AUSTRALIAN PRODUCT INFORMATION - VENOFER (IRON SUCROSE)

1 NAME OF THE MEDICINE

Iron sucrose

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each VENOFER 5 mL ampoule contains 20 mg/mL iron as iron sucrose (iron(III) hydroxide sucrose complex) as the active ingredient corresponding to 100 mg iron per 5 mL ampoule.

For the full list of excipients see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Concentrated injection for intravenous use.

VENOFER is a dark brown, non-transparent, aqueous solution with a pH of 10.5–11.0 and an osmolarity of 1250 mOsmol/L.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

VENOFER is indicated for the treatment of iron deficiency anaemia in patients undergoing chronic haemodialysis and who are receiving supplemental erythropoietin therapy.

The diagnosis of iron deficiency must be based on appropriate laboratory tests (e.g. serum ferritin, serum iron, transferrin saturation and hypochromic red cells).

4.2 DOSAGE AND METHOD OF ADMINISTRATION

The dosage of VENOFER is expressed in terms of mg of iron. Each mL contains 20 mg of iron.

Since a test dose without incident does not indicate that subsequent doses will also be reaction free, test doses may still be carried out but are not required.

Treatment of iron deficiency in haemodialysis patients receiving erythropoietin:

The recommended dosage of VENOFER for the treatment of iron deficiency in haemodialysis patients receiving erythropoietin therapy is 100 mg of iron (5 mL of

VENOFER) delivered intravenously during the dialysis session. Frequency of dosing should not be more than three times per week. Most patients will require a minimum cumulative dose of 1000 mg of iron, administered over 10 sequential dialysis sessions, to achieve a favourable haemoglobin or haematocrit response. Patients may continue to require therapy with VENOFER at the lowest dose necessary to maintain target levels of haemoglobin, haematocrit and laboratory parameters of iron storage within acceptable limits.

If no response in haematological parameters is observed after 1 to 2 weeks, the original diagnosis should be reconsidered.

Method of administration

VENOFER must only be administered by intravenous route. This may be by drip infusion or by slow injection directly into the venous line of the dialysis machine.

Ampoules should be visually inspected for sediment and damage before use. Use only those containing a sediment-free and homogenous solution.

Intravenous drip infusion

For IV infusion, the content of each ampoule must be diluted exclusively in a maximum of 100 mL of 0.9% w/v NaCl, immediately prior to infusion. The infusion should be infused at a rate of 100 mg of iron over a period of at least 15 minutes. Unused diluted solution should be discarded.

Injection into venous line of dialysis machine

VENOFER may be administered during a haemodialysis session directly into the venous line of the dialysis machine at a rate of 1 mL (20 mg iron) undiluted solution per minute (i.e. 5 minutes per ampoule), not exceeding one ampoule of VENOFER (100 mg iron) per injection. Discard any unused portion.

VENOFER is a strongly alkaline solution and must never be administered by the subcutaneous or intramuscular route.

NOTE: Do not mix VENOFER with other medication or add to parenteral nutrition solutions for intravenous infusion.

4.3 CONTRAINDICATIONS

The use of VENOFER is contraindicated in the following conditions:

- Hypersensitivity to iron sucrose, VENOFER or to any of its excipients listed in section 6.1 LIST OF EXCIPIENTS
- Anaemia not caused by iron deficiency
- iron overload or disturbances in utilisation of iron

- known haemochromatosis or genetic tendency to haemochromatosis
- pregnancy first trimester.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Because body iron excretion is limited and excess tissue iron can be hazardous, caution should be exercised to withhold iron administration in the presence of evidence of tissue iron overload. Patients receiving VENOFER require periodic monitoring of hematologic and hematinic parameters (haemoglobin, haematocrit, serum ferritin and transferrin saturation). Iron therapy should be withheld in patients with evidence of iron overload. Transferrin saturation values increase rapidly after IV administration of iron sucrose; thus, serum iron values may be reliably obtained 48 hours after IV dosing.

Parenterally administered iron preparations can cause allergic or anaphylactoid reactions, which can be potentially fatal. There have been reports of hypersensitivity reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction). Therefore, anti-allergic treatment should be available along with cardio-pulmonary resuscitation facilities and procedures. Hypersensitivity reactions have also been reported after previously uneventful doses of parenteral iron complexes including iron sucrose. Each patient should be observed for adverse effects for at least 30 minutes following each VENOFER injection.

There are no data on the safety of VENOFER when used in patients who are allergic to iron polymaltose.

In patients with a history of asthma, eczema, other atopic allergies or allergic reactions to other parenteral iron preparations, VENOFER should be administered with caution as these patients may be particularly at risk of an allergic reaction.

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.

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

Hypotension has been reported frequently in hemodialysis patients receiving intravenous iron. Hypotension following administration of VENOFER may be related to rate of administration and total dose administered.

Caution should be taken to administer VENOFER according to recommended guidelines (see section 4.2 DOSAGE AND METHOD OF ADMINISTRATION).

Care must be taken to avoid paravenous infiltration. If this occurs, the infusion of VENOFER should be discontinued immediately. Ice may be applied to cause local

vasoconstriction and decrease fluid absorption; massage of the area should be avoided.

Paravenous leakage must be avoided because leakage of VENOFER at the injection site may lead to pain, inflammation, sterile abscess and brown discolouration of the skin.

Use in the elderly

No data available.

Paediatric use

The safety and efficacy of VENOFER in children has not been established.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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, oral iron therapy should be discontinued 24 hours prior to the first injection of iron sucrose and should not be started within 5 days after the last injection of iron sucrose.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

VENOFER 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 body surface area (BSA) and weekly dose).

Use in pregnancy

Category B3

In pregnant rats, administration of iron sucrose during organogenesis at daily IV doses of 6.5 and 13 mg Fe/kg, was associated with a higher incidence of minor skeletal abnormalities, suggesting delayed development. Developmental effects were associated with maternotoxic doses (1.4–2.8 times the maximum clinical dose, based on BSA and weekly dose). Embryofetal survival was reduced in rats at daily IV doses of 20 mg Fe/kg (or 4.2 times the maximum clinical dose based on BSA and weekly dose).

In pregnant rabbits, administration of iron sucrose during organogenesis at daily IV doses of 13 mg/kg was associated with embryotoxicity. Embryofetal effects were associated with maternotoxicity (5 times the maximum clinical dose, based on BSA and weekly dose). No effects were observed at IV doses up to 6.5 mg Fe/kg/day (2.6 times the maximum clinical dose, based on BSA and weekly dose).

There are no adequate and well-controlled studies in pregnant women. 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 intravenous administration of parenteral irons to pregnant women.

Because animal reproductive studies are not always predictive of human response, VENOFER should be used during pregnancy only if the potential benefits justifies the potential risk to the foetus (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE), and should not be used in the first trimester (see section 4.3 CONTRAINDICATIONS).

Use in lactation

Iron of VENOFER is excreted in the milk of rats. There is insufficient information on the excretion of iron in human milk following administration of intravenous VENOFER. A risk of newborns /infants being exposed to iron derived from VENOFER via the mother's milk cannot be excluded.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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.

4.8 ADVERSE EFFECTS (UNDESIRABLE 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 0.5 to 1.5% of the patients. Non-serious hypersensitivity reactions occurred rarely.

In general hypersensitivity reactions are potentially the most serious adverse reactions (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). In pregnancy, foetal bradycardia associated to hypersensitivity in the mother may occur with parenteral iron preparations (see section 4.6 FERTILITY, PREGNANCY AND LACTATION).

Table 1 summarises the adverse drug reactions that have been reported in temporal relationship with the administration of VENOFER, with at least a possible causal relationship.

Table 1: List of Adverse Drug Reactions

	Observed in Clinical Trials			Spontaneous reports from post-marketing setting
System Organ Class	**Common (≥1/100, <1/10)**	**Uncommon (≥1/1,000, <1/100)**	**Rare (≥1/10,000, <1/1,000)**	**Frequency not known[1]**
Immune system disorders		hypersensitivity		angioedema, anaphylactoid reactions
Nervous system disorders	dysguesia	headache, dizziness, paraesthesia, hypoaesthesia	syncope, somnolence	depressed level of consciousness, confusional state, loss of consciousness, anxiety, tremor, light-headed feeling
Cardiac disorders			palpitations	tachycardia Bradycardia, Kounis syndrome
Vascular disorders	hypotension, hypertension	phlebitis, flushing		circulatory collapse, thrombophlebitis
Respiratory, thoracic and mediastinal disorders		dyspnoea		bronchospasm,
Renal and urinary disorders			chromaturia	
Gastrointestinal disorders	nausea	vomiting, abdominal pain, diarrhoea, constipation		
Skin and subcutaneous tissue disorders		pruritus, rash, exanthema,		urticaria, erythema
Musculoskeletal and connective tissue disorders		muscle spasms, myalgia, arthralgia, pain in extremity, back pain		swelling of joints
General disorders and administration site conditions	Injection/infusion site reactions*	chills, asthenia, fatigue, pain, oedema peripheral	chest pain, hyperhidrosis, pyrexia	cold sweat, pallor, malaise,

	Observed in Clinical Trials			Spontaneous reports from post-marketing setting
System Organ Class	**Common (≥1/100, <1/10)**	**Uncommon (≥1/1,000, <1/100)**	**Rare (≥1/10,000, <1/1,000)**	**Frequency not known[1]**
Investigations		gamma-glutamyltransferase increased, alanine aminotransferase increased, aspartate aminotransferase increased, serum ferritin increased	blood lactate dehydrogenase increased	

[1.] *Spontaneous reports from the post marketing setting*
*The most frequently reported are: injection/infusion site pain, extravasation, irritation, reaction, discolouration, haematoma, pruritus.

Reporting suspected adverse reactions

Reporting suspected adverse reactions after registration 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 at https://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Overdose can cause iron overload which may manifest itself as haemosiderosis.

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

For the information of the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

VENOFER is used to replenish body iron levels in patients with iron deficiency on chronic haemodialysis and receiving erythropoietin. In these patients iron deficiency is caused by blood loss during the dialysis procedure, increased erythropoiesis, and insufficient absorption of iron from the gastrointestinal tract. Iron is essential to the

synthesis of haemoglobin to maintain oxygen transport and to the function and formation of other physiologically important haem and non-haem compounds. Most haemodialysis patients require intravenous iron to maintain sufficient iron levels to achieve and maintain haemoglobin of 11–12 g/dL.

Clinical trials

The following pivotal studies have compared the use of intravenous (IV) and oral iron in haemodialysis patients receiving erythropoietin. Hussain et al[1] assessed the efficacy of IV iron sucrose vs. oral iron supplementation in haemodialysis (HD) patients. This was a single-centre open randomised parallel trial in patients with end stage renal failure on maintenance HD two sessions per week. The primary efficacy outcome was achievement of a target haemoglobin (Hb) concentration of 11-12 g/dL. 20 patients with serum ferritin >20 ng/mL and transferrin saturation >30% were assigned to one of two groups. Group 1 (n=10) received 100 mg as IV iron sucrose twice weekly post dialysis. Group 2 (n=10) received 200 mg oral ferrous sulfate three times daily. Both groups received subcutaneously (s.c.) erythropoietin 20 u/kg bw twice weekly post dialysis. Following three months of treatment the mean Hb and haematocrit (Hct) was significantly higher in Group 1 than Group 2 (Hb 11.6±0.64 g/dL vs. 10.5±1.14 g/dL, $p<0.01$). There was no significant difference in secondary efficacy variables (transferrin saturation, serum ferritin and erythropoietin dose) after three months of treatment.

Erten et al[2] compared an intensive IV iron regimen with a maintenance type regimen, with oral supplementation. This was a three-group (n=26, n=21 and n=22) randomised parallel study on stable haemodialysis (HD) patients receiving s.c. erythropoietin 150 u/kg for at least 3 months. Subjects treated with an intensive IV iron regimen (100 mg x 3 per week for 10 doses, then 100 mg weekly) obtained a higher haemoglobin after 6 months than those treated with oral iron (11.8 vs 9.8 g/dL) and had a greater reduction in EPO dose (27% vs 2%). Iron stores were also greater (serum ferritin 573.8 vs 195.8 ng/mL). A statistical analysis of the data was not conducted.

5.2 PHARMACOKINETIC PROPERTIES

In healthy adults treated with intravenous doses of VENOFER, its iron component exhibits first order kinetics with an elimination half-life of 6 h, total clearance of 1.2 L/h, non-steady state apparent volume of distribution of 10.0 L and steady state apparent volume of distribution of 7.9 L. Since iron disappearance from serum depends on the need for iron in the iron stores and iron utilising tissues of the body, serum clearance of iron is expected to be more rapid in iron deficient patients treated with VENOFER as compared to healthy individuals. The effects of age and gender on the pharmacokinetics of VENOFER have not been studied.

[1]Hussain R. Chishti SH; Naqvi SAJ. Experience of iron saccharate supplementation in haemodialysis patients treated with erythropoietin. Nephrology. Vol 4 (1–2) (pp 105–108), 1998.

[2] Erten Y., et al.; Comparison of the effect of intravenous and oral iron therapies on haemodialysis patients. XXXV Congress of the Europ. Renal Association/Europ. Dialysis and Transplant Association. 6–9 June 1998, Rimini, Italy.

The iron sucrose complex is not dialyzable through CA 210 (Baxter) High Efficiency or Fresenius F80A High Flux dialysis membranes. In *in vitro* studies, the amount of iron sucrose in the dialysate fluid was below the level of detection of the assay (less than 2 parts per million).

Distribution

In healthy adults receiving intravenous doses of VENOFER, its iron component appears to distribute mainly in blood and to some extent in extravascular fluid. A study evaluating VENOFER containing 100 mg of iron labelled with $^{52}Fe/^{59}Fe$ in patients with iron deficiency shows that a significant amount of the administrated iron distributes in the liver, spleen and bone marrow and that the bone marrow is an iron trapping compartment and not a reversible volume of distribution.

Metabolism and Excretion

Following intravenous administration of VENOFER, iron sucrose is dissociated into sucrose and the polynuclear iron core, which is taken up by the macrophages of the reticuloendothelial system. The sucrose component is eliminated mainly by urinary excretion. In a study evaluating a single intravenous dose of VENOFER containing 1510 mg of sucrose and 100 mg of iron in 12 healthy adults (9 female, 3 male; age range 32–52), 68.3% of the sucrose was eliminated in urine in 4 h and 75.4% in 24 h. Neither transferrin nor transferrin receptor levels changed immediately after the dose administration[3]. In this study and another study evaluating a single intravenous dose of iron sucrose containing 500–700 mg of iron in 26 anemic patients on erythropoietin therapy (23 female, 3 male; age range 16–60), approximately 5% of the iron was eliminated in urine in 24 h at each dose level[4].

5.3 PRECLINICAL SAFETY DATA

Carcinogenicity

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

Genotoxicity

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*).

[3] Danielson B., et al.; Pharmacokinetics of Iron(III)-Hydroxide Sucrose Complex after a Single Intravenous Dose in Healthy Volunteers, Drug Research 46: 615–621, 1996.
[4] Anatkov A. Gekova K.; Problems of Hem. Bld. Transfusions, Med. Physioculture, 13: 295–298, 1970.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The excipients are water for injections and sodium hydroxide for pH adjustment.

6.2 INCOMPATIBILITIES

VENOFER must not be mixed with other medicinal products except sterile 0.9% m/V sodium chloride (NaCl) solution. 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.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

Shelf-life after first opening of the container and after dilution with sterile 0.9% m/V sodium chloride (NaCl) solution: From a microbiological point of view, the product should be used immediately.

Contains no antimicrobial agent. Product is for single use in one patient only. Discard any residue.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25 ºC. Do not freeze. Store in the original package.

6.5 NATURE AND CONTENTS OF CONTAINER

5 mL solution in one ampoule (Type I glass) in pack sizes of 5.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSIOCHEMICAL PROPERTIES

Chemical structure

VENOFER solution contains a mixture of polymers, each consisting of a polynuclear iron(III) hydroxide core superficially surrounded by a larger number of non-covalently bound sucrose molecules.

The proposed molecular formula is: $[Na_2Fe_5O_8(OH)\cdot 3(H_2O)]_n \cdot m(C_{12}H_{22}O_{11})$ where n is the degree of iron polymerization and m is the number of sucrose molecules associated with the iron(III)-hydroxide.

Molecular weight range: 34000–60000.

Nominal amount of sucrose: 320 g/L.

CAS-Number

8047-67-4 (saccharated iron oxide).

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription only medicine)

8 SPONSOR

Vifor Pharma Pty Ltd

Level 9, 140 William Street

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9 DATE OF FIRST APPROVAL

19th May 2004

10 DATE OF REVISION

14th March 2023

Summary table of changes

Section Changed	Summary of New Information
4.4	Special Warnings and Precautions for use section updated to delete tissue necrosis.
4.8	Adverse reactions updated