

Ferinject®

Composition

Active substances

Iron as ferric carboxymaltose.

Excipients

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

Ferinject contains up to 5.5 mg of sodium per ml.

Pharmaceutical form and active substance quantity per unit

Dispersion for injection/infusion for intravenous (IV) administration.

1 ml of dispersion 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 (Hb), haematocrit, red cell count, MCV and MCH).

Dosage/Administration

During and after each use of Ferinject, patients must be carefully monitored for signs or symptoms 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 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".

Table 1: 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)

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:

$$\text{Total iron deficit [mg]} = \text{total cumulative dose [mg]} =$$

$$\text{Body weight}^{(A)} \text{ [kg]} \times (\text{Target Hb}^{(B)} - \text{Actual Hb})^{(C)} \text{ [g/dL]} \times 2.4^{(D)} + \text{reserve iron}^{(E)} \text{ [mg]}$$

- (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 Hb target 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 10000.
 0.0034: The iron content of Hb is 0.34%.
 0.07: Blood volume 70 mL/kg body weight ≈ 7% of body weight.
 10000 = The conversion factor 1 g/dL = 10000 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

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 IV injection) or
- 20 mg iron/kg body weight (administered as IV 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 IV injection using the undiluted dispersion. 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 IV 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 IV infusion and must be diluted in this case. The maximum permissible single dose is 20 mg iron/kg body weight, but must not exceed 1000 mg iron. 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 dispersion 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 IV 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 paediatric 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;
- known serious hypersensitivity to other parenteral iron products;
- anaemia without confirmed iron deficiency;
- evidence of iron overload;
- first trimester of pregnancy.

Warnings and precautions*Hypersensitivity reactions*

The IV 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 IV 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

Ferinject contains up to 5.5 mg (0.24 mmol) sodium per ml of undiluted solution, equivalent to 0.3% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Interactions

Ferinject should not be administered concomitantly with oral iron preparations since the absorption of oral iron can be reduced (see also "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 "Contraindications"), 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 IV 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 ($\leq 1\%$). 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 9456 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: $<1/10$, $\geq 1/100$

Uncommon: $<1/100$, $\geq 1/1000$

Rare: $<1/1000$, $\geq 1/10000$

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 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.

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 unexpected ADR compared to adults. The most common ADRs were 2 cases each of pyrexia and rash with Ferinject 7.5 mg iron/kg 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

Uncommon: 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: generalised erythematous, macular, maculopapular and pruritic rash), pruritus, urticaria, erythema.

Rare: Angiodema, distant skin discolouration, pallor.

Not known: Dermatitis, face oedema.

Musculoskeletal and connective tissue disorders

Uncommon: Arthralgia, 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, oedema 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 IV 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 dispersion 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 $\times$ /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 Hb 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 1029 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 Hb 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 $\mu\text{g/ml}$ 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-lethal intravenously 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 foetus 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 IV 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

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

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.

Special precautions for storage

Prescribed storage conditions: Store in the original packaging and not above 30°C. Do not freeze. Keep out of the reach of children.

Instructions for handling

Prior to use, the vials should be inspected for visible particles and damage

Only dispersions that are homogenous and free of visible particles should be used.

The vials are intended for single use only.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Ferinject IV 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

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Date of revision of the text

November 2024