Name of product

Venofer®

Composition

Active substance: Iron in the form of saccharated ferric oxide

Excipient

Water for Injection q.s. ad solut.

Osmolarity: approx. 1250 mOsm/L; pH: 10.5–11.0.

Pharmaceutical form and quantity of active substance per unit

Solution for injection for i.v. administration.

Each 5 mL ampoule contains 100 mg iron.

Each 5 mL vial contains 100 mg iron.

Each 2.5 mL vial contains 50 mg iron.

Therapeutic indications/applications

Iron deficiency in patients in whom oral iron therapy is not sufficiently effective or not feasible, such as:

- Intolerance to oral iron preparations.
- Inflammatory gastrointestinal disorders (e.g. ulcerative colitis) which may be aggravated by oral iron therapy.
- Treatment-refractory iron deficiency states where unreliability in taking oral iron preparations is suspected.

Venofer should only be administered where the indication is confirmed by appropriate investigations. Suitable laboratory analyses are haemoglobin, serum ferritin, transferrin saturation.

Administration of Venofer to children below 3 years of age is not recommended due to lack of experience.

Posology/administration

Venofer may only be administered slowly via the intravenous route.

Venofer must NOT be administered subcutaneously or intramuscularly.

During and after each administration of Venofer, 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).

The cumulative dose of Venofer must be calculated for each patient individually and must not be exceeded. The dose is calculated on the basis of body weight and Hb value.

If the required total dose exceeds the maximum permissible single dose of 200 mg (injection) or 500 mg (infusion), then the administration of the total dose must be divided.

Calculating the dose

The total cumulative dose of Venofer, equivalent to the total iron deficit (mg), is determined by the haemoglobin level (Hb) and body weight (BW). The dose of Venofer must be individually calculated for each patient according to the total iron deficit calculated with the following Ganzoni formula:

Total iron deficit [mg] = [BW [kg] × (target Hb - actual Hb) [g/dL] × 2.4*] + storage iron [mg]

Less than 35 kg BW: target Hb = 13 g/dL and storage iron = 15 mg/kg BW

35 kg BW and above: target Hb = 15 g/dL and storage iron = 500 mg

* Factor 2.4 = 0.0034 (iron content of Hb = 0.34%) × 0.07 (blood volume = 7% of BW) × 1000 (conversion of [g] to [mg]) x 10

Total Venofer to be administered (in mL) = Total iron deficit [mg] / 20 mg iron/mL

Total amount of Venofer (mL) to be administered according to body weight and actual Hb level:

BW	Total amount of Venofer (20 mg iron per mL) to be administered			
	Hb 6.0 g/dL	Hb 7.5 g/dL	Hb 9.0 g/dL	Hb 10.5 g/dL
10 kg	15.0 mL	15.0 mL	12.5 mL	10.0 mL
15 kg	25.0 mL	22.5 mL	17.5 mL	15.0 mL
20 kg	32.5 mL	27.5 mL	25.0 mL	20.0 mL
25 kg	40.0 mL	35.0 mL	30.0 mL	27.5 mL
30 kg	47.5 mL	42.5 mL	37.5 mL	32.5 mL
35 kg	62.5 mL	57.5 mL	50.0 mL	45.0 mL
40 kg	67.5 mL	60.0 mL	55.0 mL	47.5 mL
45 kg	75.0 mL	65.0 mL	57.5 mL	50.0 mL
50 kg	80.0 mL	70.0 mL	60.0 mL	52.5 mL
55 kg	85.0 mL	75.0 mL	65.0 mL	55.0 mL
60 kg	90.0 mL	80.0 mL	67.5 mL	57.5 mL
65 kg	95.0 mL	82.5 mL	72.5 mL	60.0 mL
70 kg	100.0 mL	87.5 mL	75.0 mL	62.5 mL
75 kg	105.0 mL	92.5 mL	80.0 mL	65.0 mL
80 kg	112.5 mL	97.5 mL	82.5 mL	67.5 mL

BW	Total amount of Venofer (20 mg iron per mL) to be administered			
	Hb 6.0 g/dL	Hb 7.5 g/dL	Hb 9.0 g/dL	Hb 10.5 g/dL
85 kg	117.5 mL	102.5 mL	85.0 mL	70.0 mL
90 kg	122.5 mL	107.5 mL	90.0 mL	72.5 mL

Target Hb value

Below 35 kg BW:	Target Hb = 13 g/dL
35 kg BW and above:	Target Hb = 15 g/dL

To convert Hb (mM) to Hb (g/dL), multiply the former by 1.6.

If the required total dose exceeds the maximum permissible single dose of 200 mg (injection) or 500 mg (infusion), then the administration of the total dose must be divided.

Normal posology

Adults: 5 – 10 mL of Venofer (100 – 200 mg iron) one to three times a week. For administration time and dilution ratio see “Administration”.

Children above 3 years of age: There is a limited amount of data in children under study conditions. If there is a clinical need, it is recommended not to exceed 0.15 mL of Venofer (3 mg iron) per kg body weight not more than three times per week. For administration time and dilution ratio, see under “Administration”.

Maximum tolerated single and weekly dose

Adults

As an injection, maximum tolerated dose per day given not more than 3 times per week:

- 10 mL of Venofer (200 mg iron) injected over at least 10 minutes.

As an infusion, maximum tolerated dose per day given not more than once per week:

- Patients above 70 kg body weight: 500 mg iron (25 mL of Venofer) over at least 3 ½ hours
- Patients of 70 kg body weight and below: 7 mg iron/kg body weight over at least 3 ½ hours

The infusion times specified in the “Administration” section must be strictly adhered to, even if the patient does not receive the maximum tolerated single dose.

If the treatment is not successful (increase in haemoglobin of approx. 0.1 g/dL of blood/day and approx. 1.0–2.0 g/dL after 1–2 weeks), the original diagnosis needs to be reviewed and any persistent blood loss ruled out.

Administration

Venofer must only be administered intravenously by drip infusion, by slow injection or directly into the venous line of the dialysis machine.

Venofer must not be administered intramuscularly or subcutaneously.

If the required total dose exceeds the maximum permissible single dose then the administration of the total dose must be divided.

Intravenous drip infusion

Venofer must only be diluted in sterile 0.9% m/v sodium chloride (NaCl) solution. Dilution must take place immediately prior to infusion and the solution should be administered as follows:

Venofer dose (mg of iron)	Venofer dose (mL of Venofer)	Maximum dilution volume of sterile 0.9% m/V NaCl solution	Minimum Infusion Time
50 mg	2.5 mL	50 mL	8 minutes
100 mg	5 mL	100 mL	15 minutes
200 mg	10 mL	200 mL	30 minutes
300 mg	15 mL	300 mL	1.5 hours
400 mg	20 mL	400 mL	2.5 hours
500 mg	25 mL	500 mL	3.5 hours

Intravenous injection

Venofer may be administered by slow intravenous injection at a rate of 1 mL undiluted solution per minute and not exceeding 10 mL (200 mg iron) per injection.

The patient's arm is to be stretched after injection. Paravenous leakage must be avoided, as the leakage of Venofer at the injection site may lead to pain, inflammation, tissue necrosis and potentially prolonged brown discoloration of the skin (please refer also to “Warnings and precautions”).

Injection into venous line of the dialysis machine

Venofer may be administered during a haemodialysis session directly into the venous line of the dialysis machine under the same conditions as for intravenous injection.

Contraindications

- Known hypersensitivity to the active substance or any of the excipients according to the composition.
- Anaemia not caused by iron deficiency (e.g. haemolytic anaemia, megaloblastic anaemia due to Vitamin B_{12} deficiency, disorders of erythropoiesis, bone marrow hypoplasia, lead anaemia).
- Evidence of iron overload (haemochromatosis, haemosiderosis) or hereditary disturbances in utilisation of iron (sidero-achrestic anaemia, thalassaemia, porphyria cutanea tarda).
- The first trimester of pregnancy.

Warnings and precautions

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. In the case of patients who have had hypersensitivity reactions to iron dextran, Venofer may only be administered in compelling situations and under strict precautionary measures.

Treatment with Venofer should be prescribed by the attendant physician only after carefully determining the indication.

Venofer 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 Venofer, 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 bronchospasm, 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).

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).

In patients with liver dysfunction, parenteral iron should only be administered after careful risk/benefit assessment. Parenteral iron administration should be avoided in patients with hepatic dysfunction where iron overload is a precipitating factor. Careful monitoring of iron status is recommended to avoid iron overload.

In patients with elevated ferritin level parenteral iron may have an unfavourable effect on the course of a bacterial or viral infection.

Parenteral iron should be used with caution in the case of acute or chronic infection. In patients with chronic infection, a risk/benefit evaluation should be performed. It is recommended that the administration of Venofer is stopped in patients with bacteraemia.

Paravenous leakage must be avoided, as the leakage of Venofer at the injection site can lead to pain, inflammation, tissue necrosis and potentially prolonged brown discoloration of the skin. If this occurs, the administration of Venofer must be stopped immediately. To date, tissue necrosis has not been found to occur in clinical studies using Venofer.

A drop in blood pressure is commonly observed in association with the intravenous administration of iron. Therefore, the infusion should be administered with caution.

Particular caution with the administration of Venofer is needed in patients with hepatic impairment, decompensated cirrhosis of the liver, epidemic hepatitis, Osler-Rendu-Weber syndrome, infectious kidney disorders in the acute phase, uncontrolled hyperparathyroidism.

Interactions

Venofer is only indicated if oral iron therapy cannot be implemented or is not adequately effective. In this last case, it is not recommended to administer Venofer at the same time as oral iron preparations, as the absorption of orally administered iron may be reduced.

Pregnancy/lactation

There is insufficient data from the use of iron sucrose in pregnant women in the first trimester. Data from the use of Venofer in pregnant women in the second and third trimester (303 pregnancy outcomes) showed no safety concerns for the mother or newborn infant.

It is so far unknown whether the iron(III) hydroxide sucrose complex, which is present in Venofer, crosses the placenta. Transferrin-bound iron does cross the placental barrier; lactoferrin-bound iron passes into breast milk.

There are no investigations on the influence on iron levels in newborn infants.

Venofer is contraindicated during the first trimester of pregnancy (see “Contraindications”) and may only be used during the 2nd and 3rd trimester if strictly indicated.

A careful 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”).

Body weight before the onset of pregnancy should be used to calculate the required quantity of iron, to avoid a potential overdose.

There is limited information on the excretion of iron in human milk following administration of intravenous iron sucrose. In one clinical study, 10 healthy breast-feeding mothers with iron deficiency received 100 mg iron in the form of iron sucrose. Four days after treatment, the iron content of the breast milk had not increased and there was no difference from the control group (n=5). It cannot be excluded that newborns/infants may be exposed to iron derived from Venofer via the mother’s milk, therefore the risk/benefit should be assessed.

For data from animal studies, see “Preclinical data”.

Effects on ability to drive and use machines

No corresponding studies have been carried out. Venofer is unlikely to influence the ability to drive or use machines. However, if symptoms such as dizziness, confusion or light-headedness occur following the administration of Venofer, affected patients should not drive a car or use machines until the symptoms have abated.

Undesirable effects

The most common adverse drug reaction (ADR) in clinical trials with Venofer was dysgeusia, which occurred with a rate of 4.5 events per 100 subjects. Other common undesirable effects included nausea, hypotension, hypertension and infusion site pain, occurring with a rate between 1 and 2 events per 100 subjects.

The most important serious adverse drug reactions associated with Venofer are hypersensitivity reactions, which occurred with a rate of 0.25 events per 100 subjects in clinical trials. Hypersensitivity reactions of an immediate nature (anaphylactoid/anaphylactic reactions) were rare. In general, anaphylactoid/anaphylactic reactions are very serious adverse effects which can be fatal (see “Warnings and precautions”). Symptoms include, among others, circulatory collapse, hypotension, tachycardia, respiratory symptoms (bronchospasm, larynx and pharynx angioedema, etc.), abdominal symptoms (abdominal pain, vomiting, etc.), and skin symptoms (urticaria, erythema, pruritus etc.).

The following adverse reactions were reported in 4,064 subjects in clinical studies in temporal relationship with the administration of Venofer, whereby a causal relationship may be assumed. The frequency of the below adverse drug reactions is classified as common (<1/10 to ≥1/100), uncommon (<1/100 to ≥1/1,000) and rare (<1/1,000 to ≥1/10,000).

Immune system disorders

Uncommon: Hypersensitivity reactions.

Metabolism and nutrition disorders

Uncommon: Serum ferritin increased.

Nervous system

Common: Dysgeusia, dizziness.

Uncommon: Headache, paraesthesia, hypoaesthesia.

Rare: Syncope, somnolence.

Cardiac disorders

Uncommon: Hypotension and collapse, tachycardia.

Rare: Palpitations.

Vascular disorders

Common: Hypotension, hypertension.

Uncommon: Flushing, phlebitis.

Respiratory organs

Uncommon: Dyspnoea.

Renal and urinary disorders

Uncommon: Chromaturia.

Gastrointestinal disorders

Common: Nausea.

Uncommon: Vomiting, abdominal pain, diarrhoea, constipation.

Hepatobiliary disorders

Uncommon: Alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased.

Rare: Blood lactate dehydrogenase increased.

Skin and subcutaneous tissue disorders

Uncommon: Pruritus, rash.

Musculoskeletal system

Uncommon: Muscle spasms, myalgia, arthralgia, pain in extremity, back pain.

General disorders and administration site conditions

Common: Injection/infusion site reactions[1)].

Uncommon: Chest pain, chills, asthenia, fatigue, oedema peripheral, pain.

Rare: Hyperhidrosis, pyrexia.

[1)] The most frequently reported adverse reactions are: pain, extravasation, irritation, reaction, discolouration, haematoma and pruritus at the injection/infusion site.

The following adverse drug reactions have been notified in spontaneous reports from the post-marketing setting:

Frequency not known: depressed level of consciousness, bradycardia, thrombophlebitis.

Overdose

Overdose can cause iron overload, which may manifest itself as haemosiderosis. Overdose should be treated, as deemed necessary by the treating physician, with an iron chelating agent or according to standard medical practice.

Properties/Effects

ATC Code: B03AC

Mechanism of action/Pharmacodynamics

Iron sucrose, the active ingredient of Venofer, is composed of a polynuclear iron(III)-hydroxide core surrounded by a large number of non-covalently bound sucrose molecules. The complex has a weight average molecular weight (Mw) of approximately 43 kDa. The polynuclear iron core has a structure similar to that of the core of the physiological iron storage protein ferritin. The complex is designed to provide, in a controlled manner, utilisable iron for the iron transport and storage proteins in the body (i.e., transferrin and ferritin, respectively).

Following intravenous administration, the polynuclear iron core from the complex is taken up predominantly by the reticuloendothelial system in the liver, spleen, and bone marrow. In a second step, the iron is used for the synthesis of Hb, myoglobin and iron-containing enzymes, or stored primarily in the liver in the form of ferritin.

Clinical efficacy

In clinical studies, it was shown that the haematological response to intravenously administered iron(III)-hydroxide sucrose complex is more rapid than the response to orally administered soluble preparations.

Pharmacokinetics

Distribution

The ferrokinetics of iron sucrose labelled with ^{52}Fe and ^{59}Fe were assessed in 6 patients with anaemia and chronic renal failure. In the first 6–8 hours, ^{52}Fe was taken up by the liver, spleen and bone marrow. The radioactive uptake by the macrophage-rich spleen is considered to be representative of the reticuloendothelial iron uptake.

Following intravenous injection of a single 100 mg iron dose of iron sucrose in healthy volunteers, maximum total serum iron concentrations were attained 10 minutes after injection and had an average concentration of 538 µmol/L. The volume of distribution of the central compartment corresponded well to the volume of plasma (approximately 3 litres).

Metabolism

Upon injection, sucrose largely dissociates and the polynuclear iron core is mainly taken up by the reticuloendothelial system of the liver, spleen, and bone marrow. At 4 weeks after administration, red cell iron utilization ranged from 68 to 97%.

Elimination

The iron sucrose complex has a weight average molecular weight (Mw) of approximately 43 kDa, which is sufficiently large to prevent renal elimination. The renal elimination of iron, occurring in the first 4 hours after injection of a Venofer dose of 100 mg iron, corresponded to less than 5% of the dose. After 24 hours, the total serum iron concentration was reduced to the pre-dose level. Renal elimination of sucrose was about 75% of the administered dose.

Kinetics in specific patient groups

It is not yet known what effect renal and hepatic impairment have on the pharmacological properties of the iron(III)-hydroxide sucrose complex (Warning: see “Warnings and precautions”).

Preclinical data

Limited preclinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity and toxicity to reproduction and development.

In embryo-foetal toxicity studies using iron replete animals, iron sucrose was associated with minor skeletal abnormalities in the rat foetus at dosages that caused maternal toxicity.

Preclinical data do not indicate direct or indirect harmful effects to the nursing child. In lactating rats treated with ^{59}Fe-labelled iron sucrose, low secretion of iron into the milk and transfer of iron into the offspring was observed. Non-metabolised iron sucrose is unlikely to pass into the mother’s milk.

Other warnings

Incompatibilities

Venofer must only be mixed with sterile 0.9% (m/V) NaCl solution under aseptic conditions. There is the potential for precipitation and/or interaction if mixed with other solutions or medicinal products. The compatibility with containers other than glass, polyethylene and PVC is not known.

Effects on diagnostic methods

None known.

Shelf life

Once opened, the ampoules or vials must be used immediately. The dilute solutions prepared with sterile 0.9% (m/V) NaCl solution must be administered as soon as possible for microbiological reasons. They must not be stored above 25°C and must be administered within 12 hours.

Venofer may not be used after the date marked "EXP" on the packaging.

Special precautions for storage

Specified storage conditions: Not above 25°C, protected from light. The Venofer solution must not be frozen or exposed to extreme heat.

Precautions for handling

Before use, the ampoules or vials should be visually inspected for sediments and damage. Use only those containing a homogeneous and sediment-free solution.

Pack sizes

5 ampoules (5 mL) each containing 100 mg iron (B)

7. *Marketing authorisation holder*

Vifor (International) AG, St. Gallen.

Local Representative

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