Ferinject®

Composition
Active substance
Iron as ferric carboxymaltose
Excipients
Sodium hydroxide, hydrochloric acid, water for injection to make up the solution
Pharmaceutical form and quantity of active substance per unit
Solution for intravenous administration.
1 ml of solution contains 50 mg iron as ferric carboxymaltose.
One 10 ml vial contains 500 mg iron as ferric carboxymaltose.
Indications / Possible therapeutic 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 / Use
A single dose of Ferinject® should not exceed 1000 mg iron (20 ml) per day or 20 mg iron (0.4 ml) per kg body weight. The maximum total weekly dose is 1000 mg (20 ml).
In patients with chronic kidney disease requiring haemodialysis, a maximum dose of 200 mg iron injected once daily must not be exceeded.
The cumulative total dose of Ferinject® (in mg iron) must be individually calculated and must not be exceeded. The total cumulative dose is calculated as follows for each patient using the Ganzoni formula:
Total iron deficit [mg] = cumulative total dose [mg] =
body weight [kg] × (target Hb – actual Hb) [g/dl] × 2.4 + iron stores [mg]
For body weight below 35 kg: Target Hb = 13 g/dl (8.1 mmol/l) and iron stores = 15 mg/kg
For body weight of 35 kg and over: Target Hb = 15 g/dl (9.3 mmol/l) and iron stores = 500 mg
To convert Hb [mM] into Hb [g/dl], multiply the Hb [mM] by a factor of 1.61145.
Factor 2.4 = 0.0034 × 0.07 × 10000 (iron content of haemoglobin ≙ 0.34% / blood volume ≙ 7% of body weight / factor 10000 = conversion of g/dl into mg/l)
The total iron deficit (mg) and the total quantity of Ferinject® (ml) for patients with a body weight less than 35 kg and a target Hb of 13 g/dl and for patients with a body weight of 35 kg and over and a target Hb of 15 g/dl were calculated using the Ganzoni formula and are shown in the following table.

Body weight	**Quantity in ml Ferinject® (mg iron) 1 ml Ferinject® corresponds to 50 mg iron**			
[kg]	**Hb 6 g/dl**	**Hb 7.5 g/dl**	**Hb 9 g/dl**	**Hb 10.5 g/dl**
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 overweight patients, the calculation should be made on the assumption of a normal body weight/blood volume relationship.
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.
Ferinject® can be administered intravenously at a dose of up to 1000 mg iron. For doses greater than 200 and up to 500 mg iron, Ferinject® should be administered at a rate of 100 mg iron/min. For doses greater than 500 and up to 1000 mg iron, Ferinject® should be administered over 15 minutes.
Ferinject® must be administered only by the intravenous route either undiluted as a bolus injection or undiluted directly into the venous limb of the dialyser during a haemodialysis session or by infusion. For an infusion Ferinject® must be diluted only with sterile 0.9% m/V sodium chloride solution (see "Instructions for handling").
Ferinject may not be administered by subcutaneous or intramuscular injection.
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" for more details).
Special dosage instructions
There is no experience with Ferinject® in liver 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 for use
The intravenous administration of parenteral iron products can cause immediate-type acute hypersensitivity reactions (anaphylactoid/anaphylactic reactions), which may be fatal. Such reactions have been reported even where previous administrations of parenteral iron products have been tolerated without complications. 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 undesirable effects from 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).
Paravenous injection should be avoided. It may cause irritation of the skin and potentially long lasting brown discoloration at the site of injection. If this occurs, the administration of Ferinject® should be stopped immediately.
Parenterally administered iron preparations can cause hypophosphataemia which in most cases is transient and without clinical symptoms. Incidental cases of hypophosphataemia requiring medical attention were reported, mainly in patients with known risk factors and after prolonged exposure.
In patients with liver function disorders, parenteral iron should be used only after a careful risk-benefit assessment.
In patients with liver function disorder resulting from iron overload, especially in cases of porphyria cutanea tarda, and in any acute liver disorder, parenteral administration of iron should be avoided.
To avoid iron overload, careful monitoring of iron status is advisable.
In patients with acute or chronic infection, asthma, eczema or atopic allergies, parenteral iron should be used with caution.
In patients with bacteraemia it is advisable to stop the administration of Ferinject®.
One ml of Ferinject® can contain up to 5.5 mg (0.24 mmol) sodium. This should be borne in mind in individuals 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 / Possible therapeutic 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.
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 subjects 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
The most commonly reported undesirable effects are nausea, injection/infusion site reactions, hypophosphataemia, headache, flushing, dizziness, hypertension.
The most serious undesirable effects related to Ferinject are hypersensitivity reactions which are uncommon (see immune system disorders).
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)
Rare: 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, gammaglutamyltransferase (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, rash erythematous, -generalised, -macular, -maculo-papular and -pruritic)

Rare: Angioedema, dermatitis, pallor and face oedema

Muscles and connective tissue disorders

Uncommon: Myalgia, back pain, arthralgia, muscle spasms, pain in the extremity

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

· Jordan

Jordan Food and Drug Administration- Rational Drug Use and Pharmacovigilance department.

e-mail: jpc@jfda.jo

Website: www.jfda.jo

Overdose

Administration of more than the calculated total cumulative dose may lead to iron accumulation in the iron stores and potentially to haemosiderosis. This can be recognised and prevented by monitoring iron parameters such as serum ferritin and transferrin saturation. If iron accumulation has occurred, treat 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.

Pharmacokinetics

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 special patient populations

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.

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 storage instructions

Prescribed storage conditions:

Do not store above 30°C. Do not freeze.

Store in the original package.

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.

Dilution table for Ferinject® in sterile 0.9% w/v saline solution

Quantity of Ferinject®	Quantity of iron	Quantity of sterile 0.9% w/v saline solution	Minimum infusion period
2 to 4 ml	100 to 200 mg	50 ml	3 minutes
>4 to 10 ml	>200 to 500 mg	100 ml	6 minutes
>10 to 20 ml	>500 to 1000 mg	250 ml	15 minutes

For stability reasons, dilutions with less than 2 mg iron/ml are not permitted.

Packs

Vial: 1 × 10 ml (B)

Marketing authorisation holder and Batch releaser

Hikma Pharmaceuticals
Bayader Wadi El Seer
Industrial Area
P.O. Box 182400
Amman 11118, Jordan
Tel: + (962-6) 5802900
Fax: + (962-6) 5817102
Website: www.hikma.com

Manufacturing site

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Germany
Bipso GmbH
Robert Gerwing -Str.4
78224 Singen
Germany

Date of revision of the text

28 March 2019

Council of Arab Health Ministers, Union of Arab Pharmacists

THIS IS A MEDICAMENT

- Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are the experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

hikma.

Keep medicament out of the reach of children
Rev.03/2019