

# PRODUCT INFORMATION

## VENOFER<sup>®</sup>

### NAME OF THE MEDICINE

VENOFER<sup>®</sup> (iron sucrose).

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:  $[\text{Na}_2\text{Fe}_5\text{O}_8(\text{OH})\cdot 3\cdot(\text{H}_2\text{O})]_n\cdot m(\text{C}_{12}\text{H}_{22}\text{O}_{11})$  where n is the degree of iron polymerization and m is the number of sucrose molecules associated with the iron(III)-hydroxide.

CAS Number: 8047-67-4 (saccharated iron oxide). Molecular weight range: 34000–60000.  
Nominal amount of sucrose: 320 g/L

### DESCRIPTION

Solution for intravenous use.

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. Inactive ingredients include water for injections and sodium hydroxide. It has a pH of 10.5–11.0 and an osmolarity of 1250 mOsmol/L.

### PHARMACOLOGY

#### Pharmacokinetics:

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.

VENOFER is not dialyzable through CA 210 (Baxter) High Efficiency or Fresenius F80A High Flux dialysis membranes. In *in vivo* 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  $^{52}\text{Fe}/^{59}\text{Fe}$  in patients with iron deficiency shows that a significant amount of the administered 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 Elimination:

Following intravenous administration of VENOFER, iron sucrose is dissociated into iron and sucrose by 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. Some iron also is eliminated in the urine. Neither transferrin nor transferrin receptor levels changed immediately after the dose administration<sup>1</sup>. 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<sup>2</sup>.

### CLINICAL TRIALS

VENOFER is used to replenish body iron stores 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 heme and non-heme compounds. Most haemodialysis patients require intravenous iron to maintain sufficient iron stores to achieve and maintain haemoglobin of 11–12 g/dL.

The following pivotal trials comparing the use of IV vs. oral iron in haemodialysis patients receiving erythropoietin have appeared in the literature: Hussain et al<sup>3</sup> 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 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 IV iron sucrose twice weekly post dialysis. Group 2 (n=10) received 200 mg oral ferrous sulfate three times daily. Both groups received s.c. erythropoietin 20 u/kg bw twice weekly post dialysis. Following three months of treatment the mean Hb and 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.

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<sup>1</sup> 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.

<sup>2</sup> Anatkov A. Gekova K.; Problems of Hem. Bld. Transfusions, Med. Physioculture, 13: 295–298, 1970.

<sup>3</sup> 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.

Erten et al<sup>4</sup> 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 (ferritin 573.8 vs 195.8 ng/dL). A statistical analysis of the data was not conducted.

## **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).

## **CONTRAINDICATIONS**

The use of VENOFER is contraindicated in cases of:

- anaemia not caused by iron deficiency,
- iron overload or disturbances in utilisation of iron,
- known haemochromatosis or genetic tendency to haemochromatosis,
- known hypersensitivity to VENOFER or any of its inactive components,
- pregnancy first trimester.

## **PRECAUTIONS**

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.

Hypersensitivity reactions: Potentially fatal hypersensitivity or anaphylactic type reactions characterised by shock, loss of consciousness, collapse, hypotension, dyspnea or convulsions have been reported rarely in patients receiving VENOFER (see Adverse Effects). Fatal immediate hypersensitivity reactions have been reported in patients receiving therapy with a variety of parenteral preparations containing iron carbohydrate complexes.

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<sup>4</sup> 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.

Facilities for cardiopulmonary resuscitation must be available during dosing in case of serious anaphylactoid reactions (see Adverse Effects). Physician vigilance is required when administering any intravenous iron product. There are no data on the safety of VENOFER when used in patients who are allergic to iron polymaltose.

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

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 Dosage and 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.

### **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).

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 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.

Because animal reproductive studies are not always predictive of human response, VENOFER should be used during pregnancy only if clearly needed, and should not be used in the first trimester (see Contraindications).

### **Use in lactation**

Iron of VENOFER is excreted in the milk of rats. It is not known whether iron of this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when VENOFER is administered to a nursing woman.

### **Use in children**

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

### **Interactions with other medicines**

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 at least be started 5 days after the last injection.

### **Effects on ability to drive and use machines**

It is unlikely that VENOFER has an influence on the ability to drive or 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 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 Precautions).

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:* hypersensitivity 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, back pain and increased sweating.

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

## **DOSAGE AND ADMINISTRATION**

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

Before administration of a therapeutic dose in a new patient, a test dose should be given. A dose of 20 mg iron (1 mL of VENOFER) diluted in a maximum of 20 mL of 0.9% w/v NaCl, should be infused over 15 minutes.

### **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 elemental 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 elemental 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.

**Administration**

VENOFER must be administered by intravenous infusion or by slow injection into the venous limb of the dialysis line for haemodialysis patients.

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. Dilution must take place 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.

In haemodialysis patients, VENOFER may be administered by slow intravenous injection into the venous limb of the dialysis line 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.

**Incompatibilities**

VENOFER must only be mixed with 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.

**OVERDOSAGE**

Overdosage can cause acute iron overloading which may manifest itself as haemosiderosis.

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

Contact the Poisons Information Centre on 131126 for management of overdose.

**PRESENTATION AND STORAGE CONDITIONS**

VENOFER is a dark brown, non-transparent aqueous solution contained in a 5 mL Type I glass ampoule. Each ampoule contains 20 mg/mL iron as iron sucrose (iron (III) hydroxide sucrose complex) corresponding to 100 mg iron per ampoule.

Pack size of 5 ampoules.

**Storage**

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

**Instructions for use/handling**

The product should be used immediately after opening the container or immediately after preparation of the diluted solution for IV infusion.

Ampoules should be visually inspected for sediment and damage before use. Only those with sediment free and homogenous solution must be used.

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

**POISON SCHEDULE**

S4 (Prescription only medicine)

**NAME AND ADDRESS OF THE SPONSOR**

Aspen Pharmacare Australia Pty Ltd  
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St Leonards 2065 NSW

**DATE OF APPROVAL**

Approved by the Therapeutic Goods Administration: 03 September 2004  
Date of most recent amendment: 2 July 2010.