NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Ferric Carboxymaltose Sandoz (ferric carboxymaltose) 50 mg/mL solution for injection

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. Ferric Carboxymaltose Sandoz is a dark brown, non-transparent, colloidal solution.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

Ferric Carboxymaltose Sandoz 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 Ferric Carboxymaltose Sandoz 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 Ferric Carboxymaltose Sandoz (>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	**Patient Body Weight**	
g/L	**35 kg to <70kg**	**70kg 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 Ferric Carboxymaltose Sandoz should be administered taking into consideration the following:

A single Ferric Carboxymaltose Sandoz administration should not exceed:

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

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

Renal impairment

A single maximum daily dose of 200 mg iron as Ferric Carboxymaltose Sandoz 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 ≥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

Ferric Carboxymaltose Sandoz must be administered only by the intravenous route:

- by bolus injection, or
- by infusion, or
- during a haemodialysis session undiluted directly into the venous limb of the dialyser.

Ferric Carboxymaltose Sandoz must not be administered by the subcutaneous or intramuscular route.

Intravenous injection:

Ferric Carboxymaltose Sandoz 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 Ferric Carboxymaltose Sandoz

Volume of Ferric Carboxymaltose Sandoz 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:

Ferric Carboxymaltose Sandoz 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, Ferric Carboxymaltose Sandoz must be diluted only in sterile 0.9% m/V sodium chloride solution as shown in **Table 3**. Note: For stability reasons, Ferric Carboxymaltose Sandoz 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 Ferric Carboxymaltose Sandoz for intravenous infusion

Ferric Carboxymaltose Sandoz	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

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

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

Ferric Carboxymaltose Sandoz 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 Ferric Carboxymaltose Sandoz is contraindicated in cases of:

- hypersensitivity to ferric carboxymaltose complex, to Ferric Carboxymaltose Sandoz 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 Ferric Carboxymaltose Sandoz 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 Ferric Carboxymaltose Sandoz 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 Ferric Carboxymaltose Sandoz 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 hypophosphataemia 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 Ferric Carboxymaltose Sandoz. Paravenous leakage of ferric carboxymaltose 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 Ferric Carboxymaltose Sandoz 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 Ferric Carboxymaltose Sandoz 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 Undesirable effects. 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 ferric carboxymaltose 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 Ferric Carboxymaltose Sandoz.

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 ferric carboxymaltose 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 ferric carboxymaltose in women in pregnancy beyond 16 weeks' gestation. A careful risk/benefit evaluation is required before use during pregnancy and Ferric Carboxymaltose Sandoz should not be used during pregnancy unless clearly necessary.

If the benefit of Ferric Carboxymaltose Sandoz 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 ferric carboxymaltose to human milk was negligible (≤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 ferric carboxymaltose 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. 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 **Table 4** 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 reported in completed clinical trials

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 (summarised in **Table 5** below):

Table 5: Adverse drug reactions reported in post-marketing surveillance

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 Disorder and Administration Site Conditions	Extravasation, infusion site discolouration, injection site discolouration

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 ferric carboxymaltose has been used in pregnancy.

Reporting suspected adverse effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems (Australia) or https://pophealth.my.site.com/carmreportnz/s/ (New Zealand).

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia) and 0800 POISON or 0800 764766 (New Zealand).

4.9. OVERDOSE

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

Administration of ferric carboxymaltose 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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: anti-anaemic preparation, ATC code: B03AC.

Chemical structure

The active substance of Ferric Carboxymaltose Sandoz 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:

$[FeO_x(OH)_y(H_2O)_z]_n$ $[\{(C_6H_{10}O_5)_m$ $(C_6H_{12}O_7)\}_l]_k$, where $n \approx 10^3$, $m \approx 8$, $l \approx 11$, and $k \approx 4$.

CAS number

1461680-64-7

Mechanism of action

Ferric carboxymaltose ferric carboxymaltosesolution 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). Ferric carboxymaltose 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 µg/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 ferric carboxymaltose than with orally administered comparators.

The phase III studies undertaken with ferric carboxymaltose 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 ferric carboxymaltose 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 ferric carboxymaltose 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 ferric carboxymaltose 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 ferric carboxymaltose 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 ferric carboxymaltose 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 ferric carboxymaltose treatment received 1 to 3 doses of ferric carboxymaltose 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 ferric carboxymaltose 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 ferric carboxymaltose-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 m^2. ferric carboxymaltose 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 ferric carboxymaltose 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 ferric carboxymaltose 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 ferric carboxymaltose subjects and 212 SMC subjects. The majority had mild anaemia (mean Hb 104 g/L in ferric carboxymaltose group and 102 g/L in control group). There were no serious adverse events assessed as related to ferric carboxymaltose. Based on these limited data and the lack of specific serious drug-related adverse reactions, the safety of single ferric carboxymaltose doses of 1,000 mg iron appeared equal to SMC.

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

IDA secondary to inflammatory bowel disease

The efficacy of infusions of ferric carboxymaltose 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 ≤110 g/L in combination with TSAT <20% and/or serum ferritin <100 µg/L. Patients were randomised in a 2:1 (ferric carboxymaltose: ferrous sulphate) ratio to receive 1 of 2 treatments: ferric carboxymaltose 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 ferric carboxymaltose group, 32.9 g/L oral iron group), the results of this study demonstrated that ferric carboxymaltose was non-inferior to ferrous sulphate. The non-inferiority criterion was lower limit of 95% CI of difference ferric carboxymaltose minus ferrous sulphate ≥–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 µg/L ferric carboxymaltose group, 38.6 µg/L oral iron group) and TSAT

(23.1% ferric carboxymaltose group, 29.2% oral iron group) demonstrated a successful repletion of the iron stores in patients treated with ferric carboxymaltose.

In another study (FER-IBD-07-COR), ferric carboxymaltose 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 ferric carboxymaltose 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 ≥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 µg/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 ferric carboxymaltose (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

	ferric carboxymaltose n=228	**Venofer® n=220**	**Difference [95% CI]**
Hb Response (increase ≥ 20g/L) at Week 12	65.8%	53.6%	12.2% [3.1%, 21.0%]
	missing n=7	missing n=8	
Hb<100 g/L – Wt 35-<70 kg	**n=59** 86.4%	**n=44** 75.0%	11.4% [-4.1%, 26.9%]
Hb<100 g/L – Wt ≥70 kg	**n=31** 90.3%	**n=24** 100.0%	-9.7% [-20.1%, 0.7%]
Hb≥100 g/L – Wt 35-<70 kg	**n=70** 75.7%	**n=78** 71.8%	3.9% [-10.2%, 18.1%]
Hb≥100 g/L – Wt ≥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 ferric carboxymaltose 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 ≤114 g/L, TSAT ≤25%, and serum ferritin ≤100 µg/L. Patients were randomised to receive either oral ferrous sulphate tablets (65 mg iron) 3 times daily for 6 weeks or weekly infusions of ferric carboxymaltose 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 ferric carboxymaltose patients and 6 ferrous sulphate patients, ferric carboxymaltose 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 ferric carboxymaltose 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 ≤25%, serum ferritin ≤100

μg/L, at least one post-baseline Hb assessment and confirmed diagnosis of heavy menstrual bleeding.

Post partum IDA

The safety and efficacy of ferric carboxymaltose 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 ferric carboxymaltose 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 ferric carboxymaltose 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 ferric carboxymaltose 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, ferric carboxymaltose was shown to be efficacious for the treatment of IDA in post partum subjects. In the first study (1VIT06011), the superiority of ferric carboxymaltose was demonstrated according to the primary efficacy endpoint (defined as Hb >120 g/L), with a greater proportion of patients in the ferric carboxymaltose 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 ferric carboxymaltose patients and one ferrous sulfate patient.

In the second study (1VIT03001), ferric carboxymaltose 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 ferric carboxymaltose 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 ferric carboxymaltose 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 ferric carboxymaltose groups compared with the oral iron groups.

In the third study (VIT-IV-CL-009), ferric carboxymaltose 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 ferric carboxymaltose 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 ferric carboxymaltose 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 ferric carboxymaltose 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 ferric carboxymaltose 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 ferric

carboxymaltose. Based on overall incidences and the lack of specific drug-related serious adverse reactions, the safety profiles of ferric carboxymaltose 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 ferric carboxymaltose than SMC in the two subgroups at 30 days (see Table 8).

Table 8: Efficacy of ferric carboxymaltose 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

	ferric carboxymaltose	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

ferric carboxymaltose: 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 1,000 mg for baseline haemoglobin 91-104 g/L or 1,500 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, randomized 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 (± 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 VO2 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 Ferric Carboxymaltose Sandoz.

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 ferric carboxymaltose 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 ferric carboxymaltose 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 ferric carboxymaltose 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

Ferric Carboxymaltose Sandoz 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 section 4.2 Dose and method of administration.

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.

6.3. SHELF LIFE

Shelf-life of the product as packaged for sale:

24 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. Store below 30 °C. Do not freeze.

For storage conditions after first opening and dilution of the medicine, see section 6.3 Shelf life.

6.5. NATURE AND CONTENTS OF CONTAINER

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

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

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

Not all presentations may be marketed.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

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

7. MEDICINE SCHEDULE

S4 – Prescription Medicine

8. SPONSOR

Australia:

Sandoz Pty Ltd
100 Pacific Highway
North Sydney, NSW 2060
Australia

Tel: 1800 726 369.

New Zealand:

Sandoz New Zealand Limited
12 Madden Street
Auckland 1010
New Zealand

Telephone: 0800 726 369

9. DATE OF FIRST APPROVAL

23/05/2024

10. DATE OF REVISION OF THE TEXT

N/A

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
N/A	New registration