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UAE and Oman SmPC

Ferinject®

Composition

Active substances

Iron as ferric carboxymaltose

Excipients

Sodium hydroxide, hydrochloric acid, water for injection to make up the solution

Pharmaceutical form and active substance quantity per unit

Solution for intravenous administration.
1 ml of solution contains ferric carboxymaltose corresponding to 50 mg of iron
One 2 ml vial contains ferric carboxymaltose corresponding to 100 mg of iron
One 10 ml vial contains ferric carboxymaltose corresponding to 500 mg of iron
One 20 ml vial contains ferric carboxymaltose corresponding to 1000 mg of iron

Indications/Uses

Iron deficiency in adult patients in whom oral iron therapy is not sufficiently effective, is ineffective or cannot be undertaken, such as cases where oral iron preparations cannot be tolerated or in the presence of inflammatory gastrointestinal diseases, e.g. ulcerative colitis, which may be exacerbated by oral iron therapy, or in the case of treatment-refractory iron-deficiency states where it is suspected that the oral iron preparations are being taken unreliably. Ferinject should only be administered if the diagnosis of iron deficiency has been established and confirmed through appropriate laboratory investigations (e.g. plasma ferritin levels, transferrin saturation (TSAT), haemoglobin, haematocrit, red cell count, MCV and MCH).

Dosage/Administration

During and after each use of Ferinject, patients must be carefully monitored for signs or symptomps of hypersensitivity reactions.

Ferinject should only be used if professionals trained in recognising and treating anaphylactic shock are immediately available, and if cardio-pulmonary resuscitation can be ensured by appropriate equipment. The patient should be observed for side effects for at least 30 minutes every time Ferinject is administered (see Warnings and Precautions for Use).

Adults Dosage

The dosage of Ferinject is determined in several stages: [1] Determination of individual iron requirements, [2] Calculation and administration of iron doses(s) and [3] Checks after replenishment of iron stores.

Step 1: Calculating the amount of iron required
The individual amount of iron needed to replenish iron stores by means of Ferinject can be determined on the basis of the patients body weight and haemoglobin (Hb) level. Iron requirements should be determined using the Ganzoni formula (Table 1) or the simplified dosing regimen (Table 2).
Use of the Ganzoni formula is recommended for patients who require a dose adjusted to their individual needs, such as patients with anorexia nervosa, cachexia, obesity or pregnant women. Iron deficiency must be confirmed by laboratory tests as indicated under Indications / Uses.

Table1: Determining iron requirements based on the Ganzoni formula

Body weight (kg)	**Hb (g/dL)**			
	6	7.5	9	10.5
	ml Ferinject (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)
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)

Hb = Haemoglobin

For body weight ≤ 66 kg the calculated total cumulative dose should be rounded down to the nearest 100 mg iron.

For body weight > 66 kg the calculated total cumulative dose should be rounded up to the nearest 100 mg iron.

Ganzoni formula:

Total iron deficit [mg] = total cumulative dose [mg] =
Body weight[(A)] [kg] x (Target Hb[(B)] - Actual Hb)[(C)] [g/dL] x 2.4[(D)] + reserve iron[(E)] [mg]

(A) It is recommended to use the ideal weight for overweight patients or the pre-pregnancy weight for pregnant women. There are different ways of determining the ideal weight e.g. by calculating the body weight that corresponds to a BMI of 25: Ideal weight = 25 * (height in metres)^2.

(B) The standard Ganzoni formula Target Hb is 15 g/dL. In special cases, e.g. pregnant women, a lower target haemoglobin value may be considered.
Treatment success should be monitored by means of blood tests. To achieve the target Hb 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 the factor 1.61145.

(D) Factor 2.4 = 0.0034 x 0.07 x 10,000.
0.0034: The iron content of the haemoglobin 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 that weigh more than 35 kg, the amount of iron stored is 500 mg or more. Iron storage values of 500 mg correspond to the lower normal range for petite women. Some guidelines recommend using 10 to 15 mg of iron per kg of body weight to calculate iron storage.

Table 2: Determining iron requirements based on the simplified dosing regimen

Hb		**Patient's body weight**		
g/dL	**mmol/L**	**less than 35 kg**	**35 kg to < 70 kg**	**70 kg and over**
< 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

Hb = Haemoglobin.

Step 2: Calculating and administering the maximum iron dose(s)

Ferinject should be administered in appropriate doses based on the determined amount of iron required. The following applies:

A single dose of Ferinject should not exceed the following values:

- 15 mg iron/kg body weight (administered as an intravenous injection) or
- 20 mg iron/kg body weight (administered as intravenous infusion)
- 1000 mg iron (20 ml Ferinject)

The maximum recommended cumulative dose of Ferinject is 1000 mg iron (20 ml Ferinject) per week. If the cumulative iron dose exceeds 20 mg iron/kg body weight or 1000 mg iron via Ferinject, 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 condition of the particular patient, the medical practitioner should carry out a re-check (including blood tests). The Hb level should be re-checked four weeks after the last administration of Ferinject at the earliest, to allow sufficient time for erythropoiesis and iron utilisation. 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”).

Mode of administration

Ferinject must only be administered intravenously:

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

Ferinject must not be administered subcutaneously or intramuscularly.

During and after each administration of Ferinject, patients must be carefully monitored for signs or symptoms of hypersensitivity reactions. Provision of appropriate emergency treatment must be assured (see “Warnings and precautions”).

Intravenous injection

Ferinject can be administered as an intravenous injection using the undiluted solution. The maximum permissible single dose is 15 mg iron/kg body weight, but must not exceed 1000 mg iron. For administration rates, see Table 3:

Table 3: Administration rates for intravenous injection of Ferinject

Required Ferinject volume	**Corresponds to an iron dose of**	**Rate of administration / minimum duration of administration**

2	to	4 ml	100	to	200 mg	No minimum duration required
>4	to	10 ml	>200	to	500 mg	100 mg iron/min
>10	to	20 ml	>500	to	1000 mg	15 minutes

Intravenous infusion

Ferinject can be administered as an intravenous 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. When infusing, Ferinject must only be diluted with sterile 0.9% (m/v) saline solution as shown in Table 4. Note: For stability reasons, Ferinject must not be diluted to concentrations below 2 mg iron/ml (without taking into account the solution volume of ferric carboxymaltose). For further instructions on diluting the medicinal product prior to administration, see section “Instructions for Handling”.

Table 4: Dilution scheme for Ferinject for intravenous infusion

Required Ferinject volume			**Corresponds to an iron dose of**			**Maximum amount of sterile 0.9% (m/v) saline solution**	**Minimum duration of administration**
2	to	4 ml	100	to	200 mg	50 ml	No minimum duration required
>4	to	10 ml	>200	to	500 mg	100 ml	6 minutes
>10	to	20 ml	>500	to	1000 mg	250 ml	15 minutes

Special dosage instructions

Children <1 year

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

Children ≥1 year of age and adolescents

Ferinject is not approved for use in children and adolescents aged ≥1 to 18 years due to limited data. No dosing recommendation can be provided. Currently available data in the pediatric population are described in the sections "Properties/Effects", "Undesirable Effects" and "Pharmacokinetics".

Patients with chronic kidney disease requiring haemodialysis

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

The efficacy and safety of Ferinject in children and adolescents with chronic kidney disease requiring haemodialysis have not been studied. Therefore, Ferinject is not recommended for use in children and adolescents with chronic kidney disease requiring hemodialysis.

Patients with hepatic disorders
There is no experience with Ferinject and hepatic insufficiency.

Contraindications

The use of Ferinject is contraindicated in the following cases:

- Hypersensitivity to the active substance or one of the excipients of the composition;
- anaemia without confirmed iron deficiency;
- evidence of iron overload;
- first trimester of pregnancy.

Warnings and precautions

Hypersensitivity reactions

The intravenous administration of parenteral iron products can cause immediate-type acute hypersensitivity reactions (anaphylactic reactions), which may be fatal.
Such reactions have been reported even where previous administrations of parenteral iron products have been tolerated without complications. There are reports of hypersensitivity reactions that can progress to Kounis syndrome (acute allergic spasm of the coronary arteries that can result in myocardial infarction). Treatment with Ferinject should be prescribed by the attendant physician only after carefully determining the indication.

Ferinject should only be used if healthcare professionals who can assess and treat anaphylactic reactions are immediately available as well as only in an institution in which all facilities for resuscitation are available. Before each administration of Ferinject, patients should be actively questioned about previous adverse reactions to intravenous iron products.

Typical symptoms of acute hypersensitivity reactions are: fall in blood pressure, tachycardia (and even anaphylactic shock), respiratory symptoms (including bronchial obstructions, laryngeal and pharyngeal oedema), abdominal symptoms (including abdominal cramps, vomiting) or skin symptoms (including urticaria, erythema, pruritus).
Patients should be carefully monitored for any signs and symptoms of a hypersensitivity reaction during and for at least 30 minutes after the administration of parenteral iron products. Should allergic reactions or signs of intolerance occur during administration, the treatment must be stopped immediately.
Adrenaline, is recommended in the first instance for the emergency drug treatment of acute anaphylactic reactions, according to the current emergency guidelines and manufacturer information, and only after this antihistamines and/or corticosteroids (later onset of action).

In rare cases, fever or delayed allergic reactions (with a delay of several hours or even days) have been observed.
The risk of hypersensitivity reactions is increased in patients with known allergies including drug intolerance, a history of severe asthma, eczema and other forms of atopy, and also in patients with immunological or inflammatory disorders (e.g. systemic lupus erythematosus, rheumatoid arthritis).

Hypophosphataemia/hypophosphataemic osteomalacia
Parenteral iron can lead to hypophosphataemia, which is transient and without clinical symptoms in most cases. Hypophosphatemia requiring treatment has mainly been reported in individual cases, in patients with known risk factors and after sustained higher dosing.
Cases of symptomatic hypophosphataemia leading to hypophosphataemic osteomalacia, and fractures requiring clinical intervention, including surgery, were reported after market introduction. In case of arthralgia or bone pain, patients should be advised to seek medical advice.
Patients receiving multiple higher doses as part of long-term treatment, and who have underlying risk factors (e.g. vitamin D deficiency, calcium and phosphate malabsorption, secondary hyperparathyroidism, hereditary haemorrhagic telangiectasia, inflammatory bowel disease and osteoporosis) should be monitored for hypophosphataemic osteomalacia, including serum phosphate control. In case of persistent hypophosphataemia, treatment with Ferinject should be re-evaluated.

Hepatic or renal insufficiency
Parenteral iron should only be administered to patients with hepatic dysfunction following a careful assessment of the risks and benefits.
Parenteral iron administration should be avoided in patients with hepatic dysfunction due to iron overload, especially those with porphyria cutanea tarda, or any acute liver disease.
Careful monitoring of the iron status is recommended to avoid iron overload.

Infections
Parenteral iron should be administered with caution in cases of acute or chronic infections, asthma, eczema or atopic allergies.
In the case of patients with bacteraemia, it is recommended to stop administration of Ferinject.

Extravasation
Paravenous administration should be avoided. It may irritate the skin and potentially cause a long-lasting, brownish discolouration on the injection/infusion site. The administration of Ferinject must be discontinued immediately if this occurs.

Other ingredients

One ml of Ferinject may contain up to 5.5 mg (0.24 mmol) of sodium. This must be taken into account when administering to people on a sodium-controlled diet.

Interactions

Ferinject should not be administered concomitantly with oral iron preparations since the absorption of oral iron can be reduced (see also section “Indications / Uses”).

Pregnancy, lactation

Pregnancy

There are limited clinical data from controlled studies on the use of Ferinject in pregnant women (see “Clinical efficacy”). Animal studies indicated reproductive toxicity (see "Preclinical data"). A careful benefit / risk benefit assessment is necessary before administration during pregnancy since hypersensitivity reactions may result in a particular risk to the mother and child (see “Warnings and precautions”).
Ferinject is contraindicated during the first trimester of pregnancy (see “Contradictions”), and should only be used during the 2nd and 3rd trimester if the indication is compelling; in this context, body weight before the onset of pregnancy should be used to calculate the required quantity of iron, to avoid a potential overdose. Particularly careful monitoring for the signs of hypersensitivity reactions should be undertaken when administering during pregnancy.
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.

Lactation

There is little clinical experience of use during lactation. One clinical study has shown that the passage of iron from Ferinject into breast milk is negligible (≤1%). Ferinject is therefore unlikely to represent a risk to the child being breast-fed.

Fertility

No clinical data are available on the effect of Ferinject on fertility. In animal studies, treatment with Ferinject showed no effect on fertility (see "Preclinical data").

Effects on ability to drive and use machines

No relevant studies have been performed. It is unlikely that Ferinject has an effect on the ability to drive and use machines.

Undesirable effects

The following undesirable effects were reported in clinical studies in which 9,456 adult patients and 82 children ≥ 1 year of age and adolescents received Ferinject, as well as those reported from the post-marketing setting.

Frequencies of undesirable effects:
Common: <1/10, ≥1/100
Uncommon: <1/100, ≥1/1000
Rare: <1/1000, ≥1/10'000
Not known: frequency cannot be estimated from the available data

The most commonly reported adverse drug reactions (ADR) are nausea, injection/infusion site reactions, hypophosphataemia, headache, facial flushing, dizziness and hypertension.
Injection/infusion site reactions include various ADRs, all of which are uncommon or rare.
The most important serious adverse drug reactions associated with Ferinject are uncommon hypersensitivity reactions (see "Immune System Disorders").
The most serious ADRs were anaphylactoid reactions (rare); deaths were reported.
In subjects who showed a decrease in serum phosphate during clinical trials, the lowest values were measured after about 2 weeks, and in most cases the values returned to baseline 12 weeks after treatment with Ferinject.
The safety profile in children and adolescents 1-17 years of age was investigated in the following studies:
In a prospective pharmacokinetic/pharmacodynamic phase 2 study (1VIT13036), 35 children were treated in consecutive dose cohorts with IV single doses of Ferinject 7.5 mg iron/kg (n=16) and Ferinject 15 mg iron/kg (n=19) (maximum dose 750 mg iron). There were no ADR compared to adults. The most common ADRs were 2 cases each of pyrexia and rash with Ferinject 7.5 mg iron/kg and 3 cases each of rhinorrhoea and urticaria and 2 cases each of hyperthermia and upper respiratory tract infection with Ferinject 15 mg iron/kg.
In a prospective, open-label, parallel-group phase 3 study (1VIT17044), 40 children were treated with 2 doses of Ferinject at 15 mg iron/kg, each administered 7 days apart (maximum single dose 750 mg). There were no unexpected ADR compared to adults. The most common ADRs after IV therapy with Ferinject were hypophosphatemia/decreased serum phosphate (n=5), vomiting (n=2), headache (n=2) and urticaria (n=2). Laboratory chemistry revealed potentially clinically relevant hypophosphatemia in 8 patients treated with Ferinject (including 4 of the reported ADRs). The lowest phosphate levels were usually measured 2 weeks after the start of therapy, and largely normalised by day 35 after the start of treatment. All cases of hypophosphataemia were asymptomatic.

For more information, see “Warnings and Precautions”.

Immune system disorders

Uncommon: Hypersensitivity reactions of an immediate-type (anaphylactic reactions), which can potentially be lethal (see "Warnings and precautions"). Symptoms of anaphylactic reactions include circulatory collapse, a fall in blood pressure, tachycardia, respiratory symptoms (including bronchial obstructions, laryngeal and pharyngeal oedema), abdominal symptoms (including abdominal cramps, vomiting) and skin symptoms (including urticaria, erythema, pruritus).

Metabolism and nutrition disorders

Common: Hypophosphataemia (based on laboratory findings)

Psychiatric disorders

Rare: Anxiety

Nervous system disorders

Common: Headache, dizziness

Uncommon: Taste disturbance (dysgeusia), paraesthesia

Not known: Loss of consciousness

Cardiac disorders

Uncommon: Tachycardia

Vascular disorders

Common: Hypertension, flushing

Uncommon: Hypotension

Rare: Presyncope, syncope, phlebitis

Respiratory, thoracic and mediastinal disorders

Uncommon: Dyspnoea

Rare: Bronchospasm

Gastrointestinal disorders

Common: Nausea

Uncommon: Abdominal pain, vomiting, constipation, diarrhoea, dyspepsia

Rare: flatulence

Hepatobiliary disorders

Common: Alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, gamma-glutamyltransferase (γ-GT) increased, alkaline phosphatase (ALP) increased, lactate dehydrogenase (LDH) increased

Skin and subcutaneous tissue disorders

Uncommon: Rash (includes the following symptoms: rash erythematous, -generalised, -macular, -maculo-papular and -pruritic), pruritus, urticaria, erythema,

Rare: Angiodema, distant skin discolouration, pallor

Not known: Dermatitis, face oedema.

Musculoskeletal and connective tissue disorders

*Uncommon: A*rthralgia, myalgia, pain in the extremities, back pain, muscle spasms

Not known: Hypophosphataemic osteomalacia.

General disorders and administration site conditions

Common: Injection/infusion site reactions (including the following symptoms: pain, haematoma, discolouration (potentially long lasting), extravasation, irritation, reaction, injection/infusion site phlebitis and injection/infusion site paraesthesia)

Uncommon: Pyrexia, fatigue, chills, chest pain, odema peripheral, pain, malaise

Rare: Influenza-like illness (whose onset may vary from a few hours to several days.)

Overdose

Accidentally exceeding the cumulative total dose, which is necessary for correcting iron deficiency, can lead to accumulation of iron in the iron stores and ultimately to haemosiderosis in these patients. This can be prevented by preventive control of the iron parameters serum ferritin and transferrin saturation. An unwanted accumulation of iron is to be treated according to standard medical practice.

Properties/Effects

Ferinject contains iron in its trivalent form as a macromolecular complex with carboxymaltose (pH 5-7).

ATC code

B03AC

Mechanism of action

After intravenous administration, the ferric carboxymaltose complex is predominantly taken up by the reticuloendothelial system of the liver, the bone marrow and the spleen. The iron is used mainly for the synthesis of haemoglobin, but also myoglobin and iron-containing enzymes and is also stored as depot iron in the liver.

Pharmacodynamics

The Ferinject solution contains iron as stable trivalent iron in the form of a complex made up of polynuclear iron(III)-hydroxide with a carbohydrate polymer, which supplies utilisable iron for the body's iron transport and iron storage proteins (transferrin and ferritin).

In a study with ^{59}Fe- and ^{52}Fe-labelled Ferinject in six patients with iron-deficiency anaemia or renal anaemia, utilisation of 61-99% in the red blood cells was demonstrated after 24 days. In patients with iron deficiency anaemia, the utilisation was 91% to 99%, and in patients with renal anaemia 61% to 84%.

Clinical efficacy

Nephrology

Non-dialysis-dependent chronic kidney disease

A comparison study of Ferinject versus orally administered iron sulphate was performed in patients with chronic kidney failure who did not require dialysis.

The primary end point for efficacy (Hb increase of ≥ 1 g/dL) was reached by 60.4% (87/144) patients treated with Ferinject compared to 34.7% (35/101) patients treated with oral iron.

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

Haemodialysis-dependent chronic kidney disease

In a comparison study (n=237) in dialysis patients, Venofer® or Ferinject (corresponding to 200 mg iron) were each administered during dialysis (2-3 ×/week) into the venous limb of the dialysis machine until the total cumulative dose calculated using the Ganzoni formula was reached (maximum of 4 weeks). The primary end point was a response with an increase in the haemoglobin of 1 g/dL. Over 60% of patients were on treatment with EPO (uniformly distributed between both groups). The response on treatment with Ferinject was 46.4% versus 37.2% with Venofer.

Women's health

Post partum

In postpartum/postoperative anaemia, three comparison studies versus oral iron administration were conducted, one in Europe (n=286, randomised on a 2:1 basis) and two in the USA (n=337, randomised on a 1:1 basis and n=289, randomised on a 1:1 basis).

In one US study 88.8% of the patients treated with Ferinject and 66.2% of the patients treated with oral iron reached an Hb value of > 12 g/dL within 42 days. In the two other studies, the treatment with Ferinject was non-inferior to oral iron administration. However, both the increase in Hb of 3 g/dL and normalisation of the Hb with a concomitant increase in iron stores (ferritin) occurred significantly more frequently with Ferinject.

Heavy uterine bleeding

In patients with iron deficiency anaemia resulting from heavy uterine bleeding, Ferinject was compared to the oral administration of iron sulphate.

The primary end point was an Hb increase > 2.0 g/dL. This was reached in 82% of cases with Ferinject and in 61.8% with oral iron.

Pregnancy

A randomised, open-label, 2-arm study in pregnant women in the second and third trimester with IDA compared Ferinject (n=121) given at 1-3 occasions up to week 3 (mean cumulative dose 1,029 mg)

versus oral ferrous sulphate (n=115) (100 mg twice daily with a median treatment duration of 65 days). The difference in mean Hb from baseline till Week 3 (primary endpoint) was 0.27 g/dL in favour of Ferinject (p=0.274); till Week 6 the difference was 0.43 g/dL (p=0.032). Newborn Apgar scores as well as iron parameters were similar between newborns in the treatment groups.

Gastroenterology

Inflammatory bowel disease

In iron deficiency anaemia in the context of chronic bowel diseases (Crohn's disease, ulcerative colitis), Ferinject was administered as an infusion once a week (up to the cumulative total dose) and compared with oral iron replacement. The primary end point was the change in the haemoglobin in week 12 compared with the baseline. Ferinject was non- inferior to treatment with iron sulphate in respect of the primary end point.

Compared with iron sulphate, Ferinject brought about a more rapid therapeutic effect: in week 4, 34.2% of patients in the Ferinject group achieved an increase in haemoglobin of >2 g/dL compared with 18.2% in the oral iron sulphate group, and the difference was statistically significant. The reticulocyte count was found to peak in week 2 in both treatment groups. In the Ferinject group, statistically significantly higher ferritin levels were achieved from week 2 onwards compared with the iron sulphate group.

Monitoring ferritin levels after replacement therapy

Limited data are available from the VIT-IV-CL-008 study that demonstrate that ferritin levels drop sharply between 2–4 weeks after replacement therapy; thereafter, its decrease slows down. The mean ferritin level did not decrease to a level that might have prompted further therapy to be considered during the 12-week follow-up. The available data therefore do not clearly indicate an optimal time to test the ferritin level again. However, checking the ferritin level before the end of the 4 weeks after the replacement therapy appears to be premature. It is therefore recommended that the physician carry out another check of the ferritin level, depending on the condition of the respective patient.

Children and adolescents 1-17 years of age

In a prospective pharmacokinetic/pharmacodynamic phase 2 study (1VIT13036), 35 children were treated in consecutive dose cohorts with IV single doses of Ferinject 7.5 mg iron/kg (n=16) and Ferinject 15 mg iron/kg (n=19) (maximum dose 750 mg iron). On day 35 after injection, the mean (SD) increase in haemoglobin was 1.9 (1.38) g/dl under 7.5 mg iron/kg and 2.8 (1.15) g/dl under 15 mg iron/kg, respectively. Ferritin and transferrin saturation also increased in a dose-dependent manner.

The efficacy and safety of IV Ferinject were compared with oral iron therapy in a prospective, open-label, parallel-group phase 3 study (1VIT17044). Forty children with iron deficiency anaemia of different aetiology received 2 doses of Ferinject at 15 mg iron/kg each administered 7 days apart (maximum single dose 750 mg) and 39 children received oral iron sulphate for 28 days. Seven children who did not

respond adequately to oral iron therapy were also treated with 2 doses of Ferinject in a single-arm extension study (1VIT18045).
In the main study, there was a clinically relevant increase in haemoglobin in both treatment arms. The mean increase in haemoglobin (LS Mean) was 2.22 g/dl (95% CI 1.69, 2.75) after Ferinject and 1.92 g/dl (95% CI 1.43, 2.41) after oral iron therapy with no statistically significant difference between the treatment groups. Thus, the primary endpoint of the study was not met. The increase in the secondary endpoints ferritin and transferrin saturation was higher under Ferinject than after oral iron therapy. In the extension study, the mean increase (SD) in haemoglobin from the end of the main study was 0.7 (1.19) g/dl.

Pharmacokinetics

Absorption

Not applicable.

Distribution

After a single Ferinject dose of 100 to 1000 mg iron in patients with iron deficiency, peak total serum iron levels of 37 µg/ml to 333 µg/ml were measured after 15 minutes and 1.21 hours, respectively. The volume of distribution of the central compartment corresponds to the plasma volume (approximately 3 litres).
It was shown by means of positron emission tomography (PET) that iron from radiolabelled Ferinject was eliminated from the blood and transported into the bone marrow and into the reticuloendothelial system of the liver and spleen.

Metabolism

Ferric carboxymaltose is mainly taken up in the reticuloendothelial system of the liver, bone marrow and to a small extent in the spleen, and is then broken down into the components iron hydroxide and carbohydrates, with the iron being bound as ferritin. The iron is made available for erythropoiesis via transferrin, as required. The carbohydrate breakdown products are maltotetraose, maltotriose, maltose and glucose.

Elimination

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

Kinetics in specific patient groups

Children and adolescents 1-17 years of age
The pharmacokinetics of i.v. iron carboxymaltose were investigated in paediatric patients ≥ 1 year of age with iron deficiency anaemia in the phase 2 pharmacokinetic/pharmacodynamic study 1VIT13036 on single doses and supplemented by population pharmacokinetic analyses including additional sparse

pharmacokinetic samples from the phase 3 clinical trial 1VIT17044. Pharmacokinetic properties at the 15 mg iron/kg dose (maximum single dose 750 mg) were similar to those for adult patients with iron deficiency treated with the recommended adult dose. Serum iron increased dose-proportionally at single doses of 7.5 mg iron/kg and 15 mg iron/kg. After a single dose of Ferinject of 15 mg iron/kg body weight (maximum 750 mg), mean maximum total serum iron levels of 310 µg/ml were measured after 1.12 hours. The terminal half-life was 9.8 hours, and the volume of distribution estimated from population pharmacokinetic analysis was 0.42 to 3.14 l.

Hepatic impairment
No studies in liver insufficiency have been performed.

Preclinical data

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeat dose toxicity and genotoxicity.

Toxicity
The highest non-lethalintravenously administered single dose in rodents was 1000 mg iron/kg body weight.

Carcinogenicity
No long-term studies in animals have been performed to evaluate the carcinogenic potential of Ferinject

Reproductive toxicity
In a fertility study in rats, there were no effects on fertility for either male or female animals.
In reproductive toxicology studies using iron replete rabbits Ferinject was associated with minor skeletal abnormalities in the fetus at maternally toxic levels. These effects are considered transient, as no findings could be observed in the pre/postnatal development.
Pre-clinical studies indicate that iron released from Ferinject crosses the placental barrier and is excreted in milk in limited, controlled amounts

Other data
No evidence of allergic or immunotoxic potential has been observed. A controlled in-vivo test demonstrated no cross-reactivity of Ferinject with anti-dextran antibodies. No local irritation or intolerance was observed after intravenous administration.

Other information

Incompatibilities

Ferinject may only be mixed with sterile 0.9% w/v saline solution. There are no compatibility studies with containers made of materials other than polyethylene or glass.

Effects on diagnostic methods
None known.

Shelf life

Shelf life after opening of the vial:
Use the product immediately for microbiological reasons.

Shelf life after dilution with sterile 0.9% saline solution:
Use the solution for infusion (after dilution) as soon as possible for microbiological reasons. It has been shown that the diluted Ferinject solution is chemically stable at room temperature for 12 hours.

Ferinject may only be used up to the date on the packaging marked “EXP”.

Special precautions for storage

Prescribed storage conditions: Store in the original packaging and not above 30°C. Do not freeze.

Instructions for handling

The vials are intended for single use only.
Prior to use, the vials should be inspected for visible particles and damage
Only solutions that are homogenous and free of visible particles should be used.
Ferinject must only be mixed with 0.9% w/v sodium chloride solution. Other intravenous diluting solutions and medicinal products must not be used because there is a risk of sediment formation and/or interaction. For instructions on dilution, see “Posology/Use”.

Packs

Vial: 1 × 2 ml (B)
Vial: 1 × 10 ml (B)
Vial: 1 × 20 ml (B)
Vials: 5 × 2 ml (B)
Vials: 5 × 10 ml (B)
Not all pack sizes might be marketed

Marketing Authorisation Holder and Batch Releasing Site:

Vifor (International) Inc.
Rechenstrasse 37
9014 St.Gallen, Switzerland

Bulk Manufacturing site

IDT Biologika GmbH
Am Pharmapark
06861 Dessau-Rosslau
Germany

Date of revision of the text

November 2022

KWT, QTR and BHR SmPC

Ferinject®

Composition

Active substances

Iron as ferric carboxymaltose

Excipients

Sodium hydroxide, hydrochloric acid, water for injection to make up the solution

Pharmaceutical form and active substance quantity per unit

Solution for intravenous administration.
1 ml of solution contains ferric carboxymaltose corresponding to 50 mg of iron One 2 ml vial contains ferric carboxymaltose corresponding to 100 mg of iron One 10 ml vial contains ferric carboxymaltose corresponding to 500 mg of iron One 20 ml vial contains ferric carboxymaltose corresponding to 1000 mg of iron

Indications/Uses

Iron deficiency in patients in whom oral iron therapy is not sufficiently effective, is ineffective or cannot be undertaken, such as cases where oral iron preparations cannot be tolerated or in the presence of inflammatory gastrointestinal diseases, e.g. ulcerative colitis, which may be exacerbated by oral iron therapy, or in the case of treatment-refractory iron-deficiency states where it is suspected that the oral iron preparations are being taken unreliably. Ferinject should only be administered if the diagnosis of iron deficiency has been established and confirmed through appropriate laboratory investigations (e.g. plasma ferritin levels, transferrin saturation (TSAT), haemoglobin, haematocrit, red cell count, MCV and MCH).

Dosage/Administration

During and after each use of Ferinject, patients must be carefully monitored for signs or symptomps of hypersensitivity reactions.

Ferinject should only be used if professionals trained in recognising and treating anaphylactic shock are immediately available, and if cardio-pulmonary resuscitation can be ensured by appropriate equipment. The patient should be observed for side effects for at least 30 minutes every time Ferinject is administered (see Warnings and Precautions for Use).

Dosage

The dosage of Ferinject is determined in several stages: [1] Determination of individual iron requirements, [2] Calculation and administration of iron doses(s) and [3] Checks after replenishment of iron stores.

Step 1: Calculating the amount of iron required

The individual amount of iron needed to replenish iron stores by means of Ferinject can be determined on the basis of the patients body weight and haemoglobin (Hb) level. Iron requirements

should be determined using the Ganzoni formula (Table 1) or the simplified dosing regimen (Table 2). Use of the Ganzoni formula is recommended for patients who require a dose adjusted to their individual needs, such as patients with anorexia nervosa, cachexia, obesity or pregnant women. Iron deficiency must be confirmed by laboratory tests as indicated under Indications / Uses.

Table1: Determining iron requirements based on the Ganzoni formula

Body weight (kg)	**Hb (g/dL)**			
	6	7.5	9	10.5
	ml Ferinject (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)
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)

Hb = Haemoglobin

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

Ganzoni formula:

Total iron deficit [mg] = total cumulative dose [mg] =
Body weight$^{(A)}$ [kg] x (Target Hb$^{(B)}$ - Actual Hb)$^{(C)}$ [g/dL] x 2.4$^{(D)}$ + reserve iron$^{(E)}$ [mg]

(A) It is recommended to use the ideal weight for overweight patients or the pre-pregnancy weight for pregnant women. There are different ways of determining the ideal weight e.g. by calculating the body weight that corresponds to a BMI of 25: Ideal weight = 25 * (height in metres)^2.

(B) The standard Ganzoni formula Target Hb is 15 g/dL. In special cases, e.g. pregnant women, a lower target haemoglobin value may be considered. Treatment success should be monitored by means of blood tests. To achieve the target Hb 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 the factor 1.61145.

(D) Factor 2.4 = 0.0034 x 0.07 x 10,000.
0.0034: The iron content of the haemoglobin 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 that weigh more than 35 kg, the amount of iron stored is 500 mg or more. Iron storage values of 500 mg correspond to the lower normal range for petite women. Some guidelines recommend using 10 to 15 mg of iron per kg of body weight to calculate iron storage.

Table 2: Determining iron requirements based on the simplified dosing regimen

Hb		**Patient's body weight**		
g/dL	**mmol/L**	**less than 35 kg**	**35 kg to < 70 kg**	**70 kg and over**
< 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

Hb = Haemoglobin.

Step 2: Calculating and administering the maximum iron dose(s)

Ferinject should be administered in appropriate doses based on the determined amount of iron required. The following applies:

A single dose of Ferinject should not exceed the following values:

- 15 mg iron/kg body weight (administered as an intravenous injection) or
- 20 mg iron/kg body weight (administered as intravenous infusion)
- 1000 mg iron (20 ml Ferinject)

The maximum recommended cumulative dose of Ferinject is 1000 mg iron (20 ml Ferinject) per week. If the cumulative iron dose exceeds 20 mg iron/kg body weight or 1000 mg iron via Ferinject, 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 condition of the particular patient, the medical practitioner should carry out a re-check (including blood tests). The Hb level should be re-checked four weeks after the last administration of Ferinject at the earliest, to allow sufficient time for erythropoiesis and iron utilisation. 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”).

Mode of administration

Ferinject must only be administered intravenously:

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

Ferinject must not be administered subcutaneously or intramuscularly.

During and after each administration of Ferinject, patients must be carefully monitored for signs or symptoms of hypersensitivity reactions. Provision of appropriate emergency treatment must be assured (see “Warnings and precautions”).

Intravenous injection

Ferinject can be administered as an intravenous injection using the undiluted solution. The maximum permissible single dose is 15 mg iron/kg body weight, but must not exceed 1000 mg iron. For administration rates, see Table 3:

Table 3: Administration rates for intravenous injection of Ferinject

Required Ferinject volume			**Corresponds to an iron dose of**			**Rate of administration / minimum duration of administration**
2	to	4 ml	100	to	200 mg	No minimum duration required
>4	to	10 ml	>200	to	500 mg	100 mg iron/min
>10	to	20 ml	>500	to	1000 mg	15 minutes

Intravenous infusion

Ferinject can be administered as an intravenous 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. When infusing, Ferinject must only be diluted with sterile 0.9% (m/v) saline solution as shown in Table 4. Note: For stability reasons, Ferinject must not be diluted to concentrations below 2 mg iron/ml

(without taking into account the solution volume of ferric carboxymaltose). For further instructions on diluting the medicinal product prior to administration, see section “Instructions for Handling”.

Table 4: Dilution scheme for Ferinject for intravenous infusion

Required Ferinject volume	**Corresponds to an iron dose of**	**Maximum amount of sterile 0.9% (m/v) saline solution**	**Minimum duration of administration**
2 to 4 ml	100 to 200 mg	50 ml	No minimum duration required
>4 to 10 ml	>200 to 500 mg	100 ml	6 minutes
>10 to 20 ml	>500 to 1000 mg	250 ml	15 minutes

Special dosage instructions

Patients with chronic kidney disease requiring haemodialysis

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

Patients with hepatic disorders

There is no experience with Ferinject and hepatic insufficiency.

Children and adolescents

The efficacy and safety of Ferinject have not been studied in children and adolescents. Ferinject is therefore not recommended for use in children and adolescents.

Contraindications

The use of Ferinject is contraindicated in the following cases:

- Hypersensitivity to the active substance or one of the excipients of the composition;
- anaemia without confirmed iron deficiency;
- evidence of iron overload;
- first trimester of pregnancy.

Warnings and precautions

Hypersensitivity reactions

The intravenous administration of parenteral iron products can cause immediate-type acute hypersensitivity reactions (anaphylactoid/anaphylactic reactions), including anaphylactoid reactions which may be fatal.
Such reactions have been reported even where previous administrations of parenteral iron products have been tolerated without complications. There are reports of hypersensitivity reactions that can progress to Kounis syndrome (acute allergic spasm of the coronary arteries that can result in myocardial infarction). Treatment with Ferinject should be prescribed by the attendant physician only after carefully determining the indication.

Ferinject should only be used if healthcare professionals who can assess and treat anaphylactic reactions are immediately available as well as only in an institution in which all facilities for resuscitation are available. Before each administration of Ferinject, patients should be actively questioned about previous adverse reactions to intravenous iron products.

Typical symptoms of acute hypersensitivity reactions are: fall in blood pressure, tachycardia (and even anaphylactic shock), respiratory symptoms (including bronchial obstructions, laryngeal and pharyngeal oedema), abdominal symptoms (including abdominal cramps, vomiting) or skin symptoms (including urticaria, erythema, pruritus).
Patients should be carefully monitored for any signs and symptoms of a hypersensitivity reaction during and for at least 30 minutes after the administration of parenteral iron products. Should allergic reactions or signs of intolerance occur during administration, the treatment must be stopped immediately.
Adrenaline, e.g. in doses of 0.3 mg intramuscularly, is recommended in the first instance for the emergency drug treatment of acute anaphylactic/anaphylactoid reactions, and only after this antihistamines and/or corticosteroids (later onset of action).
In rare cases, fever or delayed allergic reactions (with a delay of several hours or even days) have been observed.
The risk of hypersensitivity reactions is increased in patients with known allergies including drug intolerance, a history of severe asthma, eczema and other forms of atopy, and also in patients with immunological or inflammatory disorders (e.g. systemic lupus erythematosus, rheumatoid arthritis).

Hypophosphataemia/hypophosphataemic osteomalacia

Parenteral iron can lead to hypophosphataemia, which is transient and without clinical symptoms in most cases. Hypophosphatemia requiring treatment has mainly been reported in individual cases, in patients with known risk factors and after sustained higher dosing.
Cases of symptomatic hypophosphataemia leading to hypophosphataemic osteomalacia, and

fractures requiring clinical intervention, including surgery, were reported after market introduction. In case of arthralgia or bone pain, patients should be advised to seek medical advice.
Patients receiving multiple higher doses as part of long-term treatment, and who have underlying risk factors (e.g. vitamin D deficiency, calcium and phosphate malabsorption, secondary hyperparathyroidism, hereditary haemorrhagic telangiectasia, inflammatory bowel disease and osteoporosis) should be monitored for hypophosphataemic osteomalacia, including serum phosphate control. In case of persistent hypophosphataemia, treatment with Ferinject should be re-evaluated.

Hepatic or renal insufficiency

Parenteral iron should only be administered to patients with hepatic dysfunction following a careful assessment of the risks and benefits.
Parenteral iron administration should be avoided in patients with hepatic dysfunction due to iron overload, especially those with porphyria cutanea tarda, or any acute liver disease.
Careful monitoring of the iron status is recommended to avoid iron overload.

Infections

Parenteral iron should be administered with caution in cases of acute or chronic infections, asthma, eczema or atopic allergies.
In the case of patients with bacteraemia, it is recommended to stop administration of Ferinject.

Extravasation

Paravenous administration should be avoided. It may irritate the skin and potentially cause a long-lasting, brownish discolouration on the injection/infusion site. The administration of Ferinject must be discontinued immediately if this occurs.

Other ingredients

One ml of Ferinject may contain up to 5.5 mg (0.24 mmol) of sodium. This must be taken into account when administering to people on a sodium-controlled diet.

Interactions

Ferinject should not be administered concomitantly with oral iron preparations since the absorption of oral iron can be reduced.

See also section “Indications / Uses”

Pregnancy, lactation

There are limited clinical data from controlled studies on the use of Ferinject in pregnant women (see “Clinical efficacy”). A careful benefit / risk benefit assessment is necessary before administration during pregnancy since hypersensitivity reactions may result in a particular risk to the mother and child (see “Warnings and precautions”).
Ferinject is contraindicated during the first trimester of pregnancy (see “Contradictions”), and should only be used during the 2nd and 3rd trimester if the indication is compelling; in this context, body weight before the onset of pregnancy should be used to calculate the required quantity of iron, to avoid a potential overdose. Particularly careful monitoring for the signs of hypersensitivity reactions should be undertaken when administering during pregnancy.

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.

For data from animal studies, see the preclinical data.

There is little clinical experience of use during lactation. One clinical study has shown that the passage of iron from Ferinject into breast milk is negligible (≤1%). Ferinject is therefore unlikely to represent a risk to the child being breast-fed.

Effects on ability to drive and use machines

No relevant studies have been performed. It is unlikely that Ferinject has an effect on the ability to drive and use machines.

Undesirable effects

The following undesirable effects were reported in clinical studies in which 8,245 patients received Ferinject, as well as those reported from the post-marketing setting.

Frequencies of undesirable effects:
Rare: <1/1000, ≥1/10’000
Uncommon: <1/100, ≥1/1000
Common: <1/10, ≥1/100

Not known: frequency cannot be estimated from the available data
The most commonly reported adverse drug reactions (ADR) are nausea, injection/infusion site reactions, hypophosphataemia, headache, facial flushing, dizziness and hypertension.
Injection/infusion site reactions include various ADRs, all of which are uncommon or rare.
The most important serious adverse drug reactions associated with Ferinject are uncommon hypersensitivity reactions (see “Immune System Disorders”).
The most serious ADRs were anaphylactoid/anaphylactic reactions (rare); deaths were reported.
In subjects who showed a decrease in serum phosphate during clinical trials, the lowest values were measured after about 2 weeks, and in most cases the values returned to baseline 12 weeks after treatment with Ferinject.

For more information, see “Warnings and Precautions”

Immune system disorders

Uncommon: Hypersensitivity reactions of an immediate-type (anaphylactic/anaphylactoid reactions), which can potentially be lethal (see "Warnings and precautions"). Symptoms of anaphylactic/anaphylactoid reactions include circulatory collapse, a fall in blood pressure, tachycardia, respiratory symptoms (including bronchial obstructions, laryngeal and pharyngeal oedema), abdominal symptoms (including abdominal cramps, vomiting) and skin symptoms (including urticaria, erythema, pruritus).

Metabolism and nutrition disorders

Common: hypophosphataemia (based on laboratory findings)

Psychiatric disorders

Rare: Anxiety

Nervous system disorders

Common: Headache, dizziness

Uncommon: Paraesthesia, taste disturbance (dysgeusia)
Not known: Loss of consciousness

Cardiac disorders
Uncommon: Tachycardia
Vascular disorders
Common: Hypertension, flushing
Uncommon: Hypotension

Rare: Syncope, presyncope, phlebitis

Respiratory, thoracic and mediastinal disorders

Uncommon: Dyspnoea

Rare: Bronchospasm

Gastrointestinal disorders

Common: Nausea

Uncommon: Vomiting, dyspepsia, abdominal pain, constipation, diarrhoea
Rare: flatulence

Hepatobiliary disorders

Common: Alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, gamma-glutamyltransferase (γ-GT) increased, lactate dehydrogenase (LDH) increased, alkaline phosphatase (ALP) increased

Skin and subcutaneous tissue disorders

Uncommon: Pruritus, urticaria, erythema, rash (includes the following symptoms: rash erythematous, -generalised, -macular, -maculo-papular and -pruritic) *Rare:* angiodema, pallor, distant skin discolouration. *Not known:* Dermatitis, face oedema.

Musculoskeletal and connective tissue disorders

Uncommon: Myalgia, back pain, arthralgia, muscle spasms, pain in the extremity
Not known: hypophosphataemic osteomalacia.

General disorders and administration site conditions

Common: Injection/infusion site reactions (including the following symptoms: pain, haematoma, discolouration (potentially long lasting), extravasation, irritation, reaction, injection/infusion site phlebitis and injection/infusion site paraesthesia)
Uncommon: Pyrexia, fatigue, chest pain, odema peripheral, chills, pain
Rare: malaise, influenza-like illness (whose onset may vary from a few hours to several days.)

Overdose

Accidentally exceeding the cumulative total dose, which is necessary for correcting iron deficiency, can lead to accumulation of iron in the iron stores and ultimately to haemosiderosis in these patients. This can be prevented by preventive control of the iron parameters serum ferritin and transferrin saturation. An unwanted accumulation of iron is to be treated according to standard medical practice.

Properties/Effects

Ferinject contains iron in its trivalent form as a macromolecular complex with carboxymaltose (pH 5- 7).

ATC code

B03AC

Mechanism of action

After intravenous administration, the ferric carboxymaltose complex is predominantly taken up by the reticuloendothelial system of the liver, the bone marrow and the spleen. The iron is used mainly for the synthesis of haemoglobin, but also myoglobin and iron-containing enzymes and is also stored as depot iron in the liver.

Pharmacodynamics

The Ferinject solution contains iron as stable trivalent iron in the form of a complex made up of polynuclear iron(III)-hydroxide with a carbohydrate polymer, which supplies utilisable iron for the body's iron transport and iron storage proteins (transferrin and ferritin).
In a study with ^{59}Fe- and ^{52}Fe-labelled Ferinject in six patients with iron-deficiency anaemia or renal anaemia, utilisation of 61-99% in the red blood cells was demonstrated after 24 days. In patients with iron deficiency anaemia, the utilisation was 91% to 99%, and in patients with renal anaemia 61% to 84%.

Clinical efficacy

Nephrology
Non-dialysis-dependent chronic kidney disease

A comparison study of Ferinject versus orally administered iron sulphate was performed in patients with chronic kidney failure who did not require dialysis.
The primary end point for efficacy (Hb increase of ≥ 1 g/dL) was reached by 60.4% (87/144) patients treated with Ferinject compared to 34.7% (35/101) patients treated with oral iron.
A significant result was shown only in female patients with a baseline ferritin value of < 100 ng/ml.

Haemodialysis-dependent chronic kidney disease

In a comparison study (n=237) in dialysis patients, Venofer or Ferinject (corresponding to 200 mg iron) were each administered during dialysis (2-3 ×/week) into the venous limb of the dialysis machine until the total cumulative dose calculated using the Ganzoni formula was reached (maximum of 4 weeks). The primary end point was a response with an increase in the haemoglobin of 1 g/dL. Over 60% of patients were on treatment with EPO (uniformly distributed between both groups). The response on treatment with Ferinject was 46.4% versus 37.2% with Venofer.

Women's health

Post partum

In postpartum/postoperative anaemia, three comparison studies versus oral iron administration were conducted, one in Europe (n=286, randomised on a 2:1 basis) and two in the USA (n=337, randomised on a 1:1 basis and n=289, randomised on a 1:1 basis).
In one US study 88.8% of the patients treated with Ferinject and 66.2% of the patients treated with oral iron reached an Hb value of > 12 g/dL within 42 days. In the two other studies, the treatment with Ferinject was non-inferior to oral iron administration. However, both the increase in Hb of 3 g/dL and

normalisation of the Hb with a concomitant increase in iron stores (ferritin) occurred significantly more frequently with Ferinject.

Heavy uterine bleeding

In patients with iron deficiency anaemia resulting from heavy uterine bleeding, Ferinject was compared to the oral administration of iron sulphate.
The primary end point was an Hb increase > 2.0 g/dL. This was reached in 82% of cases with Ferinject and in 61.8% with oral iron.

Pregnancy

A randomised, open-label, 2-arm study in pregnant women in the second and third trimester with IDA compared Ferinject (n=121) given at 1-3 occasions up to week 3 (mean cumulative dose 1,029 mg) versus oral ferrous sulphate (n=115) (100 mg twice daily with a median treatment duration of 65 days). The difference in mean Hb from baseline till Week 3 (primary endpoint) was 0.27 g/dL in favour of Ferinject (p=0.274); till Week 6 the difference was 0.43 g/dL (p=0.032). Newborn Apgar scores as well as iron parameters were similar between treatment groups.

Gastroenterology

Inflammatory bowel disease

In iron deficiency anaemia in the context of chronic bowel diseases (Crohn's disease, ulcerative colitis), Ferinject was administered as an infusion once a week (up to the cumulative total dose) and compared with oral iron replacement. The primary end point was the change in the haemoglobin in week 12 compared with the baseline. Ferinject was non- inferior to treatment with iron sulphate in respect of the primary end point.

Compared with iron sulphate, Ferinject brought about a more rapid therapeutic effect: in week 4, 34.2% of patients in the Ferinject group achieved an increase in haemoglobin of >2 g/dL compared with 18.2% in the oral iron sulphate group, and the difference was statistically significant. The reticulocyte count was found to peak in week 2 in both treatment groups. In the Ferinject group, statistically significantly higher ferritin levels were achieved from week 2 onwards compared with the iron sulphate group.

Monitoring ferritin levels after replacement therapy

Limited data are available from the VIT-IV-CL-008 study that demonstrate that ferritin levels drop sharply between 2–4 weeks after replacement therapy; thereafter, its decrease slows down. The mean ferritin level did not decrease to a level that might have prompted further therapy to be considered during the 12-week follow-up. The available data therefore do not clearly indicate an optimal time to test the ferritin level again. However, checking the ferritin level before the end of the 4 weeks after the replacement therapy appears to be premature. It is therefore recommended that the physician carry out another check of the ferritin level, depending on the condition of the respective patient.

Pharmacokinetics

Absorption

Not applicable.

Distribution

After a single Ferinject dose of 100 to 1000 mg iron in patients with iron deficiency, peak total serum

iron levels of 37 µg/ml to 333 µg/ml were measured after 15 minutes and 1.21 hours, respectively. The volume of distribution of the central compartment corresponds to the plasma volume (approximately 3 litres).
It was shown by means of positron emission tomography (PET) that iron from radiolabelled Ferinject was eliminated from the blood and transported into the bone marrow and into the reticuloendothelial system of the liver and spleen.

Metabolism

Ferric carboxymaltose is mainly taken up in the reticuloendothelial system of the liver, bone marrow and to a small extent in the spleen, and is then broken down into the components iron hydroxide and carbohydrates, with the iron being bound as ferritin. The iron is made available for erythropoiesis via transferrin, as required. The carbohydrate breakdown products are maltotetraose, maltotriose, maltose and glucose.

Elimination

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

Kinetics in specific patient groups

No studies with children have been conducted.
No studies in liver insufficiency have been performed.

Preclinical data

Pre-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeat dose toxicity and genotoxicity. Pre-clinical studies indicate that iron released from Ferinject crosses the placental barrier and is excreted in milk in limited, controlled amounts. In reproductive toxicology studies using iron replete rabbits Ferinject was associated with minor skeletal abnormalities in the fetus at maternally toxic levels. In a fertility study in rats, there were no effects on fertility for either male or female animals. These effects are considered transient, as no findings could be observed in the pre/postnatal development.
The highest non-lethalintravenously administered single dose in rodents was 1000 mg iron/kg body weight. No long-term studies in animals have been performed to evaluate the carcinogenic potential of Ferinject No evidence of allergic or immunotoxic potential has been observed. A controlled in-vivo test demonstrated no cross-reactivity of Ferinject with anti-dextran antibodies.

No local irritation or intolerance was observed after intravenous administration.

Other information

Incompatibilities

Ferinject may only be mixed with sterile 0.9% w/v saline solution. There are no compatibility studies with containers made of materials other than polyethylene or glass.

Effects on diagnostic methods

None known.

Shelf life

Shelf life after opening of the vial:
Use the product immediately for microbiological reasons.

Shelf life after dilution with sterile 0.9% saline solution:
Use the solution for infusion (after dilution) as soon as possible for microbiological reasons. It has been shown that the diluted Ferinject solution is chemically stable at room temperature for 12 hours.

Ferinject may only be used up to the date on the packaging marked “EXP”.

Special precautions for storage

Prescribed storage conditions: Store in the original packaging and not above 30°C. Do not freeze.

Instructions for handling

The vials are intended for single use only.
Prior to use, the vials should be inspected for visible particles and damage
Only solutions that are homogenous and free of visible particles should be used.

Ferinject must only be mixed with 0.9% w/v sodium chloride solution. Other intravenous diluting solutions and medicinal products must not be used because there is a risk of sediment formation and/or interaction. For instructions on dilution, see section “Posology/Use”.

Packs

Vial: 1 × 2 ml (B)

Vial: 1 × 10 ml (B)

Vial: 1 × 20 ml (B)

Vials: 5 × 2 ml (B)

Vials: 5 × 10 ml (B)

Not all pack sizes might be marketed

Marketing Authorisation Holder and Batch Releasing Site:

Vifor (International)
Inc.

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Bulk Manufacturing site

IDT Biologika GmbH

Am Pharmapark

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Germany

Date of revision of the text

May 2021

KSA SmPC

SUMMARY OF PRODUCT CHARACTERISTICS

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

FERINJECT 50 mg iron/ml solution for injection/infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains ferric carboxymaltose correcponding to 50 g of iron. One 10 ml vial contains ferric carboxymaltose corresponding to 500 mg of iron.

Sodium hydroxide is added as excipient for pH adjustment. Therefore one milliliter of solution contains up to 5.5 mg (0.24 mmol) sodium, see section 4.2. For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for intravenous administration.
Dark brown, non-transparent, aqueous solution.

4. CLINICAL PARTICULARS

4.1 *Therapeutic indications*

Iron deficiency in patients in whom oral iron therapy is not sufficiently effective, is ineffective or cannot be undertaken, such as cases where oral iron preparations cannot be tolerated or in the presence of inflammatory gastrointestinal diseases, e.g. ulcerative colitis, which may be exacerbated by oral iron therapy, or in the case of treatment-refractory iron-deficiency states where it is suspected that the oral iron preparations are being taken unreliably. Ferinject should only be administered if the diagnosis of iron deficiency has been established and confirmed through appropriate laboratory investigations (e.g. plasma ferritin levels transferrin saturation (TSAT), haemoglobin, haematocrit, red cell count, MCV and MCH).

4.2 *Posology and method of administration*

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

Ferinject 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 Ferinject administration (see section 4.4).

Posology

The posology of Ferinject 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 Ferinject 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 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 Ferinject should be

administered taking into consideration the following:

A single Ferinject 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 Ferinject)

The maximum recommended cumulative dose of Ferinject is 1,000 mg of iron (20 mL Ferinject) 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 Ferinject administration to allow adequate time for erythropoiesis and iron utilisation. In the event the patient requires further iron repletion, the iron need should be recalculated using Table 1 above. (See section 5.1.)

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 (see also section 4.4).

Paediatric population

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

Method of administration

Ferinject 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.

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

Intravenous injection

Ferinject may be administered by intravenous injection using undiluted solution. The maximum

single dose is 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 Ferinject

Volume of Ferinject 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

Ferinject 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, Ferinject must only be diluted in sterile 0.9% m/V sodium chloride solution as shown in Table 3. Note: for stability reasons, Ferinject should not be diluted to concentrations less than 2 mg iron/mL (not including the volume of the ferric carboxymaltose solution). For further instructions on dilution of the medicinal product before administration, see section 6.6.

Table 3: Dilution plan of Ferinject for intravenous infusion

Volume of Ferinject 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 Ferinject is contraindicated in cases of:

- hypersensitivity to the active substance, to Ferinject or any of its excipients listed in section 6.1.
- 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

The intravenous administration of parenteral iron products can cause immediate-type acute hypersensitivity reactions (anaphylactoid/anaphylactic reactions), including anaphylactoid reactions which may be fatal.
Such reactions have been reported even where previous administrations of parenteral iron products have been tolerated without complications. There are reports of hypersensitivity reactions that can progress to Kounis syndrome (acute allergic spasm of the coronary arteries that can result in myocardial infarction). Treatment with Ferinject should be prescribed by the attendant physician only after carefully determining the indication.

Ferinject should only be used if healthcare professionals who can assess and treat anaphylactic reactions are immediately available as well as only in an institution in which all facilities for resuscitation are available. Before each administration of Ferinject, patients should be actively questioned about previous adverse reactions to intravenous iron products.

Typical symptoms of acute hypersensitivity reactions are: fall in blood pressure, tachycardia (and even anaphylactic shock), respiratory symptoms (including bronchial obstructions, laryngeal and pharyngeal oedema), abdominal symptoms (including abdominal cramps, vomiting) or skin symptoms (including urticaria, erythema, pruritus).

Patients should be carefully monitored for any signs and symptoms of a hypersensitivity reaction during and for at least 30 minutes after the administration of parenteral iron products. Should allergic reactions or signs of intolerance occur during administration, the treatment must be stopped immediately.

Adrenaline, e.g. in doses of 0.3 mg intramuscularly, is recommended in the first instance for the emergency drug treatment of acute anaphylactic/anaphylactoid reactions, and only after this antihistamines and/or corticosteroids (later onset of action).
In rare cases, fever or delayed allergic reactions (with a delay of several hours or even days) have been observed.
The risk of hypersensitivity reactions is increased in patients with known allergies including drug intolerance, a history of severe asthma, eczema and other forms of atopy, and also in patients with immunological or inflammatory disorders (e.g. systemic lupus erythematosus, rheumatoid arthritis).

Hypophosphataemia/hypophosphataemic osteomalacia

Parenteral iron can lead to hypophosphataemia, which is transient and without clinical symptoms in most cases. Hypophosphatemia requiring treatment has mainly been reported in individual cases, in patients with known risk factors and after sustained higher dosing.

Cases of symptomatic hypophosphataemia leading to hypophosphataemic osteomalacia, and fractures requiring clinical intervention, including surgery, were reported after market

introduction. In case of arthralgia or bone pain, patients should be advised to seek medical advice.

Patients receiving multiple higher doses as part of long-term treatment, and who have underlying risk factors (e.g. vitamin D deficiency, calcium and phosphate malabsorption, secondary hyperparathyroidism, hereditary haemorrhagic telangiectasia, inflammatory bowel disease and osteoporosis) should be monitored for hypophosphataemic osteomalacia, including serum phosphate control. In case of persistent hypophosphataemia, treatment with Ferinject should be re-evaluated.

Hepatic or renal insufficiency

Parenteral iron should only be administered to patients with hepatic dysfunction following a careful assessment of the risks and benefits.

Parenteral iron administration should be avoided in patients with hepatic dysfunction due to iron overload, especially those with porphyria cutanea tarda, or any acute liver disease.

Careful monitoring of the iron status is recommended to avoid iron overload.

Infections

Parenteral iron should be administered with caution in cases of acute or chronic infections, asthma, eczema or atopic allergies.

In the case of patients with bacteraemia, it is recommended to stop administration of Ferinject.

Extravasation

Paravenous administration should be avoided. It may irritate the skin and potentially cause a long-lasting, brownish discolouration on the injection/infusion site. The administration of Ferinject must be discontinued immediately if this occurs.

Other ingredients

One ml of Ferinject may contain up to 5.5 mg (0.24 mmol) of sodium. This must be taken into account when administering to people on a sodium-controlled diet.

4.5 *Interaction with other medicinal products and other forms of interaction*

Ferinject should not be administered concomitantly with oral iron preparations since the absorption of oral iron can be reduced.

See also section "4.1 Therapeutic indications"

4.6 *Fertility, pregnancy and lactation*

Pregnancy:
There are limited data from the use of Ferinject in pregnant women (see section 5.1). A careful benefit/risk evaluation is required before use during pregnancy and Ferinject 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 Ferinject 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 Ferinject can cross the placental barrier and that its use during pregnancy may influence skeletal development in the fetus. (see section 5.3).

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

Fertility:
There are no data on the effect of Ferinject on human fertility. Fertility was unaffected following Ferinject treatment in animal studies (see section 5.3).

4.7 *Effects on ability to drive and use machines*

No relevant studies have been performed. It is unlikely that Ferinject has an effect on 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 > 8,000 subjects received Ferinject, as well as those reported from the post-marketing

experience (see table footnotes for details).

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/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	Hypophosphataemi a			
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,	Flatulence	
		constipation, diarrhoea		
Skin and subcutaneous tissue disorders		Pruritus, urticaria, erythema, rash(3)	Angioedema(2), pallor(2), distant skin discolouration(2)	Face oedema(1)

Musculoskeletal and connective tissue disorders		Myalgia, back pain, arthralgia, pain in extremity, muscle spasms		Hypophosphataemic osteomalacia(1)
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; 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.

To reports any side effect(s):
Saudi Arabia:

- The National Pharmacovigilance Centre (NPC):

- SFDA Call Center: 19999
- E-mail: npc.drug@sfda.gov.sa
- Website: https://ade.sfda.gov.sa/

4.9 *Overdose*

Accidentally exceeding the cumulative total dose, which is necessary for correcting iron deficiency, can lead to accumulation of iron in the iron stores and ultimately to haemosiderosis in these patients. This can be prevented by preventive control of the iron parameters serum ferritin and transferrin saturation. An unwanted accumulation of iron is to be treated according to standard medical practice.

5. PHARMACOLOGICAL PROPERTIES

5.1 *Pharmacodynamic properties*

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

Ferinject 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 ^{59}Fe from radio-labelled Ferinject 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. Ferinject 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 Ferinject has been studied in different therapeutic areas necessitating 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 Ferinject (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 (correction phase), subjects received either Ferinject according to a simplified dosing grid using baseline Hb and body weight at screening (see section 4.2), placebo or no dose. At Weeks 12, 24, and 36 (maintenance phase) subjects received Ferinject (500 mg iron) or placebo if serum ferritin was
<100 ng/mL or 100-300 ng/mL with TSAT <20%. The treatment benefit of Ferinject vs. placebo was demonstrated with the primary efficacy endpoint, the change in the 6-minute walk test (6MWT) from baseline to Week 24 (33 ±11 , 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 Ferinject (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 Ferinject according to a simplified dosing grid using baseline Hb and body weight at screening (see section 4.2) or standard of care. At Week 12, (maintenance phase) subjects received Ferinject (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

Ferinject vs. standard of care was demonstrated with the primary efficacy endpoint, the change in weight- adjusted peak VO_2 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 Ferinject (n=97) to iron sucrose (n=86) in subjects with ID anaemia undergoing haemodialysis. Subjects received Ferinject 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 Ferinject: 1,700 mg). The primary efficacy endpoint was the percentage of subjects reaching an increase in Hb of
≥1.0 g/dL at 4 weeks after baseline. At 4 weeks after baseline, 44.1% responded to treatment with Ferinject (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 Ferinject (n=147) vs. oral iron (n=103). Subjects in the Ferinject 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 Ferinject 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 Ferinject group and 0.7 g/dL in the oral iron group (p=0.034, 95% CI: 0.0, 0.7).

Gastroenterology

Inflammatory bowel disease

Study VIT-IV-CL-008 was a randomised, open-label study which compared the efficacy of Ferinject vs. oral ferrous sulphate in reducing ID anaemia in subjects with inflammatory bowel disease (IBD). Subjects received either Ferinject (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 Ferinject 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 Ferinject vs. iron sucrose in subjects with remitting or mild IBD. Subjects receiving Ferinject were dosed according to a simplified dosing grid using baseline Hb and body weight (see section 4.2) 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 Ferinject (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 ≥2 g/dL). 83.8% of Ferinject-treated subjects vs. 75.9% of iron sucrose-treated subjects achieved a Hb increase ≥2 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 Ferinject (n=227) vs. ferrous sulphate (n=117) in women suffering from post-partum anaemia. Subjects received either Ferinject 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 Ferinject 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 Ferinject 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-2009-01, a randomised, open-label, study comparing Ferinject (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 Ferinject 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 Ferinject treated women and those treated with oral iron (11.4% Ferinject 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.

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*

Absorption Not applicable.

Distribution

After a single Ferinject dose of 100 to 1000 mg iron in patients with iron deficiency, peak total serum iron levels of 37 µg/ml to 333 µg/ml were measured after 15 minutes and 1.21 hours, respectively. The volume of distribution of the central compartment corresponds to the plasma volume (approximately 3 litres).

It was shown by means of positron emission tomography (PET) that iron from radiolabelled Ferinject was eliminated from the blood and transported into the bone marrow and into the reticuloendothelial system of the liver and spleen.

Metabolism

Ferric carboxymaltose is mainly taken up in the reticuloendothelial system of the liver, bone marrow and to a small extent in the spleen, and is then broken down into the components iron hydroxide and carbohydrates, with the iron being bound as ferritin. The iron is made available

for erythropoiesis via transferrin, as required. The carbohydrate breakdown products are maltotetraose, maltotriose, maltose and glucose.
Elimination
The plasma clearance of the administered iron was rapid with a terminal half-life of 7 to 12 hours and a mean residence time (MRT) of 11 to 18 hours. The renal elimination of iron was negligible.

Kinetics in specific patient groups
No studies with children have been conducted.
No studies in liver insufficiency have been performed.

5.3 *Preclinical data*

Pre-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeat dose toxicity and genotoxicity. Pre-clinical studies indicate that iron released from Ferinject crosses the placental barrier and is excreted in milk in limited, controlled amounts. In reproductive toxicology studies using iron replete rabbits Ferinject was associated with minor skeletal abnormalities in the fetus at maternally toxic levels. In a fertility study in rats, there were no effects on fertility for either male or female animals. These effects are considered transient, as no findings could be observed in the pre/postnatal development. The highest non-lethal intravenously administered single dose in rodents was 1000 mg iron/kg body weight. No long-term studies in animals have been performed to evaluate the carcinogenic potential of Ferinject. No evidence of allergic or immunotoxic potential has been observed. A controlled in-vivo test demonstrated no cross-reactivity of Ferinject with anti-dextran antibodies. No local irritation or intolerance was observed after intravenous administration.

6. PHARMACEUTICAL PARTICULARS

6.1 *List of excipients*

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

6.2 *Incompatibilities*

Ferinject may only be mixed with sterile 0.9% w/v saline solution. There are no compatibility studies with containers made of materials other than polyethylene or glass.

6.3 *Shelf life*

Shelf-life of the product as packaged for sale:

3 years.

Shelf life after opening of the vial:

Use the product immediately for microbiological reasons.

Shelf life after dilution with sterile 0.9% saline solution:

Use the solution for infusion (after dilution) as soon as possible for microbiological reasons. It has been shown that the diluted Ferinject solution is ~~is~~ chemically stable at ~~C~~room temperature for 12 hours..

Ferinject may only be used up to the date on the packaging marked “EXP”.

6.4. Special precautions for storage

Prescribed storage conditions: Store in the original packaging and not above 30°C. Do not freeze.

6.5. Nature and contents of container

Ferinject is supplied in a vial (type I glass) with a stopper (bromobutyl rubber) and an aluminium cap as: 10 mL solution containing 500 mg iron. Available in pack sizes of 1 and 5 vials.

6.6 Special precautions for disposal and other handling

The vials are intended for single use only.
Prior to use, the vials should be inspected for visible particles and damage. Only solutions that are homogenous and free of visible particles should be used.

Ferinject must only be mixed with 0.9% w/v sodium chloride solution. Other intravenous diluting solutions and medicinal products must not be used because there is a risk of sediment formation and/or interaction. For instructions on dilution, see section “Posology and method of administration”.

7. MARKETING AUTHORISATION HOLDER

Vifor (International) Inc.
Rechenstrasse 37
9014 St. Gallen
Switzerland

Manufactured by IDT Biologika GmbH, Germany for Vifor (International) Inc.

8. MARKETING AUTHORIZATION NUMBER

1x10ml vials: 2-557-15
5x10ml vials: 1-557-15

9. DATE OF FIRST AUTHORIZATION / RENEAL OF THE AUTHORIZATION

Date of the first authorization: 03 August 2015
Date of the last renewal: 10 December 2020

10. DATE OF REVISION TEXT

June 2021