Injecfer™

(Ferric Carboxymaltose Solution
for injection/infusion)

500mg Iron/10ml

COMPOSITION
Each 10ml vial contains:
Iron (as Ferric Carboxymaltose) 500mg
(Product complies to Innovator Specifications)

Dosage form and amount of active ingredient per unit
One vial of 10 ml contains iron carboxymaltose equivalent to 500 mg of iron.

INDICATIONS/POSSIBLE APPLICATIONS
Iron deficiency in adult patients for whom oral iron therapy is insufficiently effective, ineffective or impracticable, such as intolerance to oral iron supplements, inflammatory gastrointestinal diseases, e.g. ulcerative colitis, which can be aggravated by oral iron therapy, or refractory iron deficiency with suspicion of unreliable use of oral iron supplements. Iron as ferric carboxymaltose should only be administered if iron deficiency is diagnostically confirmed and confirmed by appropriate laboratory analyses (e.g., ferritin plasma levels, transferrin saturation (TSAT), haemoglobin (Hb), haematocrit, erythrocyte count, MCV and MCH).

DOSAGE/APPLICATION
During and after each application of Iron as ferric carboxymaltose, patients must be carefully monitored for signs or symptoms of hypersensitivity reactions.
Iron as ferric carboxymaltose should only be used if specialists trained in the detection and treatment of anaphylactic reactions are immediately available and cardio-pulmonary resuscitation is ensured by appropriate equipment. The patient should be monitored for at least 30 minutes after each Iron as ferric carboxymaltose administration for the occurrence of adverse reactions.
Adults
Dosage
The dosage of Iron as ferric carboxymaltose is determined in several steps:
[1] Determination of individual iron requirements,
[2] Calculation and administration of iron doses/doses, and
[3] Controls after replenishment of iron stores.
Step 1: Determine the iron requirement
The individual iron requirement to replenish iron stores with the help of Iron as ferric carboxymaltose can be determined on the basis of the patient's body weight and Hb level.
The determination of iron requirements should be determined using the Ganzoni formula (Table 1) or the simplified dosing regimen (Table 2).
For patients who require an individualized dose, such as those with anorexia nervosa, cachexia, obesity or pregnant women, the use of the Ganzoni formula is recommended.
The iron deficiency must be confirmed by laboratory tests as stated under "Indications/Possible applications".
Table 1: Determination of Iron Requirement Based on the Ganzoni Formula

Body weight (kg)	Hb (g/dl)			
	6	7,5	9	10,5
	ml Iron as ferric carboxymaltose (mg iron)			
30	18 ml (900 mg)	16 ml (800 mg)	14 ml (700 mg)	12 ml (600 mg)
35	24 ml (1200 mg)	22 ml (1100 mg)	20 ml (1000 mg)	16 ml (800 mg)

Body weight (kg)	Hb (g/dl)			
	6	7,5	9	10,5
	ml Iron as ferric carboxymaltose (mg iron)			
40	26 ml (1300 mg)	24 ml (1200 mg)	20 ml (1000 mg)	18 ml (900 mg)
45	28 ml (1400 mg)	26 ml (1300 mg)	22 ml (1100 mg)	18 ml (900 mg)
50	30 ml (1500 mg)	28 ml (1400 mg)	24 ml (1200 mg)	20 ml (1000 mg)
55	32 ml (1600 mg)	28 ml (1400 mg)	24 ml (1200 mg)	20 ml (1000 mg)
60	34 ml (1700 mg)	30 ml (1500 mg)	26 ml (1300 mg)	22 ml (1100 mg)
65	38 ml (1900 mg)	32 ml (1600 mg)	28 ml (1400 mg)	24 ml (1200 mg)
70	42 ml (2100 mg)	36 ml (1800 mg)	32 ml (1600 mg)	26 ml (1300 mg)
75	44 ml (2200 mg)	38 ml (1900 mg)	32 ml (1600 mg)	28 ml (1400 mg)
80	46 ml (2300 mg)	40 ml (2000 mg)	34 ml (1700 mg)	28 ml (1400 mg)
85	48 ml (2400 mg)	42 ml (2100 mg)	36 ml (1800 mg)	30 ml (1500 mg)
90	50 ml (2500 mg)	44 ml (2200 mg)	36 ml (1800 mg)	30 ml (1500 mg)

For body weight ≤ 66 kg, the calculated cumulative total dose should be rounded down to the nearest 100 mg of iron.
For body weight > 66 kg, the calculated cumulative total dose should be rounded up to the nearest 100 mg of iron.
Ganzoni Formula:

Total iron deficiency [mg] = cumulative total dose [mg] =
Body weight[A] [kg] x (Target Hb[B] - Is Hb)[C] [g/dl] x 2.4[D] + Spare iron[E] [mg]

A. It is recommended to use the ideal weight for overweight patients or before pregnancy for pregnant women. There are several ways to determine the ideal weight, e.g. by calculating the body weight that corresponds to a BMI of 25: Ideal weight = 25 * (height in meters)^2.
B. The standard target Hb in the Ganzoni formula is 15 g/dL. In special cases, such as pregnant women, a lower Hb target value can be considered.
Treatment success should be monitored using blood tests. In order to achieve the Hb target value, the cumulative iron dose may need to be adjusted.
C. To convert Hb [mM] to Hb [g/dl], multiply the Hb value [mM] by a factor of 1.61145.
D. Factor 2.4 = 0.0034 x 0.07 x 10 000.0.0034 : The iron content of Hb is 0.34%.
0.07: Blood volume 70 ml/kg body weight ≈ 7% of body weight.
10 000 = The conversion factor 1 g/dl = 10 000 mg/l.
E. For people weighing more than 35 kg, the amount of storage iron is 500 mg or more. Iron storage values of 500 mg correspond to the lower normal range for short women. To calculate the storage iron, some guidelines recommend using 10 to 15 mg of iron per kg of body weight.

Table 2: Determination of iron requirements based on the simplified dosing regimen

Hb		Body weight of the patient		
g/dl	mmol/l	under 35 kg	35 kg to < 70 kg	70 kg and more
< 10	< 6.2	500 mg	1500 mg	2000 mg
10 – < 14	6.2 – < 8.7	500 mg	1000 mg	1500 mg
≥14	≥8.7	500 mg	500 mg	500 mg

Step 2: Calculation and administration of the maximum iron dose/doses
Based on the determined iron requirement, Iron as ferric carboxymaltose should be administered in appropriate doses. The following applies:
A single dose of Iron as ferric carboxymaltose should not exceed the following levels:

- 15 mg iron/kg body weight (administered as IV injection) or

- 20 mg iron/kg body weight (administered as IV infusion)
- 1000 mg iron (20 ml Iron as ferric carboxymaltose)

The maximum recommended cumulative dose of Iron as ferric carboxymaltose is 1000 mg of iron (20 ml of Iron as ferric carboxymaltose) per week. If the cumulative iron dose exceeds 20 mg iron/kg body weight or 1000 mg iron as Iron as ferric carboxymaltose, the dose must be divided into two administrations, with an interval of at least one week between them.

Step 3: Checks after replenishment of iron stores

Depending on the patient's condition, the physician should carry out a new check-up (including blood tests). Hb levels should not be checked again until at the earliest four weeks after the last administration of Iron as ferric carboxymaltose to allow sufficient time for erythropoiiesis and iron utilization. If the patient requires further replenishment of iron stores, the iron requirement should be recalculated according to the Ganzoni formula or the simplified dosing regimen (see section "Properties/Effects").

METHOD OF ADMINISTRATION

Iron as ferric carboxymaltose must only be administered intravenously:

- as an injection or
- as an infusion or
- injected directly into the venous line of the dialysis machine during haemodialysis.

Iron as ferric carboxymaltose must not be administered subcutaneously or intramuscularly.

During and after each application of Iron as ferric carboxymaltose, patients must be carefully monitored for signs or symptoms of hypersensitivity reactions. Appropriate emergency treatment must be guaranteed.

Intravenous injection

Iron as ferric carboxymaltose can be administered as an IV injection using undiluted dispersion. The maximum permissible single dose is 15 mg iron/kg body weight, but must not exceed 1000 mg iron. The rates of administration are shown in Table 3:

Table 3: Administration rates for IV injection of Iron as ferric carboxymaltose

Required Iron as ferric carboxymaltc Volume			Corresponds to an iron dose			Administration rate/minimum administrati time
2	until	4 ml	100	until	200 mg	No minimum duration prescribed
> 4	until	10 ml	> 200	until	500 mg	100 mg iron/min
> 10	until	20 ml	> 500	until	1000 mg	15 minutes

Intravenous infusion

Iron as ferric carboxymaltose can be given as an IV infusion and must be diluted in this case. The maximum permissible single dose is 20 mg iron/kg body weight, but must not exceed 1000 mg iron. In the case of an infusion, Iron as ferric carboxymaltose should only be diluted with sterile 0.9% (m/V) saline, as shown in Table 4. Note: For stability reasons, Iron as ferric carboxymaltose must not be diluted to concentrations below 2 mg iron/ml (without taking into account the volume of iron carboxymaltose dispersion). For more information on dilution of the drug before administration, please refer to the section "Instructions for handling".

Table 4: Dilution regimen for Iron as ferric carboxymaltose with IV infusion

Required Iron as ferric carboxymaltose Volume			Corresponds to an iron do of			Maximum amount of sterile 0.9% (m/V) saline solution	Minimum administratio time
2	until	4 ml	100	until	200 mg	50 ml	No minimum duration prescribed
> 4	until	10 ml	> 200	until	500 mg	100 ml	6 minutes
> 10	until	20 ml	> 500	until	1000 mg	250 ml	15 minutes

Special dosing instructions

Children < 1 year old

The efficacy and safety of Iron as ferric carboxymaltose have not been studied in children < 1 year of age. Therefore, Iron as ferric carboxymaltose is not recommended for use in children in this age group.

Children ≥1 year and adolescents

Iron as ferric carboxymaltose is not approved for use in children and adolescents aged ≥1 to 18 years due to limited data. No dosage recommendation can be given. The currently available data in the paediatric population are described in the sections "Properties/effects", "Adverse reactions" and "Pharmacokinetics".

Patients with chronic kidney disease requiring haemodialysis

In patients with chronic kidney disease requiring haemodialysis, a maximum dose of 200 mg of iron injected once daily must not be exceeded.

The efficacy and safety of Iron as ferric carboxymaltose in children and adolescents with chronic renal disease requiring haemodialysis have not been studied. Therefore, Iron as ferric carboxymaltose is not recommended for use in children and adolescents with chronic renal disease requiring haemodialysis.

Patients with hepatic insufficiency

There is no experience with Iron as ferric carboxymaltose in hepatic insufficiency.

CONTRAINDICATIONS

The use of Iron as ferric carboxymaltose is contraindicated in the following cases:

- hypersensitivity to the active ingredient or to one of the excipients according to the composition;
- Severe known hypersensitivity to other parenteral iron preparations;
- anemia without confirmed iron deficiency;
- Proven iron overload;
- First trimester of pregnancy.

WARNINGS AND PRECAUTIONS

Hypersensitivity reactions

IV administration of parenteral iron supplements may cause acute immediate-type hypersensitivity reactions (anaphylactic reactions), which may be potentially lethal.

Such reactions have also been reported after previous administrations of parenteral iron preparations that were tolerated without complications. There are reports of hypersensitivity reactions that can progress to Kounis syndrome (acute allergic spasm of the coronary arteries that can lead to myocardial infarction). Treatment with Iron as ferric carboxymaltose should only be prescribed after careful indication by the attending physician.

Iron as ferric carboxymaltose should only be used if healthcare professionals who can evaluate and treat anaphylactic reactions are immediately available, and only in a facility where all resuscitation devices are available. Patients should be actively questioned prior to any administration of Iron as ferric carboxymaltose about previous adverse effects of IV iron supplements.

Typical symptoms of acute hypersensitivity reactions are: drop in blood pressure, tachycardia (up to anaphylactic shock), respiratory symptoms (bronchoobstruction, edema of the larynx and pharynx, etc.), abdominal symptoms (abdominal cramps, vomiting, etc.) or skin symptoms (urticaria, erythema, pruritus, etc.).

Patients should be observed for signs and symptoms of a hypersensitivity reaction during and for at least 30 minutes after administration of parenteral iron supplements. If allergic reactions or signs of intolerance occur during administration, treatment must be stopped immediately.

For emergency drug treatment of acute anaphylactic reactions, epinephrine is recommended first in accordance with current emergency guidelines and manufacturer information. Antihistamines and/or corticosteroids (later onset of action) only afterwards.

In rare cases, fever or allergic late reactions (delay of several hours to days) have been observed.

The risk of hypersensitivity reactions is increased in patients with known allergies including drug intolerance, history of severe asthma, eczema and other atopies, as well as in patients with immunological or inflammatory diseases (e.g. systemic lupus erythematosus, rheumatoid arthritis).

Hypophosphatemia/hypophosphatemic osteomalacia

Parenteral iron can lead to hypophosphatemia, which in most cases is transient and without clinical symptoms. In isolated cases, hypophosphatemia requiring treatment has been reported in patients, mainly with known risk factors and after sustained higher doses.

Post-marketing cases of symptomatic hypophosphatemia leading to hypophosphatemic osteomalacia and fractures have been reported, requiring clinical intervention, including surgery. In case of arthralgia or bone pain, patients should be instructed to seek medical advice.

Patients receiving multiple doses as part of long-term treatment and having underlying risk factors (e.g., vitamin D deficiency, calcium and phosphate malabsorption, secondary hyperparathyroidism, hereditary hemorrhagic telangiectasia, inflammatory bowel disease, and osteoporosis) should be monitored for hypophosphatemic osteomalacia, including serum

phosphate control. In case of persistent hypophosphatemia, treatment with Iron as ferric carboxymaltose should be reevaluated.

Hepatic or renal insufficiency

Patients with hepatic impairment should only be given parenteral iron after careful risk-benefit assessment.

Parenteral iron administration should be avoided in patients with hepatic impairment due to iron overload, especially porphyria cutanea tarda, as well as in any acute liver disease.

To avoid iron overload, careful monitoring of iron status is recommended.

Infections

In the case of acute or chronic infections, asthma, eczema or atopic allergies, parenteral iron should be administered with caution.

In patients with bacteremia, it is recommended that the administration of Iron as ferric carboxymaltose be discontinued.

Extravasation

Paravenous administration should be avoided. It can cause irritation of the skin and potentially long-lasting brown discoloration at the injection/infusion site. If this occurs, the administration of Iron as ferric carboxymaltose must be stopped immediately.

Other ingredients

Iron as ferric carboxymaltose contains up to 5.5 mg (0.24 mmol) of sodium per ml of undiluted solution, corresponding to 0.3% of the maximum dietary daily sodium intake of 2 g recommended by the WHO for an adult.

INTERACTIONS

Iron as ferric carboxymaltose should not be administered at the same time as oral iron preparations, as the absorption of orally administered iron may be reduced (see also "Indications/Possible uses").

PREGNANCY/BREASTFEEDING

Pregnancy

There are limited clinical data from controlled studies on the use of Iron as ferric carboxymaltose in pregnant women (see "Clinical efficacy"). Animal studies have shown evidence of reproductive toxicity (see "Preclinical data"). A careful risk-benefit assessment is required before use during pregnancy, as hypersensitivity reactions can lead to a particular risk to mother and child (see "Warnings and precautions").

Iron as ferric carboxymaltose is contraindicated in the first trimester of pregnancy (see "Contraindications") and should only be used in the 2nd and 3rd trimesters if absolutely indicated, whereby body weight before the onset of pregnancy should be used to calculate the amount of iron required in order to avoid a possible overdose. When administered during pregnancy, special attention should be paid to signs of hypersensitivity reactions.

After parenteral iron administration, fetal bradycardia can occur. This is usually temporary and occurs as a result of a hypersensitivity reaction in the mother. The unborn infant should be carefully monitored during an IV administration of parenteral iron supplements to pregnant women.

Nursing period

There is little clinical experience for use during breastfeeding. A clinical study has shown that the transfer of iron from Iron as ferric carboxymaltose into breast milk is negligible (≤ 1%). It is therefore unlikely that Iron as ferric carboxymaltose poses a risk to the infant being breastfed.

Fertility

There are no clinical data on the effect of Iron as ferric carboxymaltose on fertility. In animal studies, treatment with Iron as ferric carboxymaltose showed no effect on fertility (see "Preclinical data").

EFFECT ON DRIVING ABILITY AND ON THE OPERATION OF MACHINES

No corresponding studies have been carried out. Iron as ferric carboxymaltose is unlikely to have any effect on driving ability and on the operation of machines.

UNDESIRABLE EFFECTS

The following adverse reactions have occurred in clinical trials in which 9456 adult patients and 82 children ≥1 year of age and adolescents received Iron as ferric carboxymaltose and in the post-marketing experience.

Frequencies of side effects:

Common: < 1/10, ≥1/100

Uncommon: < 1/100, ≥1/1000

Rare: < 1/1000, ≥1/10 000

Not known: frequency cannot be estimated on the basis of the available data

The most commonly reported adverse drug reactions (ADRs) are nausea, injection/infusion site reactions, hypophosphatemia, headache, flushing of the face, dizziness and hypertension.
Injection/infusion site reactions include various ADRs, each of which occurs occasionally or rarely.
The main serious ADRs associated with Iron as ferric carboxymaltose are occasional hypersensitivity reactions (see "Immune system disorders").
The most serious ADRs were anaphylactic reactions (rare); deaths have been reported.
In subjects who showed a decrease in serum phosphate in clinical trials, the lowest levels were measured after about 2 weeks, and in most cases, levels returned to baseline values 12 weeks after treatment with Iron as ferric carboxymaltose.
The safety profile in children and adolescents aged 1-17 years was investigated in the following studies:
In a prospective pharmacokinetic/pharmacodynamic phase 2 study (1VIT13036), 35 children in consecutive dose cohorts were treated with IV single doses of Iron as ferric carboxymaltose 7.5 mg iron/kg (n=16) and Iron as ferric carboxymaltose 15 mg iron/kg (n=19) (maximum dose 750 mg iron). There were no unexpected ADRs compared to adults. The most common ADRs were 2 cases each of pyrexia and rash with Iron as ferric carboxymaltose 7.5 mg iron/kg, 3 cases each of rhinorrhea and urticaria, and 2 cases each of hyperthermia and upper respiratory tract infection with Iron as ferric carboxymaltose 15 mg iron/kg.
In a prospective, open-label, parallel-group phase 3 study (1VIT17044), 40 children were treated with 2 doses of Iron as ferric carboxymaltose at 15 mg iron/kg each at 7 days apart (maximum single dose 750 mg). There were no unexpected ADRs compared to adults. The most common ADRs after IV therapy with Iron as ferric carboxymaltose were hypophosphatemia/decreased serum phosphate (n=5), vomiting (n=2), headache (n=2), and urticaria (n=2). Laboratory chemistry showed potentially clinically relevant hypophosphatemia in 8 patients treated with Iron as ferric carboxymaltose (including 4 of the reported ADRs). The lowest phosphate levels were usually measured 2 weeks after initiation of therapy, and largely normalized by day 35 after initiation of treatment. All cases of hypophosphatemia were asymptomatic.
For more information, see "Warnings and precautions".
Diseases of the immune system
Occasionally: Immediate-type hypersensitivity reactions (anaphylactic reactions), which may be lethal (see "Warnings and precautions"). Symptoms of anaphylactic reactions include circulatory collapse, drop in blood pressure, tachycardia, respiratory symptoms (bronchoobstruction, edema of the larynx and pharynx, etc.), abdominal symptoms (abdominal cramps, vomiting, etc.) or skin symptoms (urticaria, erythema, pruritus, etc.).
Metabolic and nutritional disorders
Frequently: Hypophosphatemia (based on laboratory findings).
Psychiatric disorders
Seldom: Fear.
Diseases of the nervous system
Frequently: Headaches, dizziness.
Occasionally: Disturbance of taste sensation (dysgeusia), paresthesia.
Not known: Loss of consciousness.
Heart disease
Occasionally: Tachycardia.
Vascular diseases
Frequently: Hypertension, flushing of the face.
Occasionally: Hypotension.
Seldom: Presyncope, syncope, phlebitis.
Diseases of the respiratory, thoracic cavity and mediastinum
Occasionally: Dyspnea.
Seldom: Bronchospasms.
Diseases of the gastrointestinal tract
Frequently: Nausea.
Occasionally: Abdominal pain, vomiting, constipation, diarrhea, dyspepsia.
Rare: Flatulence.
Liver and Biliary Disorders
Occasionally: Increase in alanine aminotransferase (ALT), increase in aspartate aminotransferase (AST), increase in gamma-glutamyltransferase (γ-GT), increase in alkaline phosphatase (AP), increase in lactate dehydrogenase (LDH).
Diseases of the skin and subcutaneous tissue
Occasionally: rash (rash; includes the following symptoms: rash erythematous, generalized, macular, maculo-papular and itchy), pruritus, urticaria, redness of the skin (erythema).
Seldom: Angioedema, discoloration of distant skin areas, pallor.

Not known: dermatitis, facial edema.

Skeletal muscle, connective tissue and bone diseases

Occasionally: Arthralgia, myalgia, body aches, back pain, muscle spasms.

Not known: Hypophosphatemic osteomalacia.

General diseases and administration site complaints

Frequently: Injection/infusion site reactions (includes the following symptoms: pain, hematomas, discoloration (potentially long-lasting), extravasate, irritation, reaction, injection/infusion site phlebitis, and injection/infusion site paresthesia).

Occasionally: Fever, fatigue, chills, chest pain, peripheral edema, pain, malaise.

Seldom: Flu-like symptoms (which can start within a few hours or several days).

REPORTING OF SUSPECTED ADVERSE REACTIONS

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at pv@searlecompany.com

OVERDOSING

Accidentally exceeding the cumulative total dose necessary to correct iron deficiency can lead to iron accumulation in iron stores and ultimately hemosiderosis in these patients. This can be prevented by preventive control of the iron parameters serum ferritin and transferrin saturation. Unwanted iron accumulation must be treated according to standard medical practice.

PROPERTIES/EFFECTS

In Iron as ferric carboxymaltose, iron is present in trivalent form as a macromolecular complex with carboxymaltose (pH 5-7).

ATC code

B03AC

Action

After IV administration, the iron carboxymaltose complex is predominantly absorbed by the reticuloendothelial system of the liver, bone marrow and spleen. Iron is mainly used to build up hemoglobin, but also myoglobin and iron-containing enzymes, and is also stored as depot iron in the liver.

PHARMACODYNAMICS

In the Iron as ferric carboxymaltose dispersion, iron is present as a stable trivalent iron in the form of a complex of polynuclear iron(III) hydroxide with a carbohydrate polymer, which provides usable iron for the iron transport and storage proteins in the body (transferrin and ferritin).

In a study with ^{59}Fe and ^{52}Fe-labeled Iron as ferric carboxymaltose showed a utilization of 61 to 99% in the red blood cells after 24 days in six patients with iron deficiency anemia or renal anemia. In patients with iron deficiency anemia, utilization was 91 to 99%, in patients with renal anemia 61 to 84%.

CLINICAL EFFICACY

Nephrology

Chronic renal insufficiency that does not require dialysis

In 250 patients, a comparative study of Iron as ferric carboxymaltose versus orally administered iron sulfate was carried out in chronic renal failure not requiring dialysis.

The primary efficacy endpoint (Hb increase of ≥1 g/dL) was met by 60.4% (87/144) with Iron as ferric carboxymaltose versus 34.7% (35/101) with oral iron-treated patients.

A significant result was only shown in female patients with a baseline ferritin value of < 100 ng/ml.

Chronic renal insufficiency requiring dialysis

In a comparative study (n=237) in patients requiring dialysis, Venofer or Iron as ferric carboxymaltose (equivalent to 200 mg iron) was administered into the venous arm of the dialysis machine during dialysis (2-3x/week) until the cumulative total dose calculated according to the Ganzoni formula was reached (maximum 4 weeks). The primary endpoint was response with an Hb increase of 1 g/dl. Over 60% of the patients were treated with EPO (evenly distributed between both groups). The response under treatment with Iron as ferric carboxymaltose was 46.4% vs. 37.2% with Venofer.®

Women's Health

Postpartum

In postpartum/postoperative anemia, three comparative studies against oral iron administration were conducted, one in Europe (n=286, 2:1 randomized), two in the USA (n=337, 1:1 randomized and n=289, 1:1 randomized).
In a US study, 88.8% of patients with Iron as ferric carboxymaltose achieved an Hb value of > 12 g/dl and 66.2% with oral iron administration within a period of 42 days. In the other two studies, treatment with Iron as ferric carboxymaltose was not inferior to oral iron administration. However, both an Hb increase of 3 g/dl with Iron as ferric carboxymaltose and a normalization of Hb with a simultaneous increase in storage iron (ferritin) were significantly more frequent with Iron as ferric carboxymaltose.
Severe uterine bleeding
In patients with iron deficiency anaemia due to severe uterine bleeding, Iron as ferric carboxymaltose has been studied in comparison with oral administration of ferrous sulphate.
The primary endpoint was Hb increase > 2.0 g/dl. This was achieved in 82% with Iron as ferric carboxymaltose and 61.8% with oral iron.
Pregnancy
In a randomized, two-arm, open-label study in pregnant women in the second and third trimesters with iron deficiency anemia, Iron as ferric carboxymaltose (n=121) was compared in 1-3 administrations up to week 3 (mean cumulative dose 1029 mg) and oral ferrous sulfate (n=115) (100 mg twice daily with a median treatment duration of 65 days). The difference in the increase in mean Hb from baseline to week 3 (primary endpoint) was 0.27 g/dl in favor of Iron as ferric carboxymaltose (p=0.274); by week 6, this difference was 0.43 g/dl (p=0.032). The Apgar scores and iron parameters of the newborns in the treatment groups were comparable.
Gastroenterology
Inflammatory bowel disease
In iron deficiency anaemia in the context of chronic intestinal diseases (Crohn's disease, ulcerative colitis), Iron as ferric carboxymaltose was administered as an infusion 1x/week (up to the cumulative total dose) compared to oral iron substitution. The primary endpoint was the change in Hb at week 12 compared to baseline. Iron as ferric carboxymaltose was not inferior to ferrous sulfate therapy in terms of primary endpoint.
Compared to ferrous sulphate, Iron as ferric carboxymaltose achieved a faster therapeutic success: at week 4, 34.2% patients in the Iron as ferric carboxymaltose group vs. 18.2% in the oral ferrous sulphate group achieved an Hb increase of > 2 g/dl, with a statistically significant difference. Reticulocyte counts peaked at week 2 in both treatment groups. With Iron as ferric carboxymaltose, statistically significantly higher ferritin levels were achieved from week 2 onwards than in the iron sulphate group.
Monitoring ferritin levels after replacement therapy
Limited data are available from the VIT-IV-CL-008 study showing that ferritin levels drop sharply between 2–4 weeks after replacement therapy; after that, its decline slows down. The mean ferritin level did not decrease to a level that might have given reason to consider renewed therapy during the 12-week follow-up. The available data therefore do not clearly indicate an optimal time to re-examine ferritin levels. However, checking the ferritin level before the end of the 4 weeks after replacement therapy appears to be premature. It is therefore recommended that the physician carry out a new check of the ferritin level, depending on the condition of the respective patient.
Children and adolescents aged 1-17 years
In a prospective pharmacokinetic/pharmacodynamic phase 2 study (1VIT13036), 35 children in consecutive dose cohorts were treated with IV single doses of Iron as ferric carboxymaltose 7.5 mg iron/kg (n=16) and Iron as ferric carboxymaltose 15 mg iron/kg (n=19) (maximum dose 750 mg iron). On day 35 after injection, the mean increase (SD) in haemoglobin was 1.9 (1.38) g/dl below 7.5 mg iron/kg and 2.8 (1.15) g/dl below 15 mg iron/kg. Ferritin and transferrin saturation also increased in a dose-dependent manner.
The efficacy and safety of IV Iron as ferric carboxymaltose were compared with oral iron therapy in a prospective, open-label, parallel-group phase 3 study (1VIT17044). 40 children with iron deficiency anaemia of different etiologies received 2 doses of Iron as ferric carboxymaltose of 15 mg iron/kg each at an interval of 7 days (maximum single dose 750 mg) and 39 children received oral iron sulphate for 28 days. 7 children who did not respond adequately to oral iron therapy were also treated with 2 doses of Iron as ferric carboxymaltose in a single-arm extension study (1VIT18045).
In the main study, there was a clinically relevant increase in hemoglobin in both treatment arms. The mean increase in hemoglobin (LS Mean) was 2.22 g/dl (95% CI 1.69, 2.75) after Iron as ferric carboxymaltose and 1.92 g/dl (95% CI 1.43, 2.41) after oral iron therapy, with no statistically significant difference between treatment groups. Thus, the primary endpoint of the study was not met. The increase in the secondary endpoints ferritin and transferrin saturation was higher with Iron as ferric carboxymaltose than after oral iron therapy. In the extension study, the mean Hb increase (SD) from the end of the main study was 0.7 (1.19) g/dl.

PHARMACOKINETICS

Absorption

Not applicable.

Distribution

After a single dose of Iron as ferric carboxymaltose of 100 to 1000 mg iron in patients with iron deficiency, maximum total serum iron levels of 37 µg/ml to 333 µg/ml were measured at 15 minutes and 1.21 hours, respectively. The volume of distribution of the central compartment corresponds to the plasma volume (about 3 liters).

Using positron emission tomography (PET), it was shown that iron from radioactively labeled Iron as ferric carboxymaltose was eliminated from the blood, transported into the bone marrow and into the reticuloendothelial system of the liver and spleen.

Metabolism

Iron carboxymaltose is mainly absorbed in the reticuloendothelial system of the liver, bone marrow and to a lesser extent also in the spleen and is broken down into the components iron hydroxide and carbohydrates, whereby the iron is bound as ferritin. According to the needs, the iron is made available to erythropoiesis via transferrin. The carbohydrate breakdown products are maltotetraose, maltotriose, maltose and glucose.

Elimination

Plasma clearance of the administered iron was rapid with a terminal half-life of 7 to 12 hours and a mean residence time (MVD) of 11 to 18 hours. Renal elimination of iron was negligible.

Kinetics of special patient groups

Children and adolescents aged 1-17 years

The pharmacokinetics of IV iron carboxymaltose were evaluated at single doses in pediatric patients ≥1 year with iron deficiency anemia in the Phase 2 pharmacokinetic/pharmacodynamic study 1VIT13036 and supplemented by population pharmacokinetic analyses including additional sparse pharmacokinetic samples from the Phase 3 clinical trial 1VIT17044. The pharmacokinetic properties at the dosage of 15 mg iron/kg (maximum single dose 750 mg) were similar to those for adult patients with iron deficiency treated with the recommended adult dosage. Serum iron increased dose-proportionally at single doses of 7.5 mg iron/kg and 15 mg iron/kg. After a single dose of Iron as ferric carboxymaltose of 15 mg iron/kg body weight (maximum 750 mg), mean maximum total serum iron values of 310 µg/ml were measured after 1.12 hours. The terminal half-life was 9.8 hours, and the volume of distribution estimated by population pharmacokinetic analysis was 0.42 to 3.14 L.

Hepatic insufficiency

No studies have been conducted in hepatic insufficiency.

PRECLINICAL DATA

Based on the conventional studies on safety pharmacology, repeated dose toxicity and genotoxicity, the preclinical data do not indicate any particular hazards for humans.

Toxicity

The highest single non-lethal intravenous dose in rodents was 1000 mg iron/kg body weight.

Carcinogenicity

No long-term studies in animals have been conducted to assess the carcinogenic potential of Iron as ferric carboxymaltose.

Reproductive toxicity

In a fertility study in rats, no effects on the fertility of male or female animals were found.

In studies of reproductive toxicity in rabbits (without iron deficiency), Iron as ferric carboxymaltose was associated with minor skeletal abnormalities in the fetus at maternal toxic doses. These effects are considered transient as no findings were recorded in prenatal/postnatal development.

Preclinical studies suggest that the iron released from Iron as ferric carboxymaltose crosses the placental barrier and is excreted in human milk in limited, controlled amounts.

More data

There is no evidence of an allergenic or immunotoxic potential. A controlled in vivo test showed no cross-reactivity of Iron as ferric carboxymaltose with anti-dextran antibodies. After IV administration, no local irritation or intolerance was observed.

Other notes

Incompatibilities

Iron as ferric carboxymaltose must only be mixed with sterile 0.9% m/V saline solution. There are no compatibility studies with containers made of materials other than polyethylene or glass.

Influencing diagnostic methods

None known.

Durability
Iron as ferric carboxymaltose may only be used up to the date marked "EXP" on the package.
Shelf life after opening the vial:
From a microbiological point of view, the preparation should be used immediately.
Shelf life after dilution with sterile 0.9% saline:
For microbiological reasons, the infusion solution should be administered as soon as possible after preparation (after dilution). The dilute Iron as ferric carboxymaltose solution has been shown to be chemically stable for 12 hours at room temperature.
Special storage instructions
Prescribed storage conditions: Do not store above 30 °C in the original package. Do not freeze. Keep out of reach of children.
Instructions for handling
The vials must be checked for visible particles and damage before use. Only dispersions that are homogeneous and free of visible particles may be administered.
The vials are for single use. Any unused medicinal product or waste material must be disposed of in accordance with national requirements.
Iron as ferric carboxymaltose IV should only be mixed with sterile 0.9% (m/V) sodium chloride solution. Other intravenous dilution solutions and drugs must not be used because of the risk of sedimentation and/or interactions. For information on dilution, see "Dosage/Administration".

PRESENTATION
Injecfer 500mg/10ml injection is available in a pack of 1's vial.

INSTRUCTIONS
To be sold on the prescription of a registered medical practitioner only.
Do not store and transport above 30°C.
Protect from excessive heat and sunlight.
Keep all medicines out of sight and reach of children.
Do not freeze.
Injection should not be used if container is leaking, solution is cloudy or
it contains un-dissolved particle(s).
For intravenous use only.

REGISTRATION NUMBER : 125175

Manufactured by:
MTI Medical (Pvt) Ltd.,
Plot No. 586-587, Sundar Industrial
Estate, Lahore - Pakistan.
M.L. 000801

Marketed by:
The Searle Company Limited,
F-319, S.I.T.E., Karachi-Pakistan.
M.L. 000016

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Innovator Link: https://compendium.ch/product/1080876-ferinject-inj-inf-prap-500-mg-10ml\