For the use of a Registered Medical Practitioner or a Hospital only

PRESCRIBING INFORMATION

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Ferric Carboxymaltose Injection 50 mg/mL

Redsh FCM 500 mg/10 ml

1. Generic Name
Ferric carboxymaltose injection 50 mg/mL

2. Qualitative and quantitative composition
Each mL contains:
Ferric Carboxymaltose equivalent to
Elemental Iron…….....50 mg
Water for Injection IP ……q.s.

3. Dosage form and strength
It is a Solution for injection with 50 mg iron/mL strength.

4. Clinical particulars
4.1 Therapeutic indications
Ferric carboxymaltose is indicated for the treatment of iron deficiency when:

- Oral iron preparations are ineffective.
- Oral iron preparations 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 Injection.

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.

<u>Posology</u>
The accurate determination of appropriate doses of Ferric carboxymaltose injection follows a stepwise approach:

- Determination of the individual iron need,
- Calculation and administration of the iron dose{s}), and
- 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	30 mg/kg body weight	1,500 mg	2,000 mg
10 to <14	6.2 to <8.7	15 mg/kg body weight	1,000 mg	1,500 mg
≥14	≥8.7	15 mg/kg body weight	500 mg	500 mg

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

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 injection should be administered taking into consideration the following:

A single Ferric carboxymaltose Injection 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 Injection)

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

<u>*Method of administration*</u>
Ferric carboxymaltose injection 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 injection can 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 injection

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). For further instructions on dilution of the medicinal product before administration.

Table 3: Dilution plan of Ferric carboxymaltose injection 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	No minimal prescribed time
>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 injection is contraindicated in cases of:

- hypersensitivity to the active substance, to Ferric carboxymaltose injection 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 utilisation of iron.

4.4 Special warnings and precautions for use
Hypersensitivity reactions
Parenterally 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. There have been reports of hypersensitivity reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction).

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 injection should only be administered when staff 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 injection 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 osteomalacia
Symptomatic hypophosphataemia leading to osteomalacia and fractures requiring clinical intervention including surgery has been reported in the post marketing setting. Patients should be asked to seek medical advice if they experience worsening fatigue with myalgias or bone pain.Serum phosphate should be monitored in patients who receive multiple administrations at higher doses or long-term treatment, and those with existing risk factors for hypophosphataemia. In case of persisting hypophosphataemia, treatment with ferric carboxymaltose should be re-evaluated.

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 haemodialysis-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 injection is stopped in patients with ongoing bacteraemia. 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 carboxymaltosei njection. Paravenous leakage of Ferric carboxymaltose injection at the administration site may lead to irritation of the skin and potentially long lasting brown discolouration at the site of administration. In case of paravenous leakage, the administration of Ferric carboxymaltose injection must be stopped immediately.

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

4.5 Drugs interactions
The absorption of oral iron is reduced when administered concomitantly with parenteral iron prepa-rations. Therefore, if required, oral iron therapy should not be started for at least 5 days after the last administration of Ferric carboxymaltose Injection.

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 injection in pregnant women. A careful benefit/risk evaluation is required before use during pregnancy and Ferric carboxymaltose injection 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 injection 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.

Animal data suggest that iron released from Ferric carboxymaltose injection can cross the placental barrier and that its use during pregnancy may influence skeletal development in the fetus.

Breast-feeding
Clinical studies showed that transfer of iron from Ferric carboxymaltose injection to human milk was negligible (1%). Based on limited data on breast-feeding women it is unlikely that Ferric carboxymaltose injection represents a risk to the breast-fed child.

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

4.7 Effects on ability to drive and use machines
Ferric carboxymaltose injection is unlikely to impair the ability to drive and use machines.

4.8 Undesirable effects
Table 4 presents the adverse drug reactions (ADRs) reported during clinical studies in which >9,000 subjects received Ferric carboxymaltose injection, as well as those reported from the post-marketing experience (see table footnotes for details).

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 anaphylactoid/anaphylactic reactions (rare); fatalities have been reported. See section 4.4 for further details.

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

System Organ Class	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Frequency not known[1]
Immune system disorders		Hypersensitivity	Anaphylactoid/ anaphylactic reactions	
Metabolism and nutritional disorders	Hypophosphataemia			
Nervous system disorders	Headache, dizziness	Paraesthesia, dysgeusia		Loss of consciousness[1]
Psychiatric disorders			Anxiety[2]	
Cardiac disorders		Tachycardia		Kounis syndrome[1]
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] distant skin discoloration	Face oedema[1] dermatitis
Musculoskeletal and connective tissue disorders		Myalgia, back pain, arthralgia, pain in extremity, muscle spasms		Hypopho-sphataemic, osteomalacia [1]
General disorders and administration site conditions	Injection/infusion site reactions[2]	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 aminotrans-ferase increased, aspartate aminotrans-ferase increased, gamma-glutamyltrans-ferase increased, blood lactate dehydrogenase Increased, blood alkaline phosphatase increased		

[1] ADRs exclusively reported in the post-marketing setting; estimated as rare.
[2] ADRs reported in the post-marketing setting which are 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, but is not limited to, 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).

Note: ADR = Adverse drug reaction.

4.9 Overdose

Administration of Ferric carboxymaltose injection 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 satura-tion may assist in recognising 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 is a colloidal iron (III) hydroxide in complex with carboxymaltose, acarbohydrate polymer that releases iron.

Ferric carboxymaltose injection is in a class of medications called iron replacement products. It works by replenishing iron stores so that the body can make more red blood cells.

5.2 Pharmacodynamic Properties

Pharmacotherapeutic group: Iron trivalent, parenteral preparation, ATC code: B03AC

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

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

Red cell utilisation of 59Fe from radio-labelled Ferric carboxymaltose injection 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 injection treatment results in an increase in reticulocyte count, serum ferritin levels and TSAT levels to within normal ranges.

Clinical efficacy and safety

The efficacy and safety of Ferric carboxymaltose injection has been studied in different therapeutic areas neces sitating intravenous iron to correct iron deficiency. The main studies are described in more detail below.

Cardiology

Chronic heart failure

Study CONFIRM-HF was a double-blind, randomised, 2-arm study comparing Ferric carboxymaltose injection (n=150) vs. placebo (n=151) in subjects with chronic heart failure and ID for a treatment period of 52 weeks. At Day 1 and Week 6 (comection phase), subjects received either Ferric carboxymaltose injection according to a simplified dosing grid using baseline Hb and body weight at screening, placebo or no dose. At Weeks 12, 24, and 36 (maintenance phase) subjects received Ferric carboxymaltose injection (500 mg iron) or placebo if serum ferritin was <100 ng/mL or 100-300 ng/mL with TSAT <20%. The treatment benefit of Ferric carboxymaltose injection vs. placebo was demonstrated with the primary efficacy endpoint, the change in the 6-minute walk test (EMWT) from baseline to Week 24 (33 +11 metres, p=0.002). This effect was sustained throughout the study to Week 52 (36 +11 metres, p<0.001). Study EFFECT-HF was an open-label (with blinded endpoint evaluation), randomised, 2-arm study comparing Ferric carboxymaltose injection (n=86) vs. standard of care (n=86) in subjects with chronic heart failure and ID for a treatment period of 24 weeks. At Day 1 and Week 6 (correction phase), subjects received either Ferric carboxymaltose injection according to a simplified dosing grid using baseline Hb and body weight at screening or standard of care. At Week 12, (maintenance phase) subjects received Ferric carboxymaltose injection (500 mg iron) or standard of care if serum ferritin <100 ng/mL or 100 to 300 ng/mL and TSAT <20%. The treatment benefit of Ferric carboxymaltose injection vs. standard of care was demonstrated with the primary efficacy endpoint, the change in weight-adjusted peak VO2 from baseline to Week 24 (LS Mean 1.04 ±0.44, p=0.02).

Nephrology

Haemodialysis-dependent chronic kidney disease

Study VIT-IV-CL-015 was an open-label, randomised parallel group study comparing Ferric carboxymaltose injection (n=97) to iron sucrose (n=86) in subjects with ID anaemia undergoing haemodialysis. Subjects received Ferric carboxymaltose injection or iron sucrose 2-3 times per week in single doses of 200 mg iron directly into the dialyser until the individually calculated cumulative iron dose was reached {mean cumulative dose of iron as Ferric carboxymaltose injection : 1,700 mg). The primary efficacy endpoint was the percentage of subjects reaching an increase in Hb of 21.0 g/dL at 4 weeks after baseline. At 4 weeks after baseline, 44.1% responded to treatment with Ferric carboxymaltose injection (i.e. Hb increase of ≥1.0 g/dL) compared to 35.3% for iron sucrose (p=0.2254).

Non-dialysis-dependent chronic kidney disease

Study 1VIT04004 was an open-label, randomised active-control study, evaluating the safety and efficacy of Ferric carboxymaltose injection (n=147) vs. oral iron (n=103). Subjects in the Ferric carboxymaltose injection group received 1,000 mg of iron at baseline and 500 mg of iron at days 14 and 28, if TSAT was <30% and serum ferritin was <500 ng/mL at the respective visit. Subjects in the oral iron arm received 65 mg iron TID as ferrous sulphate from baseline to day 56. Subjects were followed-up until day 56. The primary efficacy endpoint was the percentage of subjects achieving an increase in Hb of ≥1.0 g/dL anytime between baseline and end of study or time of intervention. This was achieved by 60.54% of subjects receiving Ferric carboxymaltose injection vs. 34.7% of subjects in the oral iron group (p<0.001). Mean haemoglobin change to day 56/end of study was 1.0 g/dL in the Ferric carboxymaltose injection group and 0.7 g/dL in the oral iron group (p=0.034, 95% CI: 0.0, 0.7).

Gastroenterology

Inflammatory bowel disease

SStudy VIT-IV-CL-008 was a randomised, open-label study which compared the efficacy of Ferric carboxymaltose injection vs. oral ferrous sulphate in reducing ID anaemia in subjects with inflammatory bowel disease (IBD). Subjects received either Ferric carboxymaltose injection (n=111)) in single doses of up to 1,000 mg iron once per week until the individually calculated iron dose (per Ganzoni formula) was reached (mean cumulative iron dose: 1,490 mg), or 100 mg iron BID as ferrous sulphate (n=49) for 12 weeks. Subjects receiving Ferric carboxymaltose injection showed a mean increase in Hb from baseline to Week 12 of 3.83 g/dL, which was non-inferior to 12 weeks of twice daily therapy with ferrous sulphate (3.75 g/dL, p=0.8016).

Study FER-IBD-07-COR was a randomised, open-label study comparing the efficacy of Ferric carboxymaltose injection vs. iron sucrose in subjects with remitting or mild IBD. Subjects receiving Ferric carboxymaltose injection were dosed according to a simplified dosing grid using baseline Hb and body weight in single doses up to 1,000 mg iron, whereas subjects receiving iron sucrose were dosed according to individually calculated iron doses using the Ganzoni formula in doses of 200 mg iron until the cumulative iron dose was reached. Subjects were followed-up for 12 weeks. 65.8% of subjects receiving Ferric carboxymaltose injection (n=240; mean cumulative iron dose: 1,414 mg) vs. 53.6% receiving iron sucrose (n=235; mean cumulative dose 1,207 mg; p=0.004) had responded at Week 12 (defined as Hb increase 22 g/dL). 83.8% of Ferric carboxymaltose injection -treated subjects vs. 75.9% of iron sucrose-treated subjects achieved a Hb increase 22 g/dL or had Hb within normal limits at Week 12 (p=0.019).

Women's health

Post partum

Study VIT-IV-CL-009 was a randomised open-label non-inferiority study comparing the efficacy of Ferric carboxymaltose injection (n=227) vs. ferrous sulphate (n=117) in women suffering from post-partum anaemia. Subjects received either Ferric carboxymaltose injection in single doses of up to 1,000 mg iron until their individually calculated cumulative iron dose (per Ganzoni formula) was reached, or 100 mg of iron as oral ferrous sulphate BID for 12 weeks. Subjects were followed-up for 12 weeks. The mean change in Hb from baseline to Week 12 was 3.37 g/dL in the Ferric carboxymaltose injection group (n=179; mean cumulative iron dose: 1,347 mg) vs. 3.29 g/dL in the ferrous sulphate group (n=89), showing non-inferiority between the treatments.

Pregnancy

Intravenous iron medicines should not be used during pregnancy unless clearly necessary. Treatment with Ferric carboxymaltose injection 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, see section 4.6.

Limited safety data in pregnant women are available from study FER-ASAP-2008-01, a randomised, open-label, study comparing Ferric carboxymaltose injection (n=121) vs. oral ferrous sulphate (n=115) in pregnant women in the second and third trimester with ID anaemia for a treatment period of 12 weeks. Subjects received Ferric carboxymaltose injection in cumulative doses of 1,000 mg or 1,500 mg of iron (mean cumulative dose: 1,029 mg iron) based on Hb and body weight at screening, or 100 mg of oral iron BID for 12 weeks. The incidence of treatment related adverse events was similar between Ferric carboxymaltose injection treated women and those treated with oral iron (11.4% Ferric carboxymaltose injection group; 15.3% oral iron group). The most commonly reported treatment-related adverse events were nausea, upper abdominal pain and headache. Newborn Apgar scores as well as newborn iron parameters were similar between treatment groups.

Paediatric population

Adolescents aged 14 years or older were included in 4 studies performed in adults. In addition, paediatric studies wereperformed in children and adolescents aged 1 to 17 years with iron deficiency anaemia. The most common aetiologiesfor iron deficiency anaemia were gastrointestinal diseases (e.g. inflammatory bowel disease, Helicobacter pylori gastritis,coeliacic disease) and heavy uterine bleeding.

In a prospective pharmacokinetic/pharmacodynamic phase 2 study (1VIT13036), 35 children at a median age of 9.8years (range: 1.5-17.5 years) were treated in 2 consecutive dose cohorts with single doses of Ferinject 7.5 mg iron/kgbody weight (n = 16) or Ferinject 15 mg iron/kg body weight (n = 19), at a maximum dose of 750 mg iron. Hb, ferritin andTSAT increased dose-dependently. On day 35 after injection, the mean (SD) increase in Hb was 1.9 (1.38) g/dL withFerinject 7.5 mg iron/kg and 2.8 (1.15) g/dL with Ferinject 15 mg iron/kg.

In a prospective, open-label, parallel-group phase 3 study (1VIT17044), efficacy and safety of Ferinject were comparedwith oral iron therapy. 40 children at a median age of 14.5 years (range:1 to 17 years) were treated with 2 doses ofFerinject 15 mg iron/kg body weight at a 7-day interval (maximum single dose 750 mg) and 39 children at a median ageof 14.0 years (range: 1 to 17 years) with oral ferrous sulphate for 28 days. A similar increase in Hb was observed afterboth treatment with Ferinject and treatment with oral iron sulphate. The increase in Hb from baseline to day 35 (LS Mean[95%CI]) was 2.22 [1.69, 2.75] g/dL after Ferinject and 1.92 [1.43, 2.41] g/dL after oral iron sulphate. In total, 87.5% ofpatients in the intravenous iron group achieved a Hb increase >1 g/dL at EOS. The increase in ferritin and TSAT, used asa measure for the replenishment of iron stores, was higher after Ferinject 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 Ferinjectand 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.

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.

5.3 Pharmacokinetic properties

Distribution

Positron emission tomography demonstrated that ^{52}Fe and ^{59}Fe from Ferric carboxymaltose injection 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 injection of 100 to 1,000 mg of iron in ID subjects, maximum total serum iron levels of 37 pg/mL up to 333 ug/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).

Elimination

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.

Paediatric population

The pharmacokinetic properties of Ferinject at a dose of 15 mg iron/kg were similar to those for adult patients with irondeficiency. Serum iron increased proportionally to the dose after a single dose of 7.5 mg iron/kg or 15 mg iron/kg. After asingle dose of Ferinject of 15 mg iron/kg body weight (maximum 750 mg), average maximum total serum iron values of310 µg/mL were measured after 1.12 hours. The terminal half-life was 9.8 hours, and the distribution volume estimatedby the population pharmacokinetic analysis was 0.42 to 3.14 l. Based on model-based simulations, the paediatricssubjects tended to have lower systemic exposure (lower AUC0-72h) 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)).

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

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 injection does cross the placental barrier and is excreted in milk in limited, controlled amounts. In reproductive toxicology studies using iron replete rabbits Ferric carboxymaltose injection 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 injection. No evidence of allergic or immunotoxic potential has been observed. A controlled in-vivo test demonstrated no cross-reactivity of Ferric carboxymaltose injection 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-a-Dglucopyranosyl)-oxy-(R),3(S),5(R),6-tetrahydroxy-hexanoate. It has a relative molecular weight of approximately 150,000 Da Ferric carboxymaltose injection is a dark brown, sterile, aqueous solution for intravenous injection.

8. Pharmaceutical particulars

8.1 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in this product.

The compatibility with containers other than polyethylene and glass is not known.

8.2 Shelf-life

Please see manufacturing date/expiry date printed on pack. Do not use the product after the expiry date which is stated on the packaging. The expiry date refers to the last day of that month.

8.3 Packaging information

Ferric carboxymaltose is available in 10 mL clear USP Type -1 glass vial packed in the carton along with a pack insert.

8.4 Storage and handing in structions

Store below 25°C. Do not freeze. Do not use the solution, if it contains any visible particulate matter or sediments. Unused portion of each vial should be discarded. Keep the medicine out of reach of children.

9. Patient Counselling Information

What is Ferric carboxymaltose injection?

Ferric carboxymaltose injection is a prescription iron replacement medicine used to treat IDA in adults who have:

- intolerance to oral iron or who have not responded well to treatment with oral iron, or
- non-dialysis dependent chronic kidney disease

It is not known if Ferric carboxymaltose injection is safe and effective for use in children.

Who should not receive Ferric carboxymaltose injection?

Do not receive Ferric carboxymaltose injection if you are allergic to ferric carboxymaltose or any of the ingredients in Ferric carboxymaltose injection.

See the end of this leaflet for a complete list of ingredients in Ferric carboxymaltose injection.

Before receiving Ferric carboxymaltose injection, tell your healthcare provider about all of your medical conditions, including if you:

- have had an allergic reaction to iron given into your vein
- have high blood pressure
- are pregnant or plan to become pregnant. It is not known if Ferric carboxymaltose injection will harm your unborn baby.
- are breastfeeding or plan to breastfeed. Ferric carboxymaltose injection passes into your breast milk. It is unknown whether Ferric carboxymaltose injection would pose a risk to your baby. Talk to your healthcare provider about the best way to feed your baby during treatment with Ferric carboxymaltose injection.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive Ferric carboxymaltose injection?

Ferric carboxymaltose injection is given intravenously (into your vein) by your healthcare provider in 2 doses at least 7 days apart or given as a single dose.

What are the possible side effects of Ferric carboxymaltose injection?

Ferric carboxymaltose injection may cause serious side effects, including:

- Allergic (hypersensitivity) reactions. Serious life-threatening allergic reactions have happened in people who receive Ferric carboxymaltose injection. Other serious reactions including itching, hives, wheezing, and low blood pressure also have happened during treatment with Ferric carboxymaltose injection. Tell your healthcare provider if you have ever had any unusual or allergic reaction to any iron given by vein.
- High blood pressure (hypertension). High blood pressure, sometimes with face flushing, dizziness, or nausea, has happened during treatment with Ferric carboxymaltose injection. Your healthcare provider will check your blood pressure and check for any signs and symptoms of high blood pressure after you receive Ferric carboxymaltose injection.

The most common side effects of Ferric carboxymaltose injection include:

- nausea
- high blood pressure
- flushing
- low levels of phosphorous in your blood
- dizziness
- injection site reaction
- skin redness

These are not all the possible side effects of Ferric carboxymaltose injection.
Call your doctor for medical advice about side effects.

General information about Ferric carboxymaltose injection

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your pharmacist or healthcare provider for information Ferric carboxymaltose injection that is written for health professionals.

What are the ingredients in Ferric carboxymaltose injection?

Active ingredient: ferric carboxymaltose

Inactive ingredients: water for injection, Sodium hydroxide and/or hydrochloric acid (to adjust pH).

Manufactured by:
CPL Pharmaceuticals Pvt. Ltd.
SPL-2, RIICO Industrial Area
Kaladawas Extension, Udaipur
RAJASTHAN, India.

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