

DATA SHEET

VENOFER®

Iron Sucrose

Presentation

Venofer is a dark brown, non transparent, sterile aqueous solution of iron sucrose in water for injections. Venofer contains 20 mg/mL iron as iron sucrose (iron(III)-hydroxide sucrose complex) corresponding to 100 mg iron per ampoule. The inactive ingredients are: Water for Injection and sodium hydroxide.

Uses

Actions

Pharmacology:

The polynuclear iron(III)-hydroxide cores are superficially surrounded by a large number of non-covalently bound sucrose molecules resulting in a complex whose molecular mass M_w is approx. 43 kDa. This is sufficiently large to prohibit renal elimination. The resulting complex is stable and does not release ionic iron under physiological conditions. The iron in the polynuclear cores is bound in a similar structure as in the case of physiologically occurring ferritin.

Pharmacodynamics:

The ferrokinetics of Venofer labelled with ^{59}Fe and ^{52}Fe were assessed in 6 patients with anaemia and chronic renal failure. Plasma clearance of ^{52}Fe was in the range of 60 to 1090 minutes. ^{52}Fe was distributed to the liver, spleen and bone marrow. At two to four weeks after administration, the maximum red blood cell utilization of ^{59}Fe ranged from 68% to 97%.

Pharmacokinetics

Following intravenous injection of a single dose of Venofer containing 100 mg iron in healthy volunteers, maximum iron levels, averaging 538 $\mu\text{mol/l}$, were obtained 10 minutes after injection. The volume of distribution of the central compartment corresponded well to the volume of plasma (approximately 3 litres).

The iron injected was rapidly cleared from the plasma, the terminal half-life being approx. 6 h. The volume of distribution at steady state was about 8 litres, indicating a low iron distribution in the body fluid. Due to the lower stability of iron sucrose in

comparison to transferrin, a competitive exchange of iron to transferrin was observed. This resulted in iron transport of approx. 31 mg Fe(III)/24 h.

Renal elimination of iron, occurring in the first 4 h after injection, corresponds to less than 5% of the total body clearance. After 24 h the plasma levels of iron were reduced to the pre-dose iron level and about 75% of the dosage of sucrose was excreted.

Indications

Venofer is indicated for the treatment of iron deficiency in the following indications:

- Where there is a clinical need for a rapid iron supply,
- In patients who cannot tolerate oral iron therapy or who are non-compliant,
- In active inflammatory bowel disease where oral iron preparations are ineffective.

Venofer should only be administered where the indication is confirmed by appropriate investigations (e.g. Hb, serum ferritin, serum iron).

DOSAGE AND ADMINISTRATION

Administration

Venofer must only be administered by the intravenous route. This may be by a slow intravenous injection or by an intravenous drip infusion.

Venofer must not be used for intramuscular injection.

Intravenous drip infusion:

Venofer must be diluted only in sterile 0.9% m/V sodium chloride solution:

- 100 mg iron (5 ml Venofer) in maximum 100 ml sterile 0.9% m/V sodium chloride solution
- 500 mg iron (25 ml Venofer) in maximum 500 ml sterile 0.9% m/V sodium chloride solution

For stability reasons, dilutions to lower Venofer concentrations are not permissible.

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

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

Dilution must take place immediately prior to infusion the solution should be administered as follows:

- 100 mg iron (5 ml Venofer) in at least 15 minutes
- 200 mg iron (10 ml Venofer) in at least 30 minutes

- 300 mg iron (15 ml Venofer) in at least 1 ½ hours
- 400 mg iron (20 ml Venofer) in at least 2 ½ hours

Intravenous injection:

Venofer can be administered undiluted by slow intravenous injection as follows:

- 100 mg iron (5 ml Venofer) in at least 5 minutes
- 200 mg iron (10 ml Venofer) in at least 10 minutes.

Injection into dialyser:

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

DOSAGE

Calculation of dosage:

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

Total iron deficit [mg] = body weight [kg] x (target Hb-actual Hb) [g/dl] x 2.4* + depot iron [mg]

Below 35 kg body weight: Target Hb = 13 g/dl and depot iron = 15 mg/kg body weight

35 kg body weight and above: Target Hb = 15 g/dl and depot iron = 500 mg

* Factor 2.4 = 0.0034 x 0.07 x 1000: Iron content of haemoglobin ≈ 0.34%
 Blood volume ≈ 7% of body weight
 Conversion from g/dl to mg/l = Factor 1000

Total amount of Venofer to be administered (in ml) = $\frac{\text{Total iron deficit [mg]}}{20\text{mg/ml}}$

The table below indicates the total number of ampoules of Venofer to be administered (1 ampoule of Venofer corresponds to 5 mL)

Body Weight (kg)	Total number of Venofer ampoules to be administered (1 ampoule of Venofer corresponds to 5mL)			
	Hb 6 g/dL	Hb 7.5 g/dL	Hb 9 g/dL	Hb 10.5 g/dL
5	1.5	1.5	1.5	1

Body Weight (kg)	Total number of Venofer ampoules to be administered (1 ampoule of Venofer corresponds to 5mL)			
	Hb 6 g/dL	Hb 7.5 g/dL	Hb 9 g/dL	Hb 10.5 g/dL
10	3	3	2.5	2
15	5	4.5	3.5	3
20	6.5	5.5	5	4
25	8	7	6	5.5
30	9.5	8.5	7.5	6.5
35	12.5	11.5	10	9
40	13.5	12	11	9.5
45	15	13	11.5	10
50	16	14	12	10.5
55	17	15	13	11
60	18	16	13.5	11.5
65	19	16.5	14.5	12
70	20	17.5	15	12.5
75	21	18.5	16	13
80	22.5	19.5	16.5	13.5
85	23.5	20.5	17	14
90	24.5	21.5	18	14.5

To convert Hb (mM) to Hb (g/dl), multiply the former by 1.61145.

If the total necessary dose exceeds the maximum allowed single dose, then the administration has to be split, please see section "Dosage and Administration".

Calculation of iron deficit secondary to blood loss and to support autologous blood donation:

The required Venofer dose to compensate the iron deficit is calculated according to the following formulas:

If the quantity of blood lost is known:

The administration of 200 mg i.v. iron (= 10 mL Venofer) results in an increase in haemoglobin which is equivalent to 1 unit blood (= 400 mL with 15 g/dL Hb content).

Iron to be replaced [mg] = number of blood units lost x 200 or

Amount of Venofer needed (mL) = number of blood units lost x 10

If the Hb level is reduced:

Use the previous formula considering that the depot iron does not need to be restored.

Iron to be replaced [mg] = body weight [kg] x 2.4 x (target Hb -actual Hb) [g/dL],

e.g.: body weight 60 kg, Hb deficit = 1 g/dL → 150mg iron to be replaced

→ 7.5mL Venofer needed.

Normal posology:

Adults and the elderly:

5 - 10 mL Venofer (100 - 200 mg iron) one to three times a week depending on the haemoglobin level.

Children:

There is limited data on children under study conditions. If there is a clinical need, it is recommended not to exceed 0.15 mL Venofer (3 mg iron) per kg one to three times per week depending on the haemoglobin level.

Maximum tolerated single dose:

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

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

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

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

The maximum tolerated single dose is 7 mg iron per kg body weight given once per week, but not exceeding 500 mg iron. Administration time and dilution ratio see 'Dosage and Administration' section. The infusion times given in the 'Dosage and Administration' section must be strictly adhered to, even if the patient does not receive the maximum tolerated single dose.

CONTRAINDICATIONS

The use of Venofer is contra-indicated in cases of:

- Anaemia not caused by iron deficiency.
- Iron overload or disturbances in utilisation of iron.

- Known hypersensitivity to Venofer or any of its inactive components.
- Pregnancy first Trimester.

Warnings and PRECAUTIONS

Parenterally administered iron preparations can cause allergic or anaphylactoid reactions, which can be potentially fatal. Therefore, antiallergic treatment should be in place with the established cardio-pulmonary resuscitation procedures.

In patients with a history of asthma, eczema, other atopic allergies or allergic reactions to other parenteral iron preparations, Venofer should be administered with care as they are particularly at risk of an allergic reaction. However it was shown in a study with a limited number of iron dextran sensitive patients that Venofer could be administered with no complications.

Venerfer should be administered with care in patients with liver dysfunction.

Venerfer must be used with care in patients with acute or chronic infection who have excessive ferritin values as parenterally administered iron can unfavourably influence a bacterial or viral infection.

Hypotensive episodes may occur if the injection is administered too rapidly.

Paravenous leakage must be avoided because leakage of Venofer at the injection site may lead to pain, inflammation, tissue necrosis and brown discoloration of the skin.

Carcinogenesis, mutagenesis, impairment of fertility

No long term studies in animals have been performed to evaluate the carcinogenic potential of iron sucrose.

Iron sucrose was not genotoxic in assays for gene mutation (in vitro bacterial and mouse lymphoma cell assays) and chromosomal damage (human lymphocytes in vitro and mouse micronucleus test in vivo).

Venerfer did not affect the fertility of male or female rats when administered thrice weekly at IV doses of up to 15 mg Fe/kg (about 1.4 times the maximum clinical dose based on BSA and weekly dose).

Use in pregnancy (Category B3)

Data on a limited number of exposed pregnancies indicated no adverse effects of Venofer on pregnancy or on the health of the foetus/newborn child. No well-controlled studies in pregnant women are available to date. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development.

Nevertheless, risk/benefit evaluation is required.

Use in lactation

Non metabolised Venofer is unlikely to pass into the mother's milk. No well-controlled clinical studies are available to date. Animal studies do not indicate direct or indirect harmful effects to the nursing child.

Effects on ability to drive and use machines

It is unlikely that Venofer has an influence on the ability to drive and use machines.

ADVERSE EFFECTS

The most frequently reported adverse drug reactions (ADRs) of Venofer in clinical trials were transient taste perversion, hypotension, fever and shivering, injection site reactions and nausea, occurring in 0.5 to 1.5% of the patients. Non-serious anaphylactoid reactions occurred rarely.

In general anaphylactoid reactions are potentially the most serious adverse reactions (see "Warnings and Precautions for use above").

In clinical trials, the following adverse drug reactions have been reported in temporal relationship with the administration of Venofer, with at least a possible causal relationship:

Nervous system disorders

Common (greater than or equal to 1% and less than 10%): transient taste perversions (in particular metallic taste).

Uncommon (greater than or equal to 0.1% and less than 1%): headache, dizziness.

Rare (greater than or equal to 0.01% and less than 0.1%): paraesthesia.

Cardio-vascular disorders

Uncommon: hypotension and collapse, tachycardia, palpitations.

Respiratory, thoracic and mediastinal disorders

Uncommon: bronchospasm, dyspnoea.

Gastrointestinal disorders

Uncommon: nausea, vomiting, abdominal pain, diarrhoea.

Skin and subcutaneous tissue disorders

Uncommon: pruritus, urticaria, rash, exanthema, erythema.

Musculoskeletal, connective tissue and bone disorders

Uncommon: muscle cramps, myalgia.

General disorders and administration site disorders

Uncommon: fever, shivering, flushing, chest pain and tightness. Injection site disorders such as superficial phlebitis, burning, swelling.

Rare: anaphylactoid reactions (rarely involving arthralgia), peripheral oedema, fatigue, asthenia, malaise.

Moreover, in spontaneous reports the following adverse reactions have been reported:

Isolated cases: reduced level of consciousness, light-headed feeling, confusion, angio-oedema, swelling of joints, hyperhidrosis and back pain.

INTERACTIONS

As with all parenteral iron preparations, Venofer should not be administered concomitantly with oral iron preparations since the absorption of oral iron is reduced. Therefore an oral iron therapy should be started at least 5 days after the last injection.

OVERDOSAGE

Overdosage can cause acute iron overloading which may manifest itself as haemosiderosis. Overdosage should be treated with supportive measures and, if required, with an iron chelating agent.

Pharmaceutical Precautions

Instructions for use / handling

Ampoules should be visually inspected for sediment and damage before use. Only those with a sediment free and homogenous solution must be used. See also shelf-life.

The diluted solution must appear as brown and clear.

Incompatibilities

Venofer must only be mixed with sterile 0.9 % w/v NaCl solution. No other intravenous dilution solutions and therapeutic agent should be used as there is the potential for precipitation and/or interaction. The compatibility with containers other than glass, polyethylene and PVC is not known.

Shelf life

Shelf-life in the product as packaged for sale: 3 years.

Shelf-life after first opening the container:

From a microbiological point of view, the product should be used immediately.

Shelf-life after dilution with sterile 0.9% sodium chloride solution:

From a microbiological point of view, the product should be used immediately after dilution with sterile 0.9% sodium chloride.

Special precautions for storage

Store in original carton. Do not store above 25°C. Do not freeze.

MEDICINE CLASSIFICATION

Pharmacy only

Package quantities

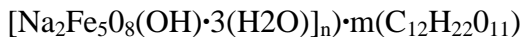
Venofer is presented in a 5 mL Type I glass ampoule containing 20 mg/mL iron as iron sucrose (iron(III)-hydroxide sucrose complex) corresponding to 100 mg iron per ampoule.

Venofer is available as a pack size of 5 x 5mL ampoules.

Further information

Chemical structure:

Venofer's proposed structural formula is:



where: n is the degree of iron polymerization and m is the number of sucrose molecules associated with the iron(III)-hydroxide. Please also refer to Pharmacology.

NAME AND ADDRESS

Pharmacy Retailing (NZ) Limited

trading as Healthcare Logistics

58 Richard Pearse Drive

Airport Oaks

Auckland, New Zealand

DATE OF PREPARATION

25 November 2005

Date of revision: 18 May 2007