For use in India only

Ferric Carboxymaltose Injection
100 mg/2mL, 500mg/10mL , 750mg/15 mL, 1000mg/20mL (50mg/mL)

FePink

To be sold by retail on the prescription of a registered medical practitioner only.

PRESCRIBING INFORMATION

1. GENERIC NAME

Ferric Carboxymaltose Injection 100 mg/2mL, 500mg/10mL, 750mg/15 mL, 1000mg/20mL (50mg/mL)

Composition

100 mg/2mL

Each mL contains Ferric Carboxymaltose
Equivalent to Elemental Iron 50mg Water for Injection IP q.s.

500 mg/10mL

Each mL contains 50 mg Iron as Ferric Carboxymaltose in water for injection

750 mg/15mL

Each mL contains 50 mg Iron as Ferric Carboxymaltose in water for injection

1000 mg/20 mL

Each mL contains 50 mg Iron as Ferric Carboxymaltose in water for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ferric carboxymaltose 50 mg iron/ml solution for injection/infusion.
Each 1 ml of solution contains 50 mg of iron as ferric carboxymaltose.

3. DOSAGE FORM AND STRENGTH

Solution for injection/infusion; 50 mg iron/ml

4. CLINICAL PARTICULARS

4.1. Indications

Ferric carboxymaltose is indicated for treatment of iron deficiency when oral iron preparations are ineffective or cannot be used. The diagnosis of iron deficiency must be based on laboratory tests.

4.2. Posology and Method of Administration

Monitor carefully patients for signs and symptoms of hypersensitivity reactions during and following each administration of Ferric carboxymaltose.

Ferric carboxymaltose should only be administered when staff trained to evaluate and manage anaphylactic reactions is immediately available, in an environment where full resuscitation facilities can be assured. The patient should be observed for adverse effects for at least 30 minutes following each Ferric carboxymaltose administration.

The posology of Ferric carboxymaltose follows a stepwise approach: [1] determination of the individual iron need, [2] calculation and administration of the iron dose(s), and [3] post-iron repletion assessments. These steps are outlined below:

Step 1: Determination of the iron need

The individual iron need for repletion using Ferric carboxymaltose is determined based on the patient's body weight and haemoglobin (Hb) level. Refer to Table 1 for determination of the iron need:

Table 1: Determination of the iron need

Hb		Patient body weight		
g/dL	**mmol/L**	**below 35 kg**	**35 kg to <70 kg**	**70 kg and above**
<10	<6.2	500 mg	1,500 mg	2,000 mg
10 to <14	6.2 to <8.7	500 mg	1,000 mg	1,500 mg
≥14	≥8.7	500 mg	500 mg	500 mg

Iron deficiency must be confirmed by laboratory tests.

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

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

A single Ferric carboxymaltose administration should not exceed:

- 15 mg iron/kg body weight (for administration by intravenous injection) or 20 mg iron/kg body weight (for administration by intravenous infusion)
- 1,000 mg of iron (20 mL Ferric carboxymaltose)

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

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 Ferric carboxymaltose 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 Table 1 above.

Special Population – patients with haemodialysis-dependent chronic kidney disease

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

Paediatric population

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

Method of administration

Ferric carboxymaltose must only be administered by the intravenous route:

- by injection, or
- by infusion, or
- During a haemodialysis session undiluted directly into the venous limb of the dialyser. Ferric carboxymaltose must not be administered by the subcutaneous or intramuscular route.

Intravenous injection

Ferric carboxymaltose may be administered by intravenous injection using undiluted solution. The maximum single dose is 15 mg iron/kg body weight but should not exceed 1,000 mg iron. The administration rates are as shown in Table 2:

Table 2: Administration rates for intravenous injection of Ferric carboxymaltose

Volume of Ferric carboxymaltose required	Equivalent 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 may be administered by intravenous infusion, in which case it must be diluted. The maximum single dose is 20 mg iron/kg body weight, but should not exceed 1,000 mg iron.

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

Volume of Ferric carboxymaltose required	Equivalent 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	-
>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

4.3. Contraindications

The use of Ferric carboxymaltose is contraindicated in cases of:

- Hypersensitivity to the active substance, to Ferric carboxymaltose or any of its excipients.
- Known serious hypersensitivity to other parenteral iron products.
- Anaemia not attributed to iron deficiency, e.g. other microcytic anaemia.
- Evidence of iron overload or disturbances in the utilization of iron.

4.4. Special Warnings and Precautions for Use

Hypersensitivity reactions

Parentally administered iron preparations can cause hypersensitivity reactions including serious and potentially fatal anaphylactic/anaphylactoid reactions. Hypersensitivity reactions have also been reported after previously uneventful doses of parenteral iron complexes.

The risk is enhanced for patients with known allergies including drug allergies, including patients with a history of severe asthma, eczema or other atopic allergy.

There is also an increased risk of hypersensitivity reactions to parenteral iron complexes in patients with immune or inflammatory conditions (e.g. systemic lupus erythematosus, rheumatoid arthritis).

Ferric carboxymaltose should only be administered when staffs trained to evaluate and manage anaphylactic reactions are immediately available, in an environment where full resuscitation facilities can be assured. Each patient should be observed for adverse effects for at least 30 minutes following each Ferric carboxymaltose administration. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately. Facilities for cardio respiratory resuscitation and equipment for handling acute anaphylactic/anaphylactoid reactions should be available, including an injectable 1:1000 adrenaline solution. Additional treatment with antihistamines and/or corticosteroids should be given as appropriate.

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 intravenous iron.

Hepatic or renal impairment

In patients with liver dysfunction, parenteral iron should only be administered after careful benefit/risk 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.

No safety data on hemodialysis-dependent chronic kidney disease patients receiving single doses of more than 200 mg iron are available.

Infection

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

Extravasation

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

Excipients

One mL of undiluted Ferric carboxymaltose contains up to 5.5 mg (0.24 mmol) of sodium. This has to be taken into account in patients on a sodium-controlled diet.

Paediatric population

The use of Ferric carboxymaltose has not been studied in children.

4.5. Drug Interactions

The absorption of oral iron is reduced when administered concomitantly with parenteral iron preparations. Therefore, if required, oral iron therapy should not be started for at least 5 days after the last injection of Ferric carboxymaltose.

4.6. Use in Special Populations (such as pregnant women, **lactating women, paediatric patients, geriatric patients etc.)**

Pregnancy

There are limited data from the use of Ferric carboxymaltose in pregnant women. A careful benefit/risk evaluation is required before use during pregnancy and Ferric carboxymaltose should not be used during pregnancy unless clearly necessary.

Iron deficiency occurring in the first trimester of pregnancy can in many cases be treated with oral iron. Treatment with Ferric carboxymaltose should be confined to the second and third trimester if the benefit is judged to outweigh the potential risk for both the mother and the foetus.

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.

Iron released from Ferric carboxymaltose can cross the placental barrier and that its use during pregnancy may influence skeletal development in the fetus.

Breast-feeding

Transfer of iron from Ferric carboxymaltose to human milk was negligible (≤1%). It is unlikely that Ferric carboxymaltose represents a risk to the breast-fed child.

Fertility

There are no data on the effect of Ferric carboxymaltose on human fertility. Fertility was unaffected following Ferric carboxymaltose treatment in animal studies.

4.7. Effects on Ability to Drive and Use Machines

Ferric carboxymaltose is unlikely to impair the ability to drive and use machines.

4.8. Undesirable Effects

The most commonly reported ADR is nausea followed by injection/infusion site reactions, hypophosphatemia, headache, flushing, dizziness and hypertension. Injection/infusion site reactions comprise several ADRs which individually are either uncommon or rare.

Table 4: Adverse drug reactions observed during clinical trials and post-marketing experience.

System Organ Class	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)	Rare (≥1/10000 to <1/1000)
Immune system disorders		Hypersensitivity	Anaphylactoid reactions
Metabolism and nutritional disorders	Hypophosphatemia		
Nervous system disorders	Headache, dizziness	Paraesthesia, dysgeusia	Loss of consciousness[1]
Psychiatric disorders			Anxiety[2]
Cardiac disorders		Tachycardia	
Vascular disorders	Flushing, hypertension	Hypotension	Phlebitis, syncope[2], presyncope[2]
Respiratory, thoracic and mediastinal disorders		Dyspnoea	Bronchospasm[2]
Gastrointestinal disorders	Nausea	Vomiting, dyspepsia, abdominal pain, constipation, diarrhoea	Flatulence
Skin and subcutaneous tissue disorders		Pruritus, urticaria, erythema, rash[3]	Angioedema[2], pallor[2], and face oedema[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[4]	Pyrexia, fatigue, chest pain, oedema peripheral, chills	Malaise, influenza like illness ((whose onset may vary from a few hours to several days) [2]
Investigations		Alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, blood lactate dehydrogenase increased, blood alkaline phosphatase increased	

[1]ADRs exclusively reported in the post-marketing setting.

[2]ADRs reported in the post-marketing setting which were also observed in the clinical setting.

[3]Includes the following preferred terms: rash (individual ADR determined to be uncommon) and rash erythematous, generalised, macular, maculo-papular, pruritic (all individual ADRs determined to be rare).

[4]Includes the following preferred terms: injection/infusion site -pain, -haematoma, -discolouration, -extravasation, -irritation, -reaction, (all individual ADRs determined to be uncommon) and -paraesthesia (individual ADR determined to be rare).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. To report Suspected Adverse Reactions, contact MSN Laboratories Private Limited at pharmacovigilance@msnlabs.com or through company website www.msnlabs.com->Contact us->Medical Enquiry/ to report a side effect.

4.9. Overdose

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 may assist in recognizing iron accumulation. If iron accumulation has occurred, treat according to standard medical practice, e.g. consider the use of an iron chelator.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of action

Ferric carboxymaltose solution for injection/infusion is a colloidal solution of the iron complex ferric carboxymaltose.

The complex is designed to provide, in a controlled way, utilizable iron for the iron transport and storage proteins in the body (transferrin and ferritin, respectively).

Red cell utilization of ^{59}Fe from radio-labeled Ferric carboxymaltose ranged from 91% to 99% in subjects with iron deficiency (ID) and 61% to 84% in subjects with renal anaemia at 24 days post-dose.

Ferric carboxymaltose treatment of patients with ID anaemia results in an increase in reticulocyte count and serum ferritin levels to within normal ranges.

5.2 Pharmacokinetic Properties

Positron emission tomography demonstrated that ^{59}Fe and ^{52}Fe from Ferric carboxymaltose was rapidly eliminated from the blood, transferred to the bone marrow, and deposited in the liver and spleen.

After administration of a single dose of Ferric carboxymaltose of 100 to 1,000 mg of iron in ID subjects, maximum total serum iron levels of 37 µg/mL up to 333 µg/mL are obtained after 15 minutes to 1.21 hours respectively. The volume of the central compartment corresponds well to the volume of the plasma (approximately 3 litres).

The iron injected or infused was rapidly cleared from the plasma, the terminal half-life ranged from 7 to 12 hours, the mean residence time (MRT) from 11 to 18 hours. Renal elimination of iron was negligible.

6. NONCLINICAL PROPERTIES

6.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeat dose toxicity and genotoxicity. Preclinical studies indicate that iron released from Ferric carboxymaltose does cross the placental barrier and is excreted in milk in limited, controlled amounts. In reproductive toxicology studies using iron replete rabbits Ferric carboxymaltose was associated with minor skeletal abnormalities in the fetus. In a fertility study in rats, there were no effects on fertility for either male or female animals. No long-term studies in animals have been performed to evaluate the carcinogenic potential of Ferric carboxymaltose. No evidence of allergic or immunotoxic potential has been observed. A controlled in- vivo test demonstrated no cross-reactivity of Ferric carboxymaltose with anti-dextran antibodies. No local irritation or intolerance was observed after intravenous administration.

7. DESCRIPTION

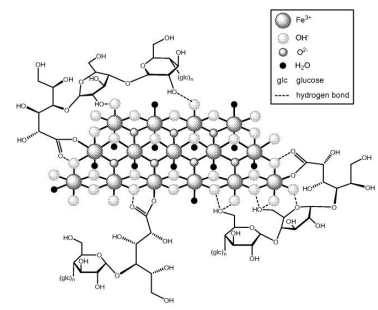
Ferric carboxymaltose, an iron replacement product, is an iron carbohydrate complex with the chemical name of polynuclear iron (III) hydroxide 4(R)-(poly-(1→4)-*O*-α-D-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate. It has a relative molecular weight of approximately 150,000 Da corresponding to the following 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 $k \approx 4$

(*l* represents the mean branching degree of the ligand).

The chemical structure is presented below:



8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

None

8.2 Packing Information

2 R Clear Glass Vial with 13 mm Grey Chlrobutyl Rubber Stopper
10 ml Clear Glass Vial with 20 mm Grey Chlorobutyl Rubber Stopper
15 R Clear Glass Vial with 20 mm Grey Chlorobutyl Rubber Stopper
20 R Clear Glass Vial with 20 mm Grey Chlorobutyl Rubber Stopper

8.3 Storage and Handling Instructions

Store at 20°C to 25°C.

9. PATIENT COUNSELING INFORMATION

- Question patients regarding any prior history of reactions to parenteral iron products.
- Advise patients of the risks associated with Ferric carboxymaltose.
- Advise patients to report any signs and symptoms of hypersensitivity that may develop during and following Ferric carboxymaltose administration, such as rash, itching, dizziness, lightheadedness, swelling and breathing problem.

10. DETAILS OF MANUFACTURER

MSN Laboratories Private Limited
(Formulations Division), Plot No. 42,
Anrich Industrial Estate, Bollaram,
Sangareddy District - 502 325,
Telangana, India.

B33382-01

11. DETAILS OF MANUFACTURING LICENCE NUMBER

38/MD/AP/2007/F/CC

12. DATE OF REVISION

October, 2023.