1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

Venofer® solution for injection and concentrate for solution for infusion.

COMPOSITION

Each 5 ml ampoule of **Venofer®** contains 100 mg iron in the form of Iron(III)-Hydroxide Sucrose Complex; 20 mg iron per ml.

Inactive ingredients include:

Water for injections and sodium hydroxide.

Contains no preservatives. Contains sugar.

PHARMACOLOGICAL CLASSIFICATION

A 8.3 - Erythropoietics (haematinics)

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

The Polynuclear Iron(III)-Hydroxide cores are superficially surrounded by a large number of non-covalently bound sucrose molecules resulting in an overall complex molecular mass

(Mw) of approximately 43 kD. This is sufficiently large to prohibit renal elimination. The resulting complex is stable and does not release ionic iron under physiologic conditions. The iron in the polynuclear cores is bound in a structure similar to ferritin.

Pharmacokinetics

After administering a single intravenous dose of 100 mg iron in the form of Iron(III)-Hydroxide Sucrose Complex in healthy volunteers, a maximum mean iron level of 538 µmol/l was reached after 10 minutes. The volume of distribution of the central compartment corresponds to the volume of plasma (approximately 3 litres).

The iron injected is quickly cleared from the plasma, the terminal half-life is approximately 6 hours. The volume of distribution at steady state is about 8 litres, which indicates a low iron distribution in the body fluid. Due to the lower stability of Iron(III)-Hydroxide Sucrose Complex in comparison to transferrin, a competitive exchange of iron to transferrin was observed. This results in an iron transport of approximately 31 mg iron/24 hours.

Renal elimination of iron, occurring in the first 4 hours after injection, corresponds to less than 5 % of the total body clearance (approximately 20 ml/minute). After 24 hours the plasma levels of iron are reduced to the pre-dose iron levels and about 75 % of the dosage of sucrose is excreted.

INDICATIONS

Severe iron deficiency in adult patients not tolerating or responding to oral iron. **Venofer®** is recommended for use only where the indication is definite and confirmed by appropriate investigations.

CONTRA-INDICATIONS

- Iron overload or disturbances in utilisation of iron (e.g. haemochromatosis, haemosiderosis).
- Anaemia not caused by iron deficiency (e. g. haemolytic anaemias).
- Known hypersensitivity to iron mono-, disaccharide complexes, **Venofer®** or any of its components
- Clinical or biochemical evidence of liver damage
- Infectious hepatitis
- Acute or chronic infection
- A history of asthma, eczema, other allergic disorders or anaphylactic reactions
- The safety in lactation and children has not been established
- Pregnancy first trimester.

WARNINGS

Venofer® has a pH of 11 and must therefore be given **strictly by the intravenous route,** and the maximum daily dose of 200 mg should not be exceeded.

Parenterally administered iron preparations can cause severe allergic or anaphylactic reactions. Therefore, facilities for cardio-pulmonary resuscitation must be available.

In the event of a serious anaphylactic or allergic reaction, administration of **Venofer ®** must be stopped, intramuscular or intravenous epinephrine (adrenaline) should be administered immediately and other supportive measures initiated in line with the established cardio-pulmonary resuscitation procedures of the clinic or hospital.

Mild allergic reactions should be managed by stopping the administration of **Venofer®** and administering antihistamines.

Hypotensive episodes may occur if the injection is administered too rapidly. Patients with low iron binding capacity and/or folic acid deficiency are particularly at risk of an allergic or anaphylactic reaction. In cases of inadvertent paravenous leakage, and while the needle is still inserted, rinse with a small amount of 0.9 % sodium chloride solution.

Venofer® should not be administered in combination with oral iron preparations. Venofer® must not be mixed with other medicines for simultaneous administration. A sterile 0.9 % m/v sodium chloride solution is the only recommended diluent for an infusion.

Ampoules should be visually inspected for damage before use and only those with a sediment-free solution may be used. From a microbiological point of view, the product should be used immediately after first opening the container or after dilution with sterile 0.9 % m/v sodium chloride. Residual solvents must be discarded, once the ampoule has been opened.

Porphyria: Safety has not been established

INTERACTIONS

Venofer® should not be administered concomitantly with oral iron preparations, since the absorption of oral preparations is reduced.

PREGNANCY AND LACTATION

Pregnancy:

Venofer® is recommended for use in the second and third trimester and not for use during the first trimester in pregnancy (see **CONTRA-INDICATIONS**).

Venofer® should only be used in pregnant women with severe iron deficiency anaemia; where there is inability to absorb or tolerate adequate amounts of oral iron.

Lactation:

Safety during lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE

Administration:

Venofer® must be administered by a slow intravenous injection, by an intravenous drip infusion or, in patients receiving haemodialysis, into the venous limb of the dialyser (see **WARNINGS**).

Venofer® is a strongly alkaline solution and must never be administered by the subcutaneous or intramuscular route. Paravenous leakage must be avoided because leakage of **Venofer®** at the injection site may lead to pain, inflammation, tissue necrosis, and brown discolouration of the skin.

Venofer® is not suitable for intramuscular use nor for TDI (Total Dose Infusion).

TEST DOSE

Before administration of the first therapeutic dose of Venofer® in a new patient, a test dose of 1 ml to 2,5 ml Venofer® (20 mg to 50 mg iron) should be given by the chosen method of administration (see below). If no adverse reaction occurs within a waiting period of at least 15 minutes after administration, the remaining portion of the initial dose may be given.

Infusion:

The content of one ampoule has to be diluted exclusively in 100 ml of sterile 0.9 % m/v sodium chloride solution, immediately prior to infusion (i.e. 2 ampoules in 200 ml sterile 0.9 % m/v NaCl). The first 25 mg of iron (i.e. 25 ml of solution) should be infused as a test dose over a period of 15 minutes (see above TEST DOSE). If no adverse reaction occurs during this time, then the remaining portion of the infusion should be given as follows:

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

Intravenous injection:

As an intravenous injection **Venofer®** must be administered slowly at a rate of 1 ml undiluted solution per minute (i.e. 5 minutes per ampoule), not exceeding 2 ampoules **Venofer®** (200 mg iron) per injection. Before administering a slow intravenous injection, a test dose of 1 ml (20 mg of iron) should be injected slowly over a period of 1 to 2 minutes. If no adverse event occurs within 15 minutes of completing the test dose, the remaining portion of the injection may be given.

Injection into dialyser:

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

DOSAGE

Calculation of dosage

Adults and the elderly:

The total cumulative dose of **Venofer®** is determined by the haemoglobin level and body weight. The dose and dosage schedule for **Venofer®** must be individually estimated for each patient based on a calculation of the total iron deficit.

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

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

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

* Factor 2.4 = 0.0034 x 0.07 x 1000 x 10

where 0.0034 = Iron content of haemoglobin = 0.34%

0.07 = Blood volume = 7% of body weight

1000 = Factor = conversion from g to mg

10 = Factor = conversion from g/dl to g/l.

TOTAL NUMBER OF Venofer® AMPOULES TO BE ADMINISTERED				
Body weight kg	Haemoglobin 6 g/dl	Haemoglobin 7.5 g/dl	Haemoglobin 9 g/dl	Haemoglobin 10.5 g/dl
30	9.5	8.5	7.5	6.5
35	12.5	11.5	10.0	9.0
40	13.5	12.0	11.0	9.5
45	15.0	13.0	11.5	10.0
50	16.0	14.0	12.0	10.5
55	17.0	15.0	13.0	11.0
60	18.0	16.0	13.5	11.5
65	19.0	16.5	14.5	12.0
70	20.0	17.5	15.0	12.5
75	21.0	18.5	16.0	13.0
80	22.5	19.5	16.5	13.5
85	23.5	20.5	17.0	14.0
90	24.5	21.5	18.0	14.5

Total ampoules of **Venofer®** to be administered = $\frac{\text{Total iron deficit (mg)}}{100 \text{ mg}}$

The total single dose must not exceed 200 mg of iron given not more than three times per week. If the total necessary dose exceeds the maximum allowed single dose, then the administration has to be split.

Children:

The use of **Venofer®** has not been adequately studied in children and therefore **Venofer®** is not recommended for use in children.

SIDE EFFECTS AND SPECIAL PRECAUTIONS

SIDE EFFECTS

Very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥1/1 000, < 1/100); rare (≥ 1/10 000, < 1/1000,) very rare (≤ 1/10 000,) including isolated cases.

Cardio-vascular disorders

Uncommon: Hypotension and collapse; tachycardia and palpitations.

Gastrointestinal disorders

Uncommon: Nausea; vomiting; abdominal pain; diarrhoea.

General disorders and administration site disorders

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

Rare: Anaphylactic and anaphylactoid reactions (involving arthralgia); peripheral oedema; fatigue, asthenia; malaise.

Isolated cases: Reduced level of consciousness, lightheaded feeling, confusion; angio-oedema; swelling of joints, hyperhidrosis, back pain.

Musculoskeletal, connective tissue and bone disorders

Uncommon: Muscle cramps, myalgia.

Nervous system disorders

Common: Transient taste perversions (in particular metallic taste).

Uncommon: Headache; dizziness.

Rare: Paraesthesia.

Respiratory, thoracic and mediastinal disorders

Uncommon: Bronchospasm, dyspnoea.

Skin and subcutaneous tissue disorders

Uncommon: Pruritus; urticaria; rash, exanthema, erythema.

SPECIAL PRECAUTIONS

Anaphylactoid reactions are the most serious adverse reactions (see **WARNINGS**).

Effects on ability to drive and use machines:

After being given **Venofer®**, the patient may feel dizzy, confused or light-headed. If this happens, the patient should be advised not to drive or use any tool or machines.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Overdosage can cause acute iron overloading which may manifest itself as haemosiderosis. Particular caution should be exercised to avoid iron overload where anaemia, non-response to treatment, has been incorrectly diagnosed as iron deficiency anaemia.

Overdosage should be treated, if required, with an iron chelating agent.

IDENTIFICATION

Brown aqueous solution in 5 ml glass ampoules.

PRESENTATION

5 ml glass ampoules in packs of 5 ampoules.

STORAGE INSTRUCTIONS

Store in the original carton until removed for use.

Store at or below 25 ºC. Do not freeze.

Store out of reach of children.

REGISTRATION NUMBER

32/8.3/0166

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

DATE OF PUBLICATION OF THE PACKAGE INSERT

02 March 2012 – Clinical Approval

23 February 2023 – P&A Approval

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