-07-COR – patients with 12-week assessment

	FCM n=228	Venofer[®] n=220	Difference [95% CI]
Hb Response (increase \geq 20 g/L) at Week 12	65.8%	53.6%	12.2% [3.1%, 21.0%]
Hb<100 g/L – Wt 35-<70 kg	missing n=7 n=59 86.4%	missing n=8 n=44 75.0%	11.4% [-4.1%, 26.9%]
Hb<100 g/L – Wt \geq 70 kg	n=31 90.3%	n=24 100.0%	-9.7% [-20.1%, 0.7%]
Hb \geq 100 g/L – Wt 35-<70 kg	n=70 75.7%	n=78 71.8%	3.9% [-10.2%, 18.1%]
Hb \geq 100 g/L – Wt \geq 70 kg	n=61 88.5%	n=66 75.8%	12.8% [-0.3%, 25.8%]

IDA secondary to heavy menstrual bleeding

The safety and efficacy of intravenous infusions of FCM solution, compared to oral administration of ferrous sulphate, in improvement of Hb levels in females with IDA secondary to heavy menstrual bleeding was assessed in a multi-centre, randomised, open-label, 6-week, Phase III study (1VIT04002/1VIT04003). At enrolment, patients had a baseline Hb \leq 114 g/L, TSAT \leq 25%, and serum ferritin \leq 100 μ g/L. Patients were randomised to receive either oral ferrous sulphate tablets (65 mg iron) 3 times daily for 6 weeks or weekly infusions of FCM solution (a maximum dose of 1,000 mg iron per infusion) until the patient's calculated cumulative dose had been reached, to a maximum of 2,500 mg iron. In a modified intent-to-treat analysis which excluded 18 FCM patients and 6 ferrous sulphate patients, FCM was shown to be superior to oral iron in achieving an increase from baseline in Hb \geq 20 g/L at any time during the study: 82.0% (187/228) in the FCM group versus 61.8% (139/225) in the oral iron group (p <0.001; 95% CI 12.2, 28.3). The modified intent-to-treat population comprised patients with at least one dose of study medication, baseline Hb \leq 110 g/L, TSAT \leq 25%, serum ferritin \leq 100 μ g/L, at least one post-baseline Hb assessment and confirmed diagnosis of heavy menstrual bleeding.

Post partum IDA

The safety and efficacy of FCM compared to oral ferrous sulphate as treatment for post partum IDA (Hb \leq 100 g/L or \leq 105 g/L) was assessed in 3 randomised, open-label, multi-centre trials. In 2 of the studies, patients were randomised 1:1 to receive either oral ferrous sulphate tablets (65 mg iron) 3 times daily for 6 weeks or weekly intravenous FCM at dosages based on the calculated iron deficit. A maximum of 1,000 mg of iron (15 mg iron/kg body weight for pre-pregnancy weight \leq 66 kg), as intravenous FCM solution, was given at weekly intervals until the individual's calculated cumulative iron dose had been reached or a maximum total iron dose of 2,500 mg had been administered. In the third study, patients were randomised 2:1 to receive either oral ferrous sulphate capsules (100 mg iron) twice daily for 12 weeks or weekly intravenous FCM at dosages based on the calculated iron deficit (to a maximum of 3 infusions and not exceeding a weekly dose of 1,000 mg iron).

In all 3 studies, FCM was shown to be efficacious for the treatment of IDA in post partum subjects. In the first study (1VIT06011), the superiority of FCM was demonstrated according to the primary efficacy endpoint (defined as Hb >120 g/L), with a greater proportion of patients in the FCM group (91.4%, 127/139) versus the oral iron group (66.7%, 98/147) achieving success at any time during the study (p <0.0001; 95% CI 15.20, 34.20). This was based on a modified intent-to-treat population which excluded 4 FCM patients and one ferrous sulfate patient.

In the second study (1VIT03001), FCM was demonstrated to be non-inferior to oral iron among subjects who achieved an increase in Hb \geq 20 g/L: 96.4% (162/168) of the FCM group versus 94.1% (159/169) of the oral iron group (95% CI -2.19, 6.88). The analysis was in a modified intent-to-treat population (6 FCM patients and 9 ferrous sulphate patients excluded) and the non-inferiority margin was 15% based on a 1-sided 97.5% CI of the treatment difference. Statistically significantly greater increases from baseline to highest Hb, TSAT, and serum ferritin values were also observed in the FCM groups compared with the oral iron groups.

In the third study (VIT-IV-CL-009), FCM was shown to be non-inferior to ferrous sulphate for the mean change in Hb from baseline to Week 12 (33.4 g/L in the FCM group (n=227) versus 31.8 g/L in the oral iron group (n=117)). The non-inferiority criterion was lower limit of 95% CI of difference FCM minus ferrous sulfate \geq -5.0 g/L. The non-inferiority criterion was met in both the intent-to-treat and per protocol populations.

In another study (1VIT07017) in patients with iron deficiency anaemia due to heavy menstrual bleeding (HMB) or post-partum, the safety and efficacy of IV injection of FCM solution, 15 mg iron/kg body weight up to 1,000 mg iron administered IV over 15 min, was assessed. The comparator was standard medical care (SMC) as determined by the investigator.

The primary endpoint was the incidence of treatment-emergent serious adverse events from Day 0 to 30 days after the last dose of study drug. The safety population contained 996 FCM subjects and 1,022 SMC subjects. Approximately 60% of the subjects had post-partum anaemia (median Hb 103 g/L) and the other 40% anaemia associated with HMB (median Hb 96 g/L). There were no serious adverse events assessed as related to FCM. Based on overall incidences and the lack of specific drug-related serious adverse reactions, the safety profiles of FCM and SMC oral iron appeared similar. There was insufficient exposure to SMC IV iron for it to be included in the assessment.

Efficacy was assessed in a modified intent-to-treat population which was approximately 30% less than the randomised population, although still balanced. Achievement of Hb >120 g/L was significantly better with FCM than SMC in the two subgroups at 30 days (see Table 5).

Table 5. Efficacy of FCM in single doses up to 1,000 mg iron versus SMC in iron deficiency anaemia associated with heavy menstrual bleeding and post-partum – trial 1VIT07017 – 30 days follow-up - modified intent-to-treat

	FCM	SMC	Difference p-value ²
Heavy Menstrual Bleeding	n=331	n=329	
Hb >120 g/L ¹	34.4%	15.8%	18.6% p<0.001
Post-Partum	n=342	n=357	
Hb >120 g/L ¹	68.1%	50.7%	17.4% p<0.001

FCM: Ferric Carboxymaltose. SMC: Standard Medical Care as determined by the investigator.

¹ Anytime between baseline and end of study of surgical intervention. ² Fisher's Exact Test.

Pregnancy

In a study in pregnant women in the second and third trimester with iron deficiency anaemia (FER-ASAP-2009-01) randomised to receive either ferric carboxymaltose (maximum permitted total dose 1000 mg for baseline haemoglobin 91-104 g/L or 1500 mg for baseline haemoglobin 80-90 g/L) or oral iron (200 mg orally twice daily). The range of gestation at study entry for the ferric carboxymaltose arm was 16.0 to 33.9 weeks.

Superiority of ferric carboxymaltose for the primary outcome of change in Hb from baseline to week 3 was not shown. The mean total iron dose was 1,028.5 mg (median 1,000 mg) in the ferric carboxymaltose group compared to 11,959.2 mg (median 12,300 mg) in the oral iron group.

Iron deficiency associated with chronic heart failure

In a population with chronic heart failure, a double-blind, placebo-controlled, randomised study (FER-CARS-02 FAIR-HF) demonstrated a statistically significant improvement in both Patient Global Assessment and New York Heart Association functional class at Week 24 (odds ratio for improvement, 2.51 (95% CI 1.75-3.61; p<0.001) and 2.40 (95% CI 1.55-3.71; p<0.001), respectively). The results applied to iron deficient patients with and without anaemia. Superior improvements (p<0.001) were also observed in the 6-minute walk test and patient quality of life (QoL) for patients treated with ferric carboxymaltose.

Study FER-CARS-05 (CONFIRM-HF) in subjects with chronic heart failure and iron deficiency demonstrated the benefit of ferric carboxymaltose relative to placebo in improving functional capacity as measured by the change in 6-minute walk test distance from baseline to Week 24, with a difference between treatment groups (least squares mean (\pm standard error)) of 33.2 ± 10.52 m ($p=0.002$), thereby confirming the hypothesis of study FER_CARS_02. The treatment benefit of ferric carboxymaltose in improvement of 6-minute walk test distance was statistically significant from week 24 ($p<0.001$) and was sustained throughout the study to Week 52 ($p<0.001$), demonstrating the long-term benefit of iron repletion over a period of 1 year. The improvements in PGA and NYHA functional class were also seen in ferric carboxymaltose - treated subjects, with statistical significance for the difference between treatment groups achieved from Week 12 (PGA) or Week 24 (NYHA functional class) onwards. At Week 52 Endpoint, 54.7% of subjects in the ferric carboxymaltose group showed some improvement in PGA score compared to 35.1% in the placebo group, and 18.0% of subjects in the ferric carboxymaltose group showed an improvement by 1 NYHA functional class, compared to only 3.3% in the placebo group. Improvements in fatigue score and overall Kansas City cardiomyopathy questionnaire score were also seen, with statistical significance for the difference between treatment groups (in favour of ferric carboxymaltose) achieved from Week 12 onwards.

Study FER-CARS-04 (EFFECT-HF) was an open-label (with blinded endpoint evaluation), randomised, 2-arm study comparing ferric carboxymaltose ($n=86$) versus standard of care ($n=86$) of which 29 patients received at least 1 dose of oral iron during the study) in subjects with chronic heart failure and iron deficiency for a treatment period of 24 weeks. At Day 1 and Week 6 (correction phase), subjects received either ferric carboxymaltose according to a simplified dosing grid using baseline Hb and body weight at screening (see section 4.2 DOSE AND METHOD OF ADMINISTRATION) or standard of care. At Week 12, (maintenance phase) subjects received ferric carboxymaltose (500 mg iron) or standard of care if serum ferritin <100 ng/mL or 100 to 300 ng/mL and TSAT $<20\%$. For the primary efficacy endpoint, the treatment difference (ferric carboxymaltose – standard of care) in LS mean change in peak VO_2 from baseline to Week 24 was 1.04 mL/kg/min [95% CI: 0.164, 1.909; $p = 0.0202$] An individual patient data meta-analysis of four double-blind, randomised studies in subjects with chronic heart failure and iron deficiency receiving ferric carboxymaltose versus placebo (studies FER-CARS-01 [12 weeks], FER-CARS-02 FAIR-HF [26 weeks], FER-CARS-03 EFFICACY-HF [26 weeks] and FER-CARS-05 CONFIRM-HF [52 weeks]) compared the efficacy and safety of ferric carboxymaltose ($n=504$) versus placebo ($n=335$) for up to 52 weeks. Ferric carboxymaltose and placebo were administered according to the dosing regimen of the individual studies. The treatment of ferric carboxymaltose versus placebo resulted in a reduction of recurrent cardiovascular hospitalisations and cardiovascular mortality (relative risk (95% CI) of 0.59 (0.40–0.88); $p=0.009$); hospitalisations and mortality as exploratory endpoints in individual studies).

There are no data available regarding the long term use of FERINJECT.

Ferritin Monitoring After Replacement Therapy

There is limited data from study VIT-IV-CL-008, which demonstrates that ferritin levels decrease rapidly 2-4 weeks following replacement and more slowly thereafter. The mean ferritin levels did not drop to levels where retreatment might be considered during the 12 weeks of study follow up. Thus, the available data does not clearly indicate an optimal time for ferritin retesting although assessing ferritin levels earlier than 4 weeks after replacement therapy appears premature. Thus, it is recommended that further re-assessment of ferritin should be made by the clinician based on the individual patient's condition.

5.2 PHARMACOKINETIC PROPERTIES

After a single 100 mg IV iron dose of FCM solution (n=6) injected over 1 min, serum iron concentration peaked at a mean of 15 min. After 500, 800 or 1,000 mg iron in 250 mL normal saline infused over 15 min (n=6 for each dose), serum iron concentration peaked at means of 20 min, 1 h and 1.2 h, respectively. The mean volume of distribution was approximately 3 L, corresponding to the plasma volume. Mean plasma clearance ranged from 2.6-4.4 mL/min and terminal half life from 7-12 h. Renal elimination was negligible.

Within 8 h of a single radiolabelled 100 mg IV iron dose of FCM to patients with iron deficiency or renal anaemia, most of the radiolabelled iron had cleared the circulation and distributed to the bone marrow, liver and spleen. Within 6-9 days, the radiolabelled iron was incorporated into the red blood cells. After 24 days, iron utilisation was 91-99% in iron deficiency anaemia and 61-84% in renal anaemia.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Ferric carboxymaltose was not genotoxic in assays for gene mutation (in vitro bacterial and mouse lymphoma cell assays) and chromosomal damage (human lymphocytes in vitro and mouse micronucleus test in vivo).

Carcinogenicity

The carcinogenic potential of FERINJECT has not been studied in animals.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
Water for injections

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

Shelf-life of the product as packaged for sale:

36 months.

Shelf-life after first opening of the container:

From a microbiological point of view, preparations for parenteral administration should be used immediately.

Shelf-life after dilution with sterile 0.9% m/V sodium chloride solution:

To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2-8°C for not more than 12 hours.

Product is for single use in one patient only. Discard any residue.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in the original package. Do not store above 30 °C. Do not freeze, do not refrigerate.

6.5 NATURE AND CONTENTS OF CONTAINER

2 mL of solution in a vial (type I glass) with bromobutyl rubber stopper and aluminium cap in pack sizes of 1 and 5 vials.

10 mL of solution in a vial (type I glass) with bromobutyl rubber stopper and aluminium cap in pack sizes of 1 and 5 vials.

20 mL of solution in a vial (type I glass) with bromobutyl rubber stopper and aluminium cap in pack sizes of 1 vial.

Not all presentations may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES**Chemical structure**

The active substance of FERINJECT is a complex of polynuclear iron(III)-hydroxide with 4(R)-(poly-(1→4)-*O*-α-D-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate.

The relative molecular weight is approximately 150,000 Da, corresponding to the empirical formula:

$[\text{FeO}_x(\text{OH})_y(\text{H}_2\text{O})_z]_n [\{ (\text{C}_6\text{H}_{10}\text{O}_5)_m (\text{C}_6\text{H}_{12}\text{O}_7) \}_1]_k$, where $n \approx 10^3$, $m \approx 8$, $l \approx 11$, and $k \approx 4$.

CAS number

1461680-64-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4

8 SPONSOR

Vifor Pharma Pty Ltd
Level 9, 140 William Street
Melbourne VIC 3000
Australia
Tel: 1800 202 674 (Australia)
Tel: 0800 996 312 (New Zealand)

9 DATE OF FIRST APPROVAL

05 April 2011

10 DATE OF REVISION

13 September 2021

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
8	Update to sponsor address

AUSTRALIAN PRODUCT INFORMATION - FERINJECT® (FERRIC CARBOXYMALTOSE) SOLUTION FOR INJECTION

1 NAME OF THE MEDICINE

Ferric carboxymaltose

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2 mL vial contains ferric carboxymaltose corresponding to 100 mg iron.

Each 10 mL vial contains ferric carboxymaltose corresponding to 500 mg iron.

Each 20 mL vial contains ferric carboxymaltose corresponding to 1000 mg iron.

Excipient(s) with known effect:

Sodium hydroxide (for pH adjustment).

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Solution for intravenous (IV) use. FERINJECT is a dark brown, non-transparent, colloidal solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

FERINJECT is indicated for the treatment of iron deficiency in adults and adolescents aged 14 years and older when:

- oral iron preparations are ineffective
- oral iron preparations cannot be used
- there is a clinical need to deliver iron rapidly

The diagnosis of iron deficiency must be based on laboratory tests.

FERINJECT is indicated for the treatment of iron deficiency anaemia in children aged 1 to 13 years when:

- oral iron preparations are ineffective
- oral iron preparations cannot be used

The diagnosis of iron deficiency anaemia must be based on laboratory tests.

4.2 DOSE AND METHOD OF ADMINISTRATION

Inspect vials visually for sediment and damage before use. Use only those containing sediment-free, homogeneous solution.

Each vial of FERINJECT is intended for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

FERINJECT must only be mixed with sterile 0.9% m/V sodium chloride solution. No other IV dilution solutions and therapeutic agents should be used, as there is the potential for precipitation and/or interaction. For dilution instructions, see below.

This medicinal product must not be mixed with other medicinal products than those mentioned below. The compatibility with containers other than polyethylene and glass is not known

4.2.1 Dosage

4.2.1.1 Adults and adolescents aged 14 years and older with iron deficiency

The dosing regimen follows a stepwise approach:

- 1) Determination of the cumulative iron dose,
- 2) Calculation and administration of the maximum individual iron dose(s), and
- 3) Post-iron repletion assessments.

Step 1: Determination of the cumulative iron dose

The cumulative dose for repletion of iron using FERINJECT is determined based on the patient's body weight and haemoglobin (Hb) level and must not be exceeded.

There are two methods for determining the cumulative dose, the Ganzoni Method and the Simplified Method. Caution is recommended with the Simplified Method since it is based on experience in a single trial in adults with median Hb 104 g/L (range 61-146 g/L) and body weight ≥ 35 kg – see section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials.

Patients should be closely monitored when large single doses of FERINJECT (>200 mg iron) are administered since the safety data are limited. See Step 2 for the maximum individual iron doses.

Post repletion, regular assessments should be done to ensure that iron levels are corrected and maintained.

Ganzoni Method

Cumulative Iron Dose = Body Weight *kg* x (Target Hb – Actual Hb *g/L*) x 0.24 + Iron Stores *mg*

Where:

Target Hb = 130 g/L for body weight <35 kg and 150 g/L for body weight ≥ 35 kg

Iron Stores = 15 mg/kg body weight for body weight <35 kg and 500 mg for body weight ≥ 35 kg.

Round down to nearest 100 mg if body weight ≤ 66 kg and round up to nearest 100 mg if body weight >66 kg.

Simplified Method (for patients of body weight ≥ 35 kg)

The cumulative iron dose is determined according to the following table.

Table 1 Determination of the Total Iron Need – Adults and Adolescents Aged 14 Years and Older

Hb g/L	Patient Body Weight	
	35 kg to <70 kg	70 kg and above
<100	1,500 mg	2,000 mg
100 to <140	1,000 mg	1,500 mg
≥ 140	500 mg	500 mg

For patients with an Hb value ≥ 140 g/L, an initial dose of 500 mg iron should be given and iron parameters should be checked prior to repeat dosing.

Iron deficiency must be confirmed by laboratory tests as stated in section 4.1 THERAPEUTIC INDICATIONS.

Step 2: Calculation and administration of the maximum individual iron dose(s)

Based on the total iron need determined using Table 1, the appropriate dose(s) of FERINJECT should be administered taking into consideration the following:

A single FERINJECT administration should not exceed:

- 20 mg iron/kg body weight
- 1,000 mg of iron (20 mL ferric carboxymaltose)

The maximum recommended cumulative dose of FERINJECT is 1,000 mg of iron (20 mL ferric carboxymaltose) per week. If the total iron need is higher, then the administration of an additional dose should be a minimum of 7 days apart from the first dose.

Step 3: Post-iron repletion assessments

Re-assessment should be performed by the clinician based on the individual patient's condition. The Hb level should be re-assessed no earlier than 4 weeks post final FERINJECT administration to allow adequate time for erythropoiesis and iron utilisation. In the event the patient requires further iron repletion, the iron need should be recalculated using either Ganzoni method or simplified method described in Table 1 above (see also section 5.1 PHARMACODYNAMIC PROPERTIES).

4.2.1.2 Children aged 1 to 13 years with iron deficiency anaemia

FERINJECT should be administered in 2 IV doses of 15 mg iron (0.3 ml) per kg body weight, with an interval of at least 7 days. The maximum single iron dose may not exceed 750 mg iron (15 ml), and the maximum cumulative dose must not exceed 1,500 mg iron (2 x 15 ml with an interval of 7 days).

Iron deficiency anaemia must be confirmed by laboratory tests as stated in section 4.1 THERAPEUTIC INDICATIONS.

Treatment with ferric carboxymaltose may be repeated if iron deficiency anaemia reoccurs.

4.2.1.3 Children below 1 year of age

The efficacy and safety of FERINJECT has not been investigated in children aged below 1 year of age. FERINJECT is therefore not recommended for use in children in this age group.

4.2.1.4 Special populations

Renal Impairment

In adult haemodialysis-dependent chronic kidney disease patients, a single maximum daily dose of 200 mg iron as FERINJECT should not be exceeded.

In children and adolescents with chronic kidney disease requiring haemodialysis, the efficacy and safety of FERINJECT has not been investigated. FERINJECT is therefore not recommended for use in children and adolescents with chronic kidney disease requiring haemodialysis.

Pregnancy

It is recommended that the maximum cumulative dose in pregnant patients is restricted to 1,000 mg for patients with Hb \geq 90 g/L, or 1,500 mg in patients with Hb <90 g/L. Do not administer more than 1,000 mg iron per week.

4.2.2 Method of Administration:

4.2.2.1 Adults and adolescents aged 14 years and older with iron deficiency

FERINJECT must be administered only by the IV route:

- by injection, or
- by infusion, or
- during a haemodialysis session undiluted directly into the venous limb of the dialyser.

FERINJECT must not be administered by the subcutaneous or intramuscular route.

Intravenous injection

FERINJECT may be administered by IV injection using undiluted solution. In adults and adolescents aged 14 years and older, the maximum single dose is 20 mg iron/kg body weight but should not exceed 1,000 mg of iron per week. The administration rates are shown in **Table 2**:

Table 2 Administration Rates for IV Injection of FERINJECT

Volume of FERINJECT Required	Equivalent of Iron Dose	Administration Rate/Minimum Administration time
2 to 4 mL	100 to 200 mg	No minimal prescribed time
>4 to 10 mL	>200 to 500 mg	100 mg iron/min
>10 to 20 mL	>500 to 1,000 mg	15 minutes

Intravenous infusion

FERINJECT may be administered by IV infusion, in which case it needs to be diluted. In adults and adolescents aged 14 years and older, the maximum single dose is 20 mg iron/kg body weight but should not exceed 1,000 mg of iron per week.

For infusion, FERINJECT must only be diluted in sterile 0.9% m/V sodium chloride solution as shown in **Table 3**. Note: for stability reasons, FERINJECT should not be diluted to concentrations less than 2 mg iron/mL (not including the volume of the ferric carboxymaltose solution).

Table 3 Dilution Plan of FERINJECT for IV infusion

FERINJECT	Equivalent of Iron Dose	MAXIMUM ¹ Amount of Sterile 0.9% m/V Sodium Chloride Solution	Minimum Administration Time
2 to 4 mL	100 to 200 mg	50 mL	3 minutes
>4 to 10 mL	>200 to 500 mg	100 mL	6 minutes
>10 to 20 mL	>500 to 1,000 mg	250 mL	15 minutes

Note: For stability reasons, dilutions to concentrations less than 2 mg iron/mL (not including the volume of the ferric carboxymaltose solution) are not permissible.

¹ The volumes indicated in this column are the **MAXIMUM** volumes of sterile 0.9% m/V of sodium chloride solution to be used.

4.2.2.2 Children aged 1 to 13 years with iron deficiency anaemia

Administration is IV, via undiluted injection solution with an injection rate of 100 mg (2 ml) of iron per minute, or diluted in a maximum of 250 ml of sterilised 0.9% saline solution as a 15-minute infusion.

Note: for stability reasons, FERINJECT should not be diluted to concentrations less than 2 mg iron/mL (not including the volume of the ferric carboxymaltose solution).

4.3 CONTRAINDICATIONS

The use of FERINJECT is contraindicated in cases of:

- hypersensitivity to ferric carboxymaltose complex, to FERINJECT or to any of its excipients
- anaemia not attributed to iron deficiency, e.g. other microcytic anaemia
- evidence of iron overload or disturbances in utilisation of iron

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Iron Overload/Haemosiderosis

Body iron excretion is limited and excess tissue iron can be hazardous causing haemosiderosis. Patients receiving FERINJECT require regular monitoring of red cell indices and serum ferritin to detect iron overload. If there is evidence of iron overload, iron therapy should be withheld.

Interchangeability

IV iron complexes are not clinically interchangeable.

Ferric carboxymaltose is different from other IV iron complexes such as iron polymaltose, iron sucrose and ferric derisomaltose. If a decision is made to discontinue FERINJECT and to begin treatment with other IV iron complexes (or vice versa), there should be careful consideration of the differences between these products in indication, pharmacokinetics, dosing, administration and safety profile.

Patients with Infections

Parenteral iron must be used with caution in case of acute or chronic infection, asthma, eczema or atopic allergies. It is recommended that the administration of FERINJECT is stopped in patients with ongoing bacteraemia. In patients with chronic infection a risk/benefit evaluation has to be performed, taking into account the suppression of erythropoiesis.

Hypersensitivity Reactions

Parenterally administered iron preparations can cause hypersensitivity reactions including anaphylactic reactions, which may be fatal. There have been reports of hypersensitivity reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction). Therefore, facilities for cardio-pulmonary resuscitation must be available. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately. Hypersensitivity reactions have also been reported after previously uneventful doses of any parenteral iron complexes, including ferric carboxymaltose. Each patient should be observed for adverse effects for at least 30 minutes following each FERINJECT administration.

Hypophosphataemia and Hypophosphataemic Osteomalacia

Parenterally administered iron preparations can cause hypophosphataemia which in most cases is transient and without clinical symptoms. Cases of hypophosphataemia requiring medical attention were reported, mainly in patients with existing risk factors and after prolonged exposure to high-dose IV iron.

Cases of hypophosphataemia leading to hypophosphataemic osteomalacia and fractures which required clinical intervention including surgery were reported in the post marketing setting. Patients should be asked to seek medical advice if they experience arthralgia or bone pain.

Patients who receive multiple higher doses for a long-term treatment and with underlying risk factors (such as Vitamin D deficiency, calcium and phosphate malabsorption, secondary hyperparathyroidism, hereditary haemorrhagic telangiectasia, inflammatory bowel disease, and osteoporosis) should be monitored for hypophosphataemic osteomalacia. In case of persisting hypophosphataemia, treatment with ferric carboxymaltose should be re-evaluated.

Paravenous Leakage

Caution should be exercised to avoid paravenous leakage when administering FERINJECT. Paravenous leakage of FERINJECT at the administration site may lead to potentially long lasting brown discolouration and irritation of the skin. In case of paravenous leakage, the administration of FERINJECT must be stopped immediately.

Sodium Content

This medicinal product contains up to 5.5 mg (0.24 mmol) sodium per mL of undiluted solution, equivalent to 0.3% of the World Health Organisation (WHO) recommended maximum daily intake of 2 g sodium for an adult. This should be considered when prescribing FERINJECT to patients on sodium-controlled diets.

Use in hepatic impairment

In patients with liver dysfunction, parenteral iron should only be administered after careful risk/benefit assessment. Parenteral iron administration should be avoided in patients with hepatic dysfunction where iron overload is a precipitating factor, in particular Porphyria Cutanea Tarda (PCT). Careful monitoring of iron status is recommended to avoid iron overload.

There are no clinical studies performed in patients with hepatic impairment. It is known that ferric carboxymaltose may lead to transient increases in liver enzymes see Section 4.8. A careful benefit/risk evaluation should be made prior to using in patients with hepatic impairment, and if prescribed, close monitoring of liver function is recommended.

Use in the elderly

No data available.

Paediatric use

The use of FERINJECT has not been investigated in children aged below 1 year of age. FERINJECT is therefore not recommended for use in children in this age group.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

As with all parenteral iron preparations the absorption of oral iron is reduced when administered concomitantly. Therefore, if required, oral iron therapy should not be started for at least 5 days after the last administration of FERINJECT.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Reduced weights of reproductive organs (prostate, seminal vesicle, epididymis, testis or uterus) were seen in rats and dogs at maternally toxic doses following repeated IV dosing with ferric carboxymaltose. There were no effects of ferric carboxymaltose on the fertility or reproductive performance of rats given thrice weekly IV doses of up to 30 mg/kg roughly equal to the maximum weekly clinical dose, based on body surface area (BSA). There are no data on the effect of ferric carboxymaltose on human fertility.

Use in pregnancy (Category B3)

Studies in rats have shown that iron released from ferric carboxymaltose can cross the placental barrier.

In pregnant and iron-replete rabbits and rats, embryotoxicity (decreased placental or litter weights and increased resorptions) and increases in fetal skeletal abnormalities (thickened/kinked ribs in rats and cranial, forepaw and/or limb abnormalities in rabbits) were observed at maternally toxic IV iron doses from 9 or 30 mg/kg/day, respectively given during organogenesis (1-2 times the maximum weekly clinical dose, based on body surface area (BSA)). No effects were observed at IV iron doses up to 4.5 or 9 mg/kg/day, respectively (0.5 times the maximum weekly clinical dose, based on BSA).

There is no efficacy and safety data on the use of FERINJECT in human pregnancy less than 16 weeks' gestation. Iron deficiency occurring in the first trimester of pregnancy can in many cases be treated with oral iron.

There are limited data from the use of FERINJECT in women in pregnancy beyond 16 weeks' gestation. A careful risk/benefit evaluation is required before use during pregnancy and FERINJECT should not be used during pregnancy unless clearly necessary.

If the benefit of FERINJECT treatment is judged to outweigh the potential risk to the fetus, it is recommended that treatment in pregnancy should be confined to women beyond the 16th week of gestation.

Foetal bradycardia may occur following administration of parenteral irons. It is usually transient and a consequence of a hypersensitivity reaction in the mother. The unborn baby should be carefully monitored during IV administration of parenteral irons to pregnant women.

Use in lactation

Clinical studies showed that transfer of iron from FERINJECT to human milk was negligible ($\leq 1\%$).

Evidence of delayed postnatal growth and development has been observed in rats exposed to ferric carboxymaltose. Milk transfer of administered iron from ferric carboxymaltose was demonstrated in lactating rats. Caution should be exercised when FERINJECT is used in lactating woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The most commonly reported ADR is nausea (occurring in 3.2% of the subjects), followed by injection/infusion site reactions, hypophosphataemia, headache, flushing, dizziness and hypertension. Injection/infusion site reactions comprise several ADRs which individually are either uncommon or rare. The most serious ADR is anaphylactic reaction (rare). See section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE for further details. In pregnancy, foetal bradycardia associated to hypersensitivity in the mother may occur with parenteral iron preparations (see section 4.6 FERTILITY, PREGNANCY AND LACTATION).

Clinical studies experience

Adverse drug reactions reported in patients treated with ferric carboxymaltose (more than 9000 subjects including more than 100 children and adolescents aged 1 to 17 years year) from completed clinical trials are summarized in the table below.

For subjects in clinical trials that showed a decrease in serum phosphorous, the minimum values were obtained after approximately 2 weeks, and in most cases returned to baseline values by 12 weeks following ferric carboxymaltose treatment.

Table 4 Adverse Drug Reactions Detected in Clinical Trials (n=9,456)

System Organ Class	Common ($\geq 1/100$, $< 1/10$)	Uncommon ($\geq 1/1,000$, $< 1/100$)	Rare ($\geq 1/10,000$, $< 1/1,000$)
Immune System Disorders	–	Hypersensitivity	Anaphylactic reactions
Metabolism and Nutritional Disorders	Hypophosphataemia [#]	–	–
Nervous System Disorders	Headache, dizziness	Dysgeusia, paraesthesia,	–
Cardiac Disorders	–	Tachycardia	–
Vascular Disorders	Flushing, hypertension	Hypotension	–
Respiratory, Thoracic and Mediastinal Disorders	–	Dyspnoea	–
Gastrointestinal Disorders	Nausea	flatulence, Abdominal pain, vomiting, constipation, diarrhoea, dyspepsia	–
Skin and Subcutaneous Tissue Disorders	–	Rash ⁽¹⁾ , pruritus, urticaria, erythema,	–
Musculoskeletal and Connective Tissue Disorders	–	Arthralgia, myalgia, pain in extremity, back pain, muscle spasms	–
General Disorders and Administration Site Conditions	Injection/Infusion site reactions ⁽²⁾	Pyrexia, fatigue, chills, chest pain, oedema peripheral, pain, malaise	-
Investigations	-	Alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased	–

[#]: Based on laboratory findings

1 Includes the following preferred terms: rash (individual ADR frequency determined as uncommon) and rash erythematous, -generalised, -macular, -maculo-papular, -pruritic (all individual ADRs frequencies determined as rare).

2 Includes, but is not limited to the following preferred terms: injection/infusion site -pain, -haematoma, -discolouration, -extravasation, -irritation, reaction, (all individual ADRs frequencies determined as uncommon) and -paraesthesia (individual ADR frequency determined as rare).

Note: ADR = Adverse drug reaction.

Paediatric Population

Forty (40) paediatric patients received ferric carboxymaltose in Study 1VIT17044. No serious ADRs were reported. The reported non-serious ADRs were hypophosphataemia (n=5), urticaria (n=2), injection/infusion site hypoesthesia (n=1), liver function tests increased (n=1) and flushing (n=1).

Undesirable Effects from Post-marketing Spontaneous Reporting

As part of the continuing post-marketing surveillance of ferric carboxymaltose, the following adverse reactions have been observed:

Table 5 Adverse Drug Reactions Detected during Post-marketing Experience

System Organ Class	Rare ($\geq 1/10,000$, $< 1/1,000$)	Frequency not known
Psychiatric Disorders	Anxiety ⁽³⁾	
Nervous System Disorders		Loss of consciousness ⁽²⁾
Cardiac Disorders		Kounis syndrome
Vascular Disorders	Pre-syncope ⁽³⁾ , syncope ⁽³⁾	
Respiratory, Thoracic and Mediastinal Disorders	Bronchospasm ⁽³⁾	
Skin and Subcutaneous Tissue Disorders	Angioedema, distant skin discolouration ⁽³⁾ , pallor ⁽³⁾	Dermatitis ⁽²⁾ , face oedema ⁽²⁾
Musculoskeletal and Connective Tissue Disorders		Hypophosphataemic osteomalacia ⁽²⁾
General Disorders and Administration Site Conditions	Influenza like illness ^(1,3)	

¹ whose onset may vary from a few hours to several days.

² ADRs exclusively reported in the post marketing setting ; estimated as rare

³ ADRs reported in the post-marketing setting which are also observed in the clinical setting.

Table 6 Post-marketing Spontaneous Reports in Pregnancy Cases

System Organ Class	Preferred Terms ⁽¹⁾
Immune System Disorders	Hypersensitivity, anaphylactic reactions
Nervous System Disorders	Headache, dizziness
Vascular Disorders	Hypotension, Blood pressure systolic decreased
Respiratory, Thoracic and Mediastinal Disorders	Dyspnoea
Skin and Subcutaneous Tissue Disorders	Rash, urticaria
General Disorders and Administration Site Conditions	Extravasation, infusion site discolouration, injection site discolouration

¹ Frequency not known.

There have been individual case reports of temporally-related, but not causally-related, events of: antenatal foetal ductus venosus thrombosis, uterine hypertonia or contractions and foetal demise when Ferinject has been used in pregnancy.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Ferinject has a low toxicity and is well tolerated. The risk for accidental overdosing is minimal.

Administration of FERINJECT in quantities exceeding the amount needed to correct iron deficit at the time of administration may lead to accumulation of iron in storage sites eventually leading to haemosiderosis. Monitoring of iron parameters such as serum ferritin and transferrin saturation (TSAT) may assist in recognising iron accumulation. If iron accumulation has occurred, the use of an iron chelator may be considered.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Ferric carboxymaltose (FCM) solution for injection/infusion contains iron in a stable ferric state as a complex with a carbohydrate polymer designed to provide iron for the iron transport and storage proteins in the body (transferrin and ferritin). FCM was effective in increasing haemoglobin (Hb) and serum ferritin concentrations in patients with mild to moderate iron-deficiency anaemia. The IV iron dose was 500 mg weekly for up to 4 weeks (n=20) or 1,000 mg weekly for up to 2 weeks (n=26). With the 500 mg iron dose, 37% of patients achieved normal Hb levels within 8 weeks and 75% achieved a ≥ 20 g/L increase in Hb on at least one occasion. With 1,000 mg iron, 48% of patients achieved normal Hb levels within 6 weeks and 73% achieved a ≥ 20 g/L increase in Hb on at least one occasion. The target serum ferritin concentration 100-500 $\mu\text{g/L}$ was reached with both doses and remained within the target range at 2 weeks follow-up (at 6 and 4 weeks respectively for the two dose groups)-data were only available for about half the 500 mg iron dose group.

Clinical trials

Clinical studies showed that the haematological response and the filling of the iron stores was faster after IV administration of FCM than with orally administered comparators.

The phase III studies undertaken with FCM included patients with iron deficiency of different aetiologies, i.e. associated with non-dialysis and dialysis dependent chronic kidney disease (CKD), inflammatory bowel disease, heavy menstrual bleeding, post-partum iron deficiency

anaemia (IDA), pregnancy (second and third trimester) or patients with chronic heart failure and iron deficiency.

Additionally, there are limited data available with FCM in patients with iron deficiency associated with chemotherapy related anaemia and gastric bypass.

IDA associated with haemodialysis-dependent chronic kidney disease

The efficacy and safety of FCM compared to Venofer[®] (iron sucrose, IV) for the treatment of IDA secondary to chronic renal failure was assessed in a multi-centre, open-label, randomised, parallel-group, Phase III study (VIT-IV-CL-015) in 237 patients on haemodialysis or haemodiafiltration. IDA was defined as Hb \leq 115 g/L in addition to transferrin saturation (TSAT) $<$ 20% and/or serum ferritin $<$ 200 μ g/L. Patients received 200 mg iron 2 or 3 times weekly (depending on the timing of dialysis sessions) until their individual calculated cumulative dose had been reached. The mean duration of treatment was 15.8 days (range 1 to 27) and 16.2 days (range 1 to 43 days) for the FCM and Venofer[®] groups, respectively.

Patients treated with erythropoietin (EPO) should have had received this treatment for at least 8 weeks prior to inclusion in the study and increases in the dose of EPO were not permitted. The primary efficacy endpoint was defined as the percentage of patients reaching an increase in Hb of \geq 10 g/L at 4 weeks. The percentage of responders was 44.1% (52/118) in the FCM group and 35.3% (41/116) in the Venofer[®] group; the difference between groups was not statistically significant ($\chi^2 = 0.2254$). At follow-up 4 weeks after the final dose of medication, secondary efficacy parameters (Hb \geq 110-120 g/L, serum ferritin 200-800 μ g/L, TSAT 20-50%) demonstrated successful increase in iron stores for both treatment groups.

IDA associated with non-dialysis-dependent chronic kidney disease

A multi-centre, randomised, open-label, controlled, 8-week, Phase III study (1VIT04004) in 255 patients was conducted to compare the safety and efficacy of IV infusions of the FCM solution with oral administration of ferrous sulphate, independent of Hb response to EPO, in treating IDA in non-dialysis-dependent chronic kidney disease (ND-CKD). IDA was defined as Hb \leq 110 g/L, TSAT \leq 25%, and serum ferritin \leq 300 μ g/L. Patients treated with EPO should have had received this treatment for at least 8 weeks prior to inclusion in the study and increases in the dose of EPO were not permitted. Patients randomised to FCM treatment received 1 to 3 doses of FCM solution intravenously at 2-4 week intervals: 15 mg iron/kg for weight \leq 66 kg to a maximum of 1,000 mg iron for the initial dose and a maximum of 500 mg iron for subsequent doses. Patients randomised to oral iron treatment received ferrous sulphate tablets (65 mg iron) 3 times daily for 8 weeks.

In a modified intent-to-treat analysis which excluded 8 FCM patients and 2 ferrous sulfate patients, the primary efficacy endpoint, defined as the percentage of patients with an increase in Hb \geq 10 g/L at any time between baseline and end of study, or time of intervention, was reached by 60.4% (87/144) of FCM-treated patients compared to 34.7% (35/101) of oral iron-treated patients ($p < 0.001$; 95% confidence interval (CI) 13.0, 38.5). The modified intent-to-treat population comprised patients with at least one dose of study medication, stable erythropoietin dose, at least one post-baseline Hb assessment and GFR \leq 45 mL/min/1.73 m². FCM was also demonstrated to be superior to oral iron across all secondary ranked efficacy endpoints: Hb change \geq 10 g/L and a serum ferritin change \geq 160 μ g/L at any time during the study (60.4% versus 0.0%, respectively; $p < 0.001$; 95% CI 48.2, 72.6) or a Hb change \geq 10 g/L before Day 42 (54.2% versus 28.7%, respectively; $p < 0.001$; 95% CI 12.8, 38.1).

In a 44-week extension to this study (1VIT05005), the efficacy of FCM in the long-term maintenance treatment of anaemia in ND-CKD was evaluated in 140 patients. Clinical success

(Hb \geq 110 g/L, serum ferritin 100-800 μ g/L, TSAT 30-50%) was achieved in 51.4% (72/140) of patients, with 10% (14/140) exhibiting sustained clinical success at 50% or more of the assessments.

In the ND-CKD subgroup of another study (1VIT07018), the safety and efficacy of IV injection of FCM solution, 15 mg iron/kg body weight up to 1,000 mg iron administered over 15 min. was assessed. The comparator was standard medical care (SMC) as determined by the investigator.

The primary endpoint was the incidence of treatment-emergent serious adverse events from Day 0 to 30 days after the last dose of study drug. The safety population contained 204 FCM subjects and 212 SMC subjects. The majority had mild anaemia (mean Hb 104 g/L in FCM group and 102 g/L in control group). There were no serious adverse events assessed as related to FCM. Based on these limited data and the lack of specific serious drug-related adverse reactions, the safety of single FCM doses of 1,000 mg iron appeared equal to SMC.

Efficacy was assessed in a modified intent-to-treat population of 202 FCM subjects and 203 SMC subjects. Achievement of Hb \geq 120 g/L was comparable in the two groups at 30 days - FCM 9.9% and SMC 6.9% (Fisher's Exact Test $p = 0.29$).

IDA secondary to inflammatory bowel disease

The efficacy of infusions of FCM solutions compared to oral administration of ferrous sulphate in the treatment of IDA secondary to chronic inflammatory bowel disease was examined in a multi-centre, open-label, randomised, 12-week, Phase III study (VIT-IV-CL-008) in 200 patients. 4 patients did not receive study drug and were excluded from the analysis. IDA was defined as Hb \leq 110 g/L in combination with TSAT $<$ 20% and/or serum ferritin $<$ 100 μ g/L. Patients were randomised in a 2:1 (FCM: ferrous sulphate) ratio to receive 1 of 2 treatments: FCM IV on Day 1 with subsequent doses at 1-week intervals until the patient's calculated cumulative dose had been reached (a maximum dose of 1,000 mg iron per infusion) or oral ferrous sulphate capsules (100 mg iron) twice daily for 12 weeks. Based on the primary response parameter of change in mean Hb from baseline to Week 12 (36.0 g/L FCM group, 32.9 g/L oral iron group), the results of this study demonstrated that FCM was non-inferior to ferrous sulphate. The non-inferiority criterion was lower limit of 95% CI of difference FCM minus ferrous sulphate \geq -5.0 g/L. The non-inferiority criterion was met in both the intent-to-treat and per protocol populations. Furthermore, the mean Week-12 values of serum ferritin (80.2 μ g/L FCM group, 38.6 μ g/L oral iron group) and TSAT (23.1% FCM group, 29.2% oral iron group) demonstrated a successful repletion of the iron stores in patients treated with FCM.

In another study (FER-IBD-07-COR), FCM dosing based on a simplified dosing scheme with four Hb-weight subgroups (see section 4.2 DOSE AND METHOD OF ADMINISTRATION) was compared with Venofer[®] dosing based on the Ganzoni formula. The FCM dose was given in up to three IV infusions on Days 1, 8 and 15 in single doses of up to 1000 mg iron. The Venofer[®] dose was given in up to 11 IV infusions in doses not exceeding 200 mg iron not more than three times per week. The primary endpoint was the percentage of patients achieving a Hb increase \geq 20 g/L at Week 12. The demographic and haematological characteristics of the two groups were similar. About 60% of subjects were female, median age was 39 years (range 18-81), median weight 67 kg (range 39-137), median baseline Hb 104 g/L (range 61-146) and median baseline serum ferritin 7 μ g/L (range 2-299). Subjects in the two treatment groups achieved at least comparable Hb response overall and in the Hb-weight subgroups (see **Table 7**).

Table 7 Efficacy of FCM (new dosing method) versus Venofer® (Ganzoni dose calculation) in iron deficiency anaemia associated with inflammatory bowel diseases - trial FER-IBD-07-COR – patients with 12-week assessment

	FCM n=228	Venofer® n=220	Difference [95% CI]
Hb Response (increase \geq 20 g/L) at Week 12	65.8%	53.6%	12.2% [3.1%, 21.0%]
Hb<100 g/L – Wt 35-<70 kg	missing n=7 n=59 86.4%	missing n=8 n=44 75.0%	11.4% [-4.1%, 26.9%]
Hb<100 g/L – Wt \geq 70 kg	n=31 90.3%	n=24 100.0%	-9.7% [-20.1%, 0.7%]
Hb \geq 100 g/L – Wt 35-<70 kg	n=70 75.7%	n=78 71.8%	3.9% [-10.2%, 18.1%]
Hb \geq 100 g/L – Wt \geq 70 kg	n=61 88.5%	n=66 75.8%	12.8% [-0.3%, 25.8%]

IDA secondary to heavy menstrual bleeding

The safety and efficacy of IV infusions of FCM solution, compared to oral administration of ferrous sulphate, in improvement of Hb levels in females with IDA secondary to heavy menstrual bleeding was assessed in a multi-centre, randomised, open-label, 6-week, Phase III study (1VIT04002/1VIT04003). At enrolment, patients had a baseline Hb \leq 114 g/L, TSAT \leq 25%, and serum ferritin \leq 100 μ g/L. Patients were randomised to receive either oral ferrous sulphate tablets (65 mg iron) 3 times daily for 6 weeks or weekly infusions of FCM solution (a maximum dose of 1,000 mg iron per infusion) until the patient's calculated cumulative dose had been reached, to a maximum of 2,500 mg iron. In a modified intent-to-treat analysis which excluded 18 FCM patients and 6 ferrous sulphate patients, FCM was shown to be superior to oral iron in achieving an increase from baseline in Hb \geq 20 g/L at any time during the study: 82.0% (187/228) in the FCM group versus 61.8% (139/225) in the oral iron group (p <0.001; 95% CI 12.2, 28.3). The modified intent-to-treat population comprised patients with at least one dose of study medication, baseline Hb \leq 110 g/L, TSAT \leq 25%, serum ferritin \leq 100 μ g/L, at least one post-baseline Hb assessment and confirmed diagnosis of heavy menstrual bleeding.

Post partum IDA

The safety and efficacy of FCM compared to oral ferrous sulphate as treatment for post partum IDA (Hb \leq 100 g/L or \leq 105 g/L) was assessed in 3 randomised, open-label, multi-centre trials. In 2 of the studies, patients were randomised 1:1 to receive either oral ferrous sulphate tablets (65 mg iron) 3 times daily for 6 weeks or weekly IV FCM at dosages based on the calculated iron deficit. A maximum of 1,000 mg of iron (15 mg iron/kg body weight for pre-pregnancy weight \leq 66 kg), as IV FCM solution, was given at weekly intervals until the individual's calculated cumulative iron dose had been reached or a maximum total iron dose of 2,500 mg had been administered. In the third study, patients were randomised 2:1 to receive either oral ferrous sulphate capsules (100 mg iron) twice daily for 12 weeks or weekly IV FCM at dosages based on the calculated iron deficit (to a maximum of 3 infusions and not exceeding a weekly dose of 1,000 mg iron).

In all 3 studies, FCM was shown to be efficacious for the treatment of IDA in post partum subjects. In the first study (1VIT06011), the superiority of FCM was demonstrated according to the primary efficacy endpoint (defined as Hb >120 g/L), with a greater proportion of patients in the FCM group (91.4%, 127/139) versus the oral iron group (66.7%, 98/147) achieving success at any time during the study (p <0.0001; 95% CI 15.20, 34.20). This was based on a modified intent-to-treat population which excluded 4 FCM patients and one ferrous sulfate patient.

In the second study (1VIT03001), FCM was demonstrated to be non-inferior to oral iron among subjects who achieved an increase in Hb ≥ 20 g/L: 96.4% (162/168) of the FCM group versus 94.1% (159/169) of the oral iron group (95% CI -2.19, 6.88). The analysis was in a modified intent-to-treat population (6 FCM patients and 9 ferrous sulphate patients excluded) and the non-inferiority margin was 15% based on a 1-sided 97.5% CI of the treatment difference. Statistically significantly greater increases from baseline to highest Hb, TSAT, and serum ferritin values were also observed in the FCM groups compared with the oral iron groups.

In the third study (VIT-IV-CL-009), FCM was shown to be non-inferior to ferrous sulphate for the mean change in Hb from baseline to Week 12 (33.4 g/L in the FCM group (n=227) versus 31.8 g/L in the oral iron group (n=117). The non-inferiority criterion was lower limit of 95% CI of difference FCM minus ferrous sulfate ≥ -5.0 g/L. The non-inferiority criterion was met in both the intent-to-treat and per protocol populations.

In another study (1VIT07017) in patients with iron deficiency anaemia due to heavy menstrual bleeding (HMB) or post-partum, the safety and efficacy of IV injection of FCM solution, 15 mg iron/kg body weight up to 1,000 mg iron administered IV over 15 min, was assessed. The comparator was standard medical care (SMC) as determined by the investigator.

The primary endpoint was the incidence of treatment-emergent serious adverse events from Day 0 to 30 days after the last dose of study drug. The safety population contained 996 FCM subjects and 1,022 SMC subjects. Approximately 60% of the subjects had post-partum anaemia (median Hb 103 g/L) and the other 40% anaemia associated with HMB (median Hb 96 g/L). There were no serious adverse events assessed as related to FCM. Based on overall incidences and the lack of specific drug-related serious adverse reactions, the safety profiles of FCM and SMC oral iron appeared similar. There was insufficient exposure to SMC IV iron for it to be included in the assessment.

Efficacy was assessed in a modified intent-to-treat population which was approximately 30% less than the randomised population, although still balanced. Achievement of Hb >120 g/L was significantly better with FCM than SMC in the two subgroups at 30 days (see **Table 8**).

Table 8 Efficacy of FCM in single doses up to 1,000 mg iron versus SMC in iron deficiency anaemia associated with heavy menstrual bleeding and post-partum – trial 1VIT07017 – 30 days follow-up - modified intent-to-treat

	FCM	SMC	Difference p-value ²
Heavy Menstrual Bleeding	n=331	n=329	
Hb >120 g/L ¹	34.4%	15.8%	18.6% p<0.001
Post-Partum	n=342	n=357	
Hb >120 g/L ¹	68.1%	50.7%	17.4% p<0.001

FCM: Ferric Carboxymaltose. SMC: Standard Medical Care as determined by the investigator.

¹ Anytime between baseline and end of study of surgical intervention. ² Fisher's Exact Test.

Pregnancy

In a study in pregnant women in the second and third trimester with iron deficiency anaemia (FER-ASAP-2009-01) randomised to receive either ferric carboxymaltose (maximum permitted total dose 1000 mg for baseline Hb 91-104 g/L or 1500 mg for baseline Hb 80-90 g/L) or oral iron (200 mg orally twice daily). The range of gestation at study entry for the ferric carboxymaltose arm was 16.0 to 33.9 weeks.

Superiority of ferric carboxymaltose for the primary outcome of change in Hb from baseline to week 3 was not shown. The mean total iron dose was 1,028.5 mg (median 1,000 mg) in the ferric carboxymaltose group compared to 11,959.2 mg (median 12,300 mg) in the oral iron group.

Iron deficiency associated with chronic heart failure

In a population with chronic heart failure (HF), a double-blind, placebo-controlled, randomised study (FER-CARS-02 FAIR-HF) demonstrated a statistically significant improvement with ferric carboxymaltose relative to placebo in both Patient Global Assessment (PGA) and New York Heart Association (NYHA) functional class at Week 24 (odds ratio for improvement, 2.51 (95% CI 1.75-3.61; $p < 0.001$) and 2.40 (95% CI 1.55-3.71; $p < 0.001$), respectively). The results applied to iron deficient patients with and without anaemia. Superior improvements ($p < 0.001$) were also observed in the 6-minute walk test and patient quality of life (QoL) for patients treated with ferric carboxymaltose.

Study FER-CARS-05 (CONFIRM-HF) in subjects with chronic HF and iron deficiency demonstrated the benefit of ferric carboxymaltose relative to placebo in improving functional capacity as measured by the change in 6-minute walk test distance from baseline to Week 24, with a difference between treatment groups (least squares mean (\pm standard error)) of 33.2 ± 10.52 m ($p = 0.002$), thereby confirming the hypothesis of study FER_CARS_02. The treatment benefit of ferric carboxymaltose in improvement of 6-minute walk test distance was statistically significant from week 24 ($p < 0.001$) and was sustained throughout the study to Week 52 ($p < 0.001$), demonstrating the long-term benefit of iron repletion over a period of 1 year. The improvements in PGA and NYHA functional class were also seen in ferric carboxymaltose - treated subjects, with statistical significance for the difference between treatment groups achieved from Week 12 (PGA) or Week 24 (NYHA functional class) onwards. At Week 52 Endpoint, 54.7% of subjects in the ferric carboxymaltose group showed some improvement in PGA score compared to 35.1% in the placebo group, and 18.0% of subjects in the ferric carboxymaltose group showed an improvement by 1 NYHA functional class, compared to only 3.3% in the placebo group.

Improvements in fatigue score and overall Kansas City cardiomyopathy questionnaire score were also seen, with statistical significance for the difference between treatment groups (in favour of ferric carboxymaltose) achieved from Week 12 onwards.

Study FER-CARS-04 (EFFECT-HF) was an open-label (with blinded endpoint evaluation), randomised, 2-arm study comparing ferric carboxymaltose ($n = 86$) versus standard of care ($n = 86$) of which 29 patients received at least 1 dose of oral iron during the study) in subjects with chronic HF and iron deficiency for a treatment period of 24 weeks. At Day 1 and Week 6 (correction phase), subjects received either ferric carboxymaltose according to a simplified dosing scheme (see section 4.2 DOSE AND METHOD OF ADMINISTRATION) or standard of care. At Week 12, (maintenance phase) subjects received ferric carboxymaltose (500 mg iron) or standard of care if serum ferritin < 100 ng/mL or 100 to 300 ng/mL and TSAT $< 20\%$. For the primary efficacy endpoint, the treatment difference (ferric carboxymaltose – standard of care) in LS mean change in peak VO_2 from baseline to Week 24 was 1.04 mL/kg/min [95% CI: 0.164, 1.909; $p = 0.0202$] An individual patient data meta-analysis of four double-blind, randomised studies in subjects with chronic heart failure and iron deficiency receiving ferric carboxymaltose versus placebo (studies FER-CARS-01 [12 weeks], FER-CARS-02 FAIR-HF [26 weeks], FER-CARS-03 EFFICACY-HF [26 weeks] and FER-CARS-05 CONFIRM-HF [52 weeks]) compared the efficacy and safety of ferric carboxymaltose ($n = 504$) versus placebo ($n = 335$) for up to 52 weeks. Ferric carboxymaltose and placebo were administered according to the dosing regimen of the individual studies. The treatment of ferric carboxymaltose versus placebo resulted in a reduction of recurrent cardiovascular hospitalisations and cardiovascular mortality (relative

risk (95% CI) of 0.59 (0.40–0.88); $p=0.009$); hospitalisations and mortality as exploratory endpoints in individual studies).

There are no data available regarding the long term use of FERINJECT.

Ferritin Monitoring After Replacement Therapy

There is limited data from study VIT-IV-CL-008, which demonstrates that ferritin levels decrease rapidly 2-4 weeks following replacement and more slowly thereafter. The mean ferritin levels did not drop to levels where retreatment might be considered during the 12 weeks of study follow up. Thus, the available data does not clearly indicate an optimal time for ferritin retesting although assessing ferritin levels earlier than 4 weeks after replacement therapy appears premature. Thus, it is recommended that further re-assessment of ferritin should be made by the clinician based on the individual patient's condition.

Paediatric Population

Adolescents aged 14 years or older were included in 4 studies performed in adults. In addition, 3 paediatric studies were performed in children and adolescents aged 1 to 17 years with iron deficiency anaemia. The 3 paediatric studies are described below.

In a prospective pharmacokinetic/pharmacodynamic Phase 2 study (1VIT13036), 35 children with iron deficiency anemia, defined as Hb <11 g/dL and TSAT <20%, were treated in 2 consecutive dose cohorts with single doses of IV FCM 7.5 mg iron/kg body weight (n=16) or IV FCM 15 mg iron/kg body weight (n=19), at a maximum dose of 750 mg iron. The median age was 12.0 years (range: 1.5-17.5 years). The most common aetiologies for iron deficiency anaemia were gastrointestinal diseases (e.g. inflammatory bowel disease, Helicobacter pylori gastritis, coeliac disease), insufficient dietary iron intake and heavy uterine bleeding. Hb, ferritin and TSAT increased dose-dependently. On day 35 after injection, the mean (SD) increase in Hb from baseline was 19 (13.8) g/L with IV FCM 7.5 mg iron/kg and 28 (11.5) g/L with IV FCM 15 mg iron/kg. Post treatment Hb levels were within the normal range or marginally above (n=1) in 9 (56%) of the patients in the IV FCM 7.5 mg iron/kg dose cohort, and in 18 (95%) of the patients in the IV FCM 15 mg iron/kg dose cohort.

In a prospective, randomised, open-label, parallel-group Phase 3 study (1VIT17044), efficacy and safety of IV FCM were compared with oral iron therapy in children with iron deficiency anaemia (Hb < 11 g/dL, TSAT <30% and serum ferritin <300 ng/mL) and inadequate response to oral iron for at least 8 weeks. 79 children at a median age of 14.0 years (range: 1 to 17 years) were randomized (ITT population), 40 children to treatment with IV FCM whereof 39 were treated with 2 doses of IV FCM 15 mg iron/kg body weight at a 7-day interval (maximum single dose 750 mg) and 39 children to treatment with oral ferrous sulphate for 28 days whereof 38 received treatment. Underlying conditions for iron deficiency anaemia were insufficient iron dietary intake, gastrointestinal, irregular menses/heavy uterine bleeding and multifactorial. Children from the oral treatment arm who did not respond adequately to treatment could be included into a single arm extension study (1VIT18045) for treatment with intravenous IV FCM at the same dose as in the main study.

In the main study, a similar, clinically meaningful increase in Hb was observed after treatment with IV FCM and treatment with oral iron sulphate. The increase in Hb from baseline to Day 35 (LS Mean [95%CI]) was 22.2 [16.9, 27.5] g/L after IV FCM and 19.2 [14.3, 24.1] g/L after oral iron sulphate, with no superiority shown for the treatment with IV FCM (primary endpoint). Normal ranges of Hb were achieved in 28 (70%) of the patients treated with IV FCM and in 22 (58%) of the patients treated with oral iron sulphate. The increase in ferritin and TSAT, used as a measure for the replenishment of iron stores, was higher after IV FCM therapy compared to oral iron sulphate therapy, with an increase in ferritin from baseline to Day 35 (LS Mean

[95%CI]) of 132.1 [105.44, 158.76] ng/ml after IV FCM and 11.0 [-15.62, 37.65] ng/mL after oral iron sulphate. The corresponding increase in TSAT was 24.3 [19.19, 29.41] % and 8.7 [3.70, 13.63] %, respectively. In the extension study, after treatment with IV FCM, the increase in Hb, ferritin and TSAT (mean (SD)) was 7.0 (11.9) g/L, 188.9 (128.94) ng/mL and 11.7 (10.13) %, respectively with post treatment Hb levels being in the normal range in 2/7 patients (29%). See also section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).

5.2 PHARMACOKINETIC PROPERTIES

After a single 100 mg IV iron dose of FCM solution (n=6) injected over 1 min, serum iron concentration peaked at a mean of 15 min. After 500, 800 or 1,000 mg iron in 250 mL normal saline infused over 15 min (n=6 for each dose), serum iron concentration peaked at means of 20 min, 1 h and 1.2 h, respectively. The mean volume of distribution was approximately 3 L, corresponding to the plasma volume. Mean plasma clearance ranged from 2.6-4.4 mL/min and terminal half life from 7-12 h. Renal elimination was negligible.

Within 8 h of a single radiolabelled 100 mg IV iron dose of FCM to patients with iron deficiency or renal anaemia, most of the radiolabelled iron had cleared the circulation and distributed to the bone marrow, liver and spleen. Within 6-9 days, the radiolabelled iron was incorporated into the red blood cells. After 24 days, iron utilisation was 91-99% in iron deficiency anaemia and 61-84% in renal anaemia.

Paediatric Populations

The pharmacokinetic properties of IV FCM at a dose of 15 mg iron/kg were similar to those for adult patients with iron deficiency. Serum iron increased proportionally to the dose after a single dose of 7.5 mg iron/kg or 15 mg iron/kg. After a single dose of IV FCM of 15 mg iron/kg body weight (maximum 750 mg), average maximum total serum iron values of 310 µg/mL were measured after 1.12 hours. The terminal half-life was 9.8 hours, and the distribution volume estimated by the population pharmacokinetic analysis was 0.42 to 3.14 L. Based on model-based simulations, the paediatrics subjects tended to have lower systemic exposure (lower AUC_{0-72h}) compared to the adults (median per age group: 3,340 µg×h/mL (1 to 2 years), 4,110 µg×h/mL (3 to 12 years), 4,740 µg×h/mL (13 to 17 years), 8,864 µg×h/mL (adults)).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Ferric carboxymaltose was not genotoxic in assays for gene mutation (in vitro bacterial and mouse lymphoma cell assays) and chromosomal damage (human lymphocytes in vitro and mouse micronucleus test in vivo).

Carcinogenicity

The carcinogenic potential of FERINJECT has not been studied in animals.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium hydroxide (for pH adjustment)

Hydrochloric acid (for pH adjustment)

Water for injections

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

Shelf-life of the product as packaged for sale:

36 months.

Shelf-life after first opening of the container:

From a microbiological point of view, preparations for parenteral administration should be used immediately.

Shelf-life after dilution with sterile 0.9% m/V sodium chloride solution:

To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2-8°C for not more than 12 hours.

Product is for single use in one patient only. Discard any residue.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in the original package. Do not store above 30 °C. Do not freeze, do not refrigerate.

6.5 NATURE AND CONTENTS OF CONTAINER

2 mL of solution in a vial (type I glass) with bromobutyl rubber stopper and aluminium cap in pack sizes of 1 and 5 vials.

10 mL of solution in a vial (type I glass) with bromobutyl rubber stopper and aluminium cap in pack sizes of 1 and 5 vials.

20 mL of solution in a vial (type I glass) with bromobutyl rubber stopper and aluminium cap in pack sizes of 1 vial.

Not all presentations may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waster material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The active substance of FERINJECT is a complex of polynuclear iron(III)-hydroxide with 4(R)-(poly-(1→4)-*O*-α-D-glucopyranosyl)-oxy-2(R),3(R),5(R),6-tetrahydroxy-hexanoate.

The relative molecular weight is approximately 150,000 Da, corresponding to the empirical formula:

$[\text{FeO}_x(\text{OH})_y(\text{H}_2\text{O})_z]_n \{ \{ (\text{C}_6\text{H}_{10}\text{O}_5)_m (\text{C}_6\text{H}_{12}\text{O}_7) \}_1 \}_k$, where $n \approx 10^3$, $m \approx 8$, $l \approx 11$, and $k \approx 4$.

CAS number

1461680-64-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4

8 SPONSOR

Vifor Pharma Pty Ltd
655 Elizabeth Street
Melbourne VIC 3000
Australia
Tel: 1800 202 674 (Australia)
Tel: 0800 996 312 (New Zealand)

9 DATE OF FIRST APPROVAL

05 April 2011

10 DATE OF REVISION

26 July 2023

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
2	Editorial change to clarify content in vial.
4.1	Indication extended to add paediatric patients (1-17 years).

4.2	Updated to add paediatric dosing details.
4.8	Updated to include Adverse effects observed in the new studies.
5.1	Updated to include clinical trial details for heart failure patients and paediatric patients (1-17 years).
5.2	Updated to include details for paediatric patients (1-17 years)
6.7	Correction of the chemical structure of the active substance
8	Sponsor address updated

FERINJECT®

Ferric carboxymaltose (fer-rik car-boxy-malt-ose) – solution for injection

Consumer Medicine Information

WHAT IS IN THIS LEAFLET

This leaflet answers some common questions about FERINJECT. It does not contain all the available information. This does not replace talking with your doctor.

All medicines have risks and benefits. Your doctor has weighed the risks of using FERINJECT against the benefits this medicine is expected to have for you.

If you have any concerns about this medicine, ask your doctor.

Keep this leaflet.

You may need to read it again.

WHAT IS FERINJECT

FERINJECT is an intravenous iron preparation, a medicine that is given in the treatment of iron deficiency conditions. It contains iron in the form of ferric carboxymaltose, an iron carbohydrate compound. Iron is an essential element required for the oxygen-carrying capacity of haemoglobin in red blood cells and of myoglobin in muscle tissue. Moreover, iron plays an important role in many other vital processes in the human body.

WHAT FERINJECT IS GIVEN FOR

FERINJECT is given for the treatment of patients with iron deficiency, when oral iron preparations are ineffective or cannot be used. The aim of the therapy is to replenish body iron stores and to remedy anaemia, a reduced level of haemoglobin due to iron deficiency.

Before administration, your doctor will perform a blood test to calculate the dose of FERINJECT you require.

BEFORE YOU ARE GIVEN FERINJECT

When you must not be given FERINJECT

- if you are hypersensitive (allergic) to ferric carboxymaltose or any of the other ingredients of FERINJECT,
- if you have anaemia **not** caused by iron deficiency,
- if you have iron overload (too much iron in your body) or disturbances in utilisation of iron.

You must tell your doctor if

- if you are under the age of 14 years.
- you have an infection, asthma, eczemas, allergies or liver disorders.

- you are pregnant or breastfeeding.
- if you have or have had low levels of phosphate in the blood.

Taking other medicines

If FERINJECT is given together with oral iron preparations, then these oral preparations will be less effective.

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without prescription.

Important information about some of the ingredients of FERINJECT

This medicinal product contains 5.5 mg (or 0.24 mmol) sodium per millilitre of undiluted solution and is to be taken into consideration by patients on a controlled sodium diet.

HOW FERINJECT IS GIVEN

Your doctor can administer FERINJECT by three possible routes: undiluted by injection, during haemodialysis, or diluted by infusion.

- by injection, you may receive up to 20 mL of FERINJECT, corresponding to 1000 mg of iron, once a week directly into the vein.
- if you are on dialysis, you may receive FERINJECT during a haemodialysis

session via the dialyser. The maximum dose of FERINJECT during haemodialysis is 200 mg (4 mL).

- by infusion, you may receive up to 20 mL of FERINJECT, corresponding to 1000 mg of iron, once a week directly into the vein. Because FERINJECT is diluted with sodium chloride solution for the infusion, it may have a volume of up to 250 mL and appear as a brown solution.

Your doctor will take responsibility for determining the appropriate dose and choosing the method, frequency and duration of your treatment. Ferinject will be administered in a setting where possible allergic reactions can receive appropriate and prompt treatment.

You will be observed for about 30 minutes by your doctor or nurse after each administration.

Overdose

Overdose can cause accumulation of iron in storage sites. Your doctor will monitor iron parameters such as serum ferritin and transferrin saturation to avoid iron accumulation.

POSSIBLE UNWANTED EFFECTS

Like all medicines, FERINJECT can cause unwanted effects, although not everybody gets them.

Clinical studies experience

Reported side effects are either common (occurring in less than 1 in 10 and more than 1 in 100 patients) or uncommon

(occurring in less than 1 in 100 and more than 1 in 1000 patients).

The following symptoms were common: headache, dizziness, high blood pressure, flushing, nausea, injection/infusion site reactions, low blood phosphate levels.

The following symptoms were uncommon: allergic reaction, tingling or numbness of the hands or feet, fast heart rate (tachycardia), low blood pressure, difficulty breathing, taste disturbance, vomiting, indigestion, wind, stomach pain, constipation, diarrhoea, itchiness, hives (urticaria), redness of skin (erythema), rash, muscle pain, muscle spasm, back pain, joint pain, pain in extremity, fever, fatigue, chest pain, swelling of hands, ankles or feet, pain and chills. Long-lasting brown discoloration of the skin may occur due to leakage of the drug at the injection site.

The following symptoms were rare: anaphylactoid reactions, generally feeling unwell.

Some blood parameters may change temporarily, which could be detected in laboratory tests.

The following changes in blood parameters are uncommon: increase of the liver enzyme alanine aminotransferase, increase of the liver enzymes aspartate aminotransferase, gamma-glutamyltransferase, blood lactate dehydrogenase and blood alkaline phosphatase.

Post marketing experience

As part of the continuing post-marketing surveillance of

FERINJECT, the following side effects have been reported:

Anxiety, loss of consciousness, dizziness (vertigo), feeling faint (pre-syncope), fainting (syncope), wheeze (bronchospasm), swelling (angioedema), dermatitis, pallor, face swelling and influenza like illness.

There is no efficacy or safety data on the use of FERINJECT in pregnancy before 16 weeks' gestation. Iron deficiency occurring in the first trimester of pregnancy can in many cases be treated with oral iron.

There is limited experience with the use of FERINJECT in women in pregnancy from 16 weeks' gestation). If iron treatment is needed in pregnancy, oral iron should be used where possible and FERINJECT only used where the benefit outweighs the risk.

Iron treatment including FERINJECT may worsen infection.

Ask your doctor for more information.

If any of the side effects becomes serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

AFTER TAKING FERINJECT

Storage

Keep FERINJECT out of the reach and sight of children.

Do not use FERINJECT after the expiry date which is stated on the label. The expiry date

refers to the last day of that month.

FERINJECT should be stored in the original package and should not be stored above 30° C. FERINJECT should not be refrigerated or frozen.

Once a FERINJECT vial has been opened, it should be given immediately. After dilution with sodium chloride solution, the diluted solution should be given as soon as possible, if storage is necessary hold at 2 - 8°C for not more than 12 hours.

FERINJECT will normally be stored for you by your doctor or the hospital.

Product is for single use in one patient only. Discard any residue.

Further information

This is not all the information that is available on FERINJECT. If you need more information, ask your doctor.

PRODUCT DESCRIPTION

What it looks like

FERINJECT, solution for injection/infusion is a dark brown, non-transparent solution.

FERINJECT is supplied in the following presentations:

- 2 mL of solution in a glass vial containing the equivalent of 100 mg of iron (AUST R: 162636),
- 10 mL of solution in a glass vial containing the equivalent of 500 mg of iron (AUST R: 162641), or
- 20 mL of solution in a glass vial containing the equivalent of 1000 mg of iron (AUST R: 289045).

Not all strengths may be marketed.

Ingredients

Active ingredient
The active substance is iron (as ferric carboxymaltose, an iron carbohydrate compound). The

concentration of iron present in the product is 50 mg per milliliter.

Inactive ingredients
The other ingredients are sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment), and water for injection.

Supplier

Supplied in Australia by:

Vifor Pharma Pty Ltd
Level 8, 80 Dorcas Street
South Bank, Melbourne VIC
3006 Australia
Tel: 1800 202 674

Supplied in New Zealand by:

Pharmacy Retailing
(trading as Healthcare Logistics)
58 Richard Pearce Drive,
Airport Oaks
Mangere
Auckland 2022 New Zealand
Tel: 0800 996 312

This leaflet was prepared in January 2019.

FERINJECT®

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- if you are on dialysis, you may receive FERINJECT during a haemodialysis

session via the dialyser. The maximum dose of FERINJECT during haemodialysis is 200 mg (4 mL).

- by infusion, you may receive up to 20 mL of FERINJECT, corresponding to 1000 mg of iron, once a week directly into the vein. Because FERINJECT is diluted with sodium chloride solution for the infusion, it may have a volume of up to 250 mL and appear as a brown solution.

Your doctor will take responsibility for determining the appropriate dose and choosing the method, frequency and duration of your treatment. Ferinject will be administered in a setting where possible allergic reactions can receive appropriate and prompt treatment.

You will be observed for about 30 minutes by your doctor or nurse after each administration.

In patients with liver disorders, iron status will be carefully monitored by the doctor to avoid iron overload.

Overdose

Overdose can cause accumulation of iron in storage sites. Your doctor will monitor iron parameters such as serum ferritin and transferrin saturation to avoid iron accumulation.

POSSIBLE UNWANTED EFFECTS

Like all medicines, FERINJECT can cause unwanted effects, although not everybody gets them.

Clinical studies experience

Reported side effects are either common (occurring in less than 1 in 10 and more than 1 in 100 patients) or uncommon (occurring in less than 1 in 100 and more than 1 in 1000 patients).

The following symptoms were common: headache, dizziness, high blood pressure, flushing, nausea, injection/infusion site reactions, low blood phosphate levels.

The following symptoms were uncommon: allergic reaction, tingling or numbness of the hands or feet, fast heart rate (tachycardia), low blood pressure, difficulty breathing, taste disturbance, vomiting, indigestion, wind, stomach pain, constipation, diarrhoea, itchiness, hives (urticaria), redness of skin (erythema), rash, muscle pain, muscle spasm, back pain, joint pain, pain in extremity, fever, fatigue, chest pain, swelling of hands, ankles or feet, pain and chills. Long-lasting brown discoloration of the skin may occur due to leakage of the drug at the injection site.

The following symptoms were rare: anaphylactoid reactions, generally feeling unwell.

Some blood parameters may change temporarily, which could be detected in laboratory tests.

The following changes in blood parameters are uncommon: increase of the liver enzyme alanine aminotransferase, increase of the liver enzymes aspartate aminotransferase, gamma-glutamyltransferase, blood lactate dehydrogenase and blood alkaline phosphatase.

Post marketing experience

As part of the continuing post-marketing surveillance of FERINJECT, the following side effects have been reported:

Anxiety, loss of consciousness, dizziness (vertigo), feeling faint (pre-syncope), fainting (syncope), wheeze (bronchospasm), swelling (angioedema), dermatitis, pallor, face swelling and influenza like illness.

There is no efficacy or safety data on the use of FERINJECT in pregnancy before 16 weeks' gestation. Iron deficiency occurring in the first trimester of pregnancy can in many cases be treated with oral iron.

There is limited experience with the use of FERINJECT in women in pregnancy from 16 weeks' gestation). If iron treatment is needed in pregnancy, oral iron should be used where possible and FERINJECT only used where the benefit outweighs the risk.

Slow heartbeat may occur in unborn babies whose mothers have been administered FERINJECT due to allergic reactions in the mother.

Iron treatment including FERINJECT may worsen infection.

Ask your doctor for more information.

If any of the side effects becomes serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

AFTER TAKING FERINJECT

Storage

Keep FERINJECT out of the reach and sight of children.

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Once a FERINJECT vial has been opened, it should be given immediately. After dilution with sodium chloride solution, the diluted solution should be given as soon as possible, if storage is necessary hold at 2 - 8°C for not more than 12 hours.

FERINJECT will normally be stored for you by your doctor or the hospital.

Product is for single use in one patient only. Discard any residue.

Further information

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PRODUCT DESCRIPTION

What it looks like

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- 10 mL of solution in a glass vial containing the equivalent of 500 mg of iron (AUST R: 162641), or
- 20 mL of solution in a glass vial containing the equivalent of 1000 mg of iron (AUST R: 289045).

Not all strengths may be marketed.

Ingredients

Active ingredient
The active substance is iron (as ferric carboxymaltose, an iron carbohydrate compound). The concentration of iron present in the product is 50 mg per milliliter.

Inactive ingredients
The other ingredients are sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment), and water for injection.

Supplier

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This leaflet was prepared in
January 2020

FERINJECT®

Ferric carboxymaltose (fer-rik car-boxy-malt-ose) – solution for injection

Consumer Medicine Information

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FERINJECT is an intravenous iron preparation, a medicine that is given in the treatment of iron deficiency conditions. It contains iron in the form of ferric carboxymaltose, an iron carbohydrate compound. Iron is an essential element required for the oxygen-carrying capacity of haemoglobin in red blood cells and of myoglobin in muscle tissue. Moreover, iron plays an important role in many other vital processes in the human body.

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FERINJECT is given for the treatment of patients with iron deficiency, when oral iron preparations are ineffective or cannot be used. The aim of the therapy is to replenish body iron stores and to remedy anaemia, a reduced level of haemoglobin due to iron deficiency.

Before administration, your doctor will perform a blood test to calculate the dose of FERINJECT you require.

BEFORE YOU ARE GIVEN FERINJECT

When you must not be given FERINJECT

- if you are hypersensitive (allergic) to ferric carboxymaltose or any of the other ingredients of FERINJECT,
- if you have anaemia **not** caused by iron deficiency,
- if you have iron overload (too much iron in your body) or disturbances in utilisation of iron.

You must tell your doctor if

- if you are under the age of 14 years.
- you have an infection, asthma, eczemas, allergies or liver disorders.

- you are pregnant or breastfeeding.
- if you have or have had low levels of phosphate in the blood.

You should be aware that:

Intravenous iron preparations can cause severe allergic reactions. These allergic reactions may include chest pain. Tell your doctor immediately if you experience it.

Taking other medicines

If FERINJECT is given together with oral iron preparations, then these oral preparations will be less effective.

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without prescription.

Important information about some of the ingredients of FERINJECT

This medicinal product contains 5.5 mg (or 0.24 mmol) sodium per millilitre of undiluted solution and is to be taken into consideration by patients on a controlled sodium diet.

HOW FERINJECT IS GIVEN

Your doctor can administer FERINJECT by three possible routes: undiluted by injection, during haemodialysis, or diluted

by infusion.

- by injection, you may receive up to 20 mL of FERINJECT, corresponding to 1000 mg of iron, once a week directly into the vein.
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Your doctor will take responsibility for determining the appropriate dose and choosing the method, frequency and duration of your treatment. Ferinject will be administered in a setting where possible allergic reactions can receive appropriate and prompt treatment.

You will be observed for about 30 minutes by your doctor or nurse after each administration.

In patients with liver disorders, iron status will be carefully monitored by the doctor to avoid iron overload.

Overdose

Overdose can cause accumulation of iron in storage sites. Your doctor will monitor iron parameters such as serum ferritin and transferrin saturation to avoid iron accumulation.

POSSIBLE UNWANTED EFFECTS

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Clinical studies experience

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Anxiety, loss of consciousness, dizziness (vertigo), feeling faint (pre-syncope), fainting (syncope), wheeze (bronchospasm), swelling (angioedema), dermatitis, pallor, face swelling and influenza like illness.

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AFTER TAKING FERINJECT

Storage

Keep FERINJECT out of the reach and sight of children.

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Not all strengths may be

marketed.

Ingredients

Active ingredient

The active substance is iron (as ferric carboxymaltose, an iron carbohydrate compound). The concentration of iron present in the product is 50 mg per milliliter.

Inactive ingredients

The other ingredients are sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment), and water for injection.

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This leaflet was prepared in June 2020

FERINJECT®

Ferric carboxymaltose (fer-rik car-boxy-malt-ose) – solution for injection

Consumer Medicine Information

WHAT IS IN THIS LEAFLET

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You may need to read it again.

WHAT IS FERINJECT

FERINJECT is an intravenous iron preparation, a medicine that is given in the treatment of iron deficiency conditions. It contains iron in the form of ferric carboxymaltose, an iron carbohydrate compound. Iron is an essential element required for the oxygen-carrying capacity of haemoglobin in red blood cells and of myoglobin in muscle tissue. Moreover, iron plays an important role in many other vital processes in the human body.

WHAT FERINJECT IS GIVEN FOR

FERINJECT is given for the treatment of patients with iron deficiency, when oral iron preparations are ineffective or cannot be used. The aim of the therapy is to replenish body iron stores and to remedy anaemia, a reduced level of haemoglobin due to iron deficiency. It is also used when there is a clinical need to deliver iron rapidly.

Before administration, your doctor will perform a blood test to calculate the dose of FERINJECT you require.

BEFORE YOU ARE GIVEN FERINJECT

When you must not be given FERINJECT

- if you are hypersensitive (allergic) to ferric carboxymaltose or any of the other ingredients of FERINJECT,
- if you have anaemia **not** caused by iron deficiency,
- if you have iron overload (too much iron in your body) or disturbances in utilisation of iron.

You must tell your doctor if

- if you are under the age of 14 years.
- you have an infection,

asthma, eczemas, allergies or liver disorders.

- you are pregnant or breastfeeding.
- if you have or have had low levels of phosphate in the blood.

You should be aware that:

Intravenous iron preparations can cause severe allergic reactions. These allergic reactions may include chest pain. Tell your doctor immediately if you experience it.

Taking other medicines

If FERINJECT is given together with oral iron preparations, then these oral preparations will be less effective.

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without prescription.

Important information about some of the ingredients of FERINJECT

This medicinal product contains 5.5 mg (or 0.24 mmol) sodium per millilitre of undiluted solution and is to be taken into consideration by patients on a controlled sodium diet.

HOW FERINJECT IS GIVEN

Your doctor can administer FERINJECT by three possible routes: undiluted by injection,

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- by injection, you may receive up to 20 mL of FERINJECT, corresponding to 1000 mg of iron, once a week directly into the vein.
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Your doctor will take responsibility for determining the appropriate dose and choosing the method, frequency and duration of your treatment. You may be re-assessed after 4 weeks to determine whether you need more Ferinject injections. Ferinject will be administered in a setting where possible allergic reactions can receive appropriate and prompt treatment.

You will be observed for about 30 minutes by your doctor or nurse after each administration.

In patients with liver disorders, iron status will be carefully monitored by the doctor to avoid iron overload.

Overdose

Overdose can cause accumulation of iron in storage sites. Your doctor will monitor

iron parameters such as serum ferritin and transferrin saturation to avoid iron accumulation.

The risk of accidental overdosing is minimal.

POSSIBLE UNWANTED EFFECTS

Like all medicines, FERINJECT can cause unwanted effects, although not everybody gets them.

Clinical studies experience

Reported side effects are either common (occurring in less than 1 in 10 and more than 1 in 100 patients) or uncommon (occurring in less than 1 in 100 and more than 1 in 1000 patients).

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rare: anaphylactoid reactions, generally feeling unwell.

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Post marketing experience

As part of the continuing post-marketing surveillance of FERINJECT, the following side effects have been reported:

Anxiety, loss of consciousness, dizziness (vertigo), feeling faint (pre-syncope), fainting (syncope), wheeze (bronchospasm), swelling (angioedema), dermatitis, pallor, face swelling, influenza like illness, low blood phosphate levels which might cause your bones to become soft (hypophosphataemic osteomalacia), skin discolouration distant to the injection site and chest pain which can be a sign of a potentially serious allergic reaction called Kounis syndrome.

There is no efficacy or safety data on the use of FERINJECT in pregnancy before 16 weeks' gestation. Iron deficiency occurring in the first trimester of pregnancy can in many cases be treated with oral iron.

There is limited experience with the use of FERINJECT in women in pregnancy from 16

weeks' gestation). If iron treatment is needed in pregnancy, oral iron should be used where possible and FERINJECT only used where the benefit outweighs the risk.

Slow heartbeat may occur in unborn babies whose mothers have been administered intravenous iron due to allergic reactions in the mother.

Iron treatment including FERINJECT may worsen infection.

Ask your doctor for more information.

If any of the side effects becomes serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

AFTER TAKING FERINJECT

Storage

Keep FERINJECT out of the reach and sight of children.

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Further information

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Ingredients

Active ingredient

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Inactive ingredients

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Consumer Medicine Information

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AFTER TAKING FERINJECT

Storage

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This leaflet was prepared in July 2021

FERINJECT[®]

Consumer Medicine Information (CMI) summary

The [full CMI](#) on the next page has more details. If you are worried about using this medicine, speak to your doctor, nurse, or pharmacist.

1. Why am I being given FERINJECT?

FERINJECT contains the active ingredient ferric carboxymaltose. FERINJECT is used to treat adults and adolescents aged 14 years and older with iron deficiency and children aged 1 to 13 years with iron deficiency anaemia, when oral iron preparations are ineffective or cannot be used.

For more information, see Section [1. Why am I using FERINJECT?](#) in the full CMI.

2. What should I know before I am given FERINJECT?

Do not use if you have ever had an allergic reaction to ferric carboxymaltose or any of the ingredients listed at the end of the CMI.

Talk to your doctor if you have any other medical conditions, take any other medicines, or are pregnant or plan to become pregnant or are breastfeeding.

For more information, see Section [2. What should I know before I use FERINJECT?](#) in the full CMI.

3. What if I am taking other medicines?

Some medicines may interfere with FERINJECT and affect how it works. If FERINJECT is given together with oral iron preparations, then these oral preparations will be less effective.

4. How do I use FERINJECT?

Your doctor can administer FERINJECT by three possible routes: undiluted by injection, during haemodialysis, or diluted by infusion.

More instructions can be found in Section [4. How do I use FERINJECT?](#) in the full CMI.

5. What should I know while using FERINJECT?

Things you should do	<ul style="list-style-type: none"> Intravenous iron preparations can cause severe allergic reactions. These allergic reactions may include chest pain. Tell your doctor immediately if you experience it.
Things you should not do	<ul style="list-style-type: none"> Do not use this medicine if you have anaemia not caused by iron deficiency Do not use this medicine if you have iron overload (too much iron in your body) or disturbances in utilisation of iron Do not give this medicine to children under 1 year.
Looking after your medicine	<ul style="list-style-type: none"> FERINJECT will normally be stored for you by your doctor or the hospital

For more information, see Section [5. What should I know while using FERINJECT?](#) in the full CMI.

6. Are there any side effects?

Common side effects include headache, dizziness, high blood pressure, flushing, nausea, and injection/infusion site reactions. Persistent bone pain and joint pain may be a sign of low blood phosphate levels. Serious but rare side effects include allergic reactions which are sometimes life threatening, such as breathing difficulty, swelling, lightheadedness, fast heartbeat, sweating, and nausea (anaphylactic reactions).

For more information, including what to do if you have any side effects, see Section [6. Are there any side effects?](#) in the full CMI.

FERINJECT[®]

Active ingredient(s): Ferric carboxymaltose (fer-rik car-boxy-malt-ose) – solution for injection

Consumer Medicine Information (CMI)

This leaflet provides important information about using FERINJECT.

You should also speak to your doctor, nurse, or pharmacist if you would like further information or if you have any concerns or questions about using FERINJECT.

Where to find information in this leaflet:

1. [Why am I using FERINJECT?](#)
2. [What should I know before I use FERINJECT?](#)
3. [What if I am taking other medicines?](#)
4. [How do I use FERINJECT?](#)
5. [What should I know while using FERINJECT?](#)
6. [Are there any side effects?](#)
7. [Product details](#)

1. Why am I using FERINJECT?

FERINJECT contains the active ingredient ferric carboxymaltose. FERINJECT is an intravenous iron preparation, a medicine that is given in the treatment of iron deficiency conditions. It contains ferric carboxymaltose, a carbohydrate complex containing iron. Iron is an essential element required for the oxygen-carrying capacity of haemoglobin in red blood cells and of myoglobin in muscle tissue. Moreover, iron plays an important role in many other vital processes in the human body.

FERINJECT is given for treatment of adults as well as adolescents aged 14 years and older with iron deficiency when oral iron preparations are ineffective or cannot be used. FERINJECT is also used in children 1 to 13 years old with iron deficiency anaemia when oral iron preparations are ineffective or cannot be used. The aim of the therapy is to replenish body iron stores and to remedy anaemia, a reduced level of haemoglobin due to iron deficiency. It is also used when there is a clinical need to deliver iron rapidly.

Before administration, your doctor will perform a blood test to calculate the dose of FERINJECT you require.

All medicines have risks and benefits. Your doctor has weighed the risks of using FERINJECT against the benefits this medicine is expected to have for you.

2. What should I know before I use FERINJECT?

Warnings

Always check the ingredients to make sure you can use this medicine.

Do not use FERINJECT if:

- you are allergic to ferric carboxymaltose, or any of the ingredients listed at the end of this leaflet.
- if you have anaemia **not** caused by iron deficiency.
- if you have iron overload (too much iron in your body) or disturbances in utilisation of iron.

Check with your doctor if you:

- take any medicines for any other condition.
- have an infection, asthma, eczemas, allergies or liver disorders.
- you are pregnant or breastfeeding.
- if your doctor has told you that you have, or have had low levels of phosphate in the blood.

Intravenous iron preparations can cause severe allergic reactions. These allergic reactions may include chest pain. Tell your doctor immediately if you experience it.

During treatment, you may be at risk of developing certain side effects. It is important you understand these risks and how to monitor for them. See additional information under Section [6. Are there any side effects?](#)

Pregnancy and breastfeeding

Check with your doctor if you are pregnant or intend to become pregnant.

Talk to your doctor if you are breastfeeding or intend to breastfeed.

There is no efficacy or safety data on the use of FERINJECT in pregnancy before 16 weeks' gestation. Iron deficiency occurring in the first trimester of pregnancy can in many cases be treated with oral iron.

There is limited experience with the use of FERINJECT in women in pregnancy from 16 weeks' gestation). If iron treatment is needed in pregnancy, oral iron should be used where possible and FERINJECT only used where the benefit outweighs the risk.

Slow heartbeat may occur in unborn babies whose mothers have been administered intravenous iron due to allergic reactions in the mother.

Iron treatment including FERINJECT may worsen infection.

What if I am taking other medicines?

Tell your doctor, nurse, or pharmacist if you are taking any other medicines, including any medicines, vitamins, or supplements that you buy without a prescription from your pharmacy, supermarket, or health food shop.

If FERINJECT is given together with oral iron preparations, then these oral preparations will be less effective.

Important information about some of the ingredients of FERINJECT:

This medicinal product contains 5.5 mg (or 0.24 mmol) sodium per millilitre of undiluted solution and is to be taken into consideration by patients on a controlled sodium diet.

Check with your doctor, nurse, or pharmacist if you are not sure about what medicines, vitamins or supplements you are taking and if these affect FERINJECT.

3. How do I use FERINJECT?

FERINJECT will be administered in a setting where possible allergic reactions can receive appropriate and prompt treatment.

Your doctor will take responsibility for determining the appropriate dose and choosing the method, frequency, and duration of your treatment. You may be re-assessed after 4 weeks to determine whether you need more FERINJECT injections.

How much to take

Adults and adolescents aged 14 years and older:

Your doctor can administer FERINJECT by three possible routes: undiluted by injection, during haemodialysis, or diluted by infusion.

- by injection, you may receive up to 20 mL of FERINJECT, corresponding to 1000 mg of iron, once a week directly into the vein.
- if you are on dialysis, you may receive FERINJECT during a haemodialysis session via the dialyser. The maximum dose of FERINJECT during haemodialysis is 200 mg (4 mL).
- by infusion, you may receive up to 20 mL of FERINJECT, corresponding to 1000 mg of iron, once a week directly into the vein. Because FERINJECT is diluted with sodium chloride solution for the infusion, it may have a volume of up to 250 mL and appear as a brown solution.

Children and adolescents aged 1 to 13 years:

Your doctor can administer FERINJECT undiluted by injection or diluted by infusion.

- by injection, your child may receive up to 15 mL of FERINJECT, corresponding to 750 mg of iron, once a week directly into the vein.
- by infusion, your child may receive up to 15 mL of FERINJECT, corresponding to 750 mg of iron, once a week directly into the vein. Because FERINJECT is diluted with sodium chloride solution for the infusion, it may have a volume of up to 250 mL and appear as a brown solution.

If your child is on dialysis, FERINJECT should not be administered.

FERINJECT should not be given to children under 1 year.

Your or your child may receive two doses of FERINJECT with an interval of at least 7 days directly into the vein.

You will be observed for about 30 minutes by your doctor or nurse after each administration.

Overdose

Overdose can cause accumulation of iron in storage sites. Your doctor will monitor iron parameters such as serum ferritin and transferrin saturation to avoid iron accumulation.

The risk of accidental overdosing is minimal.

4. What should I know while using FERINJECT?

Things you should do

You should be aware that:

Intravenous iron preparations can cause severe allergic reactions. These allergic reactions may include chest pain. Tell your doctor immediately if you experience it.

Remind any doctor, nurse, dentist or pharmacist you visit that you are using FERINJECT.

In patients with liver disorders, iron status will be carefully monitored by the doctor to avoid iron overload.

Driving or using machines

Be careful before you drive or use any machines or tools until you know how FERINJECT affects you.

Looking after your medicine

FERINJECT will normally be stored for you by your doctor or the hospital. However, if you need to store FERINJECT,

- FERINJECT should be stored in the original package and should not be stored above 30° C. FERINJECT should not be refrigerated or frozen.
- Once a FERINJECT vial has been opened, it should be given immediately. After dilution with sodium chloride solution, the diluted solution should be given as soon as possible, if storage is necessary hold at 2 - 8°C for not more than 12 hours.

5. Are there any side effects?

All medicines can have side effects. If you or your child do experience any side effects, most of them are minor and temporary. However, some side effects may need medical attention.

See the information below and, if you need to, ask your doctor, nurse, or pharmacist if you have any further questions about side effects.

Less serious side effects

Less serious side effects	What to do
<p>Head related</p> <ul style="list-style-type: none"> • headache • dizziness • flushing • taste disturbance • pallor • anxiety <p>Skin related</p> <ul style="list-style-type: none"> • injection/infusion site reactions • long-lasting brown discoloration of the skin may occur due to leakage of the drug at the injection site • redness of skin (erythema) • rash • dermatitis <p>Blood related</p> <ul style="list-style-type: none"> • low blood phosphate levels which might cause your bones to become soft (hypophosphataemic osteomalacia) • increase of the liver enzyme alanine aminotransferase, increase of the liver enzymes aspartate aminotransferase, gamma-glutamyltransferase, blood lactate dehydrogenase and blood alkaline phosphatase <p>Stomach related</p> <ul style="list-style-type: none"> • nausea • vomiting • indigestion • wind • stomach pain • diarrhoea • constipation <p>Allergy related</p> <ul style="list-style-type: none"> • generally feeling unwell • tingling or numbness of the hands or feet • itchiness • hives (urticaria) • swelling of hands, ankles or feet <p>Heart related</p> <ul style="list-style-type: none"> • fast heart rate (tachycardia), • high blood pressure • low blood pressure 	<p>Speak to your doctor or nurse if you have any of these less serious side effects and they worry you.</p>

<p>Muscle and joint related</p> <ul style="list-style-type: none"> • muscle pain • muscle spasm • back pain • joint pain • pain in extremity <p>General</p> <ul style="list-style-type: none"> • fever • fatigue • influenza type illness • pain, chills and generally feeling unwell 	
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Serious side effects

Serious side effects	What to do
<p>Chest related</p> <ul style="list-style-type: none"> • chest pain which can be a sign of a potentially serious allergic reaction called Kounis syndrome <p>Head related</p> <ul style="list-style-type: none"> • feeling faint and fainting • loss of consciousness <p>Allergy related</p> <ul style="list-style-type: none"> • allergic reactions which sometimes can be life threatening: breathing difficulty, swelling, lightheadedness, fast heartbeat, sweating, and nausea (anaphylactic reactions) • wheeze 	<p>Call your doctor or nurse straight away or go straight to the Emergency Department at your nearest hospital if you notice any of these serious side effects.</p>

Tell your doctor, nurse, or pharmacist if you notice anything else that may be making you feel unwell.

Other side effects not listed here may occur in some people.

If any of the side effects becomes serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or nurse.

Reporting side effects

After you have received medical advice for any side effects you or your child experience, you can report side effects to the Therapeutic Goods Administration online at www.tga.gov.au/reporting-problems. By reporting side effects, you can help provide more information on the safety of this medicine.

Always make sure you speak to your doctor, nurse, or pharmacist before you decide to stop taking any of your medicines.

6. Product details

This medicine is only available with a doctor's prescription.

What FERINJECT contains

Active ingredient (main ingredient)	iron (as ferric carboxymaltose, an iron carbohydrate compound). The concentration of iron present in the product is 50 mg per milliliter.
Other ingredients (inactive ingredients)	sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment), and water for injection.

Do not take this medicine if you are allergic to any of these ingredients.

What FERINJECT looks like

FERINJECT, solution for injection/infusion is a dark brown, non-transparent solution.

FERINJECT is supplied in the following presentations:

- 2 mL of solution in a glass vial containing the equivalent of 100 mg of iron (AUST R: 162636),
- 10 mL of solution in a glass vial containing the equivalent of 500 mg of iron (AUST R: 162641), or
- 20 mL of solution in a glass vial containing the equivalent of 1000 mg of iron (AUST R: 289045).

Not all strengths may be marketed.

Who distributes FERINJECT

Supplied in Australia by:

Vifor Pharma Pty Ltd
655 Elizabeth Street
Melbourne VIC 3000
Australia
Tel: 1800 202 674

Supplied in New Zealand by:

Pharmacy Retailing
(trading as Healthcare Logistics)
58 Richard Pearce Drive, Airport Oaks
Mangere
Auckland 2022 New Zealand
Tel: 0800 996 312

This leaflet was prepared in July 2023.