

## **DATA SHEET**

### **VENOFER®**

#### *Iron Sucrose*

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#### **PRESENTATION**

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Venofer is a dark brown, non transparent, sterile aqueous solution of iron sucrose in water for injections with a pH of 10.5-11.0 and an osmolarity of 1,150- 1,350 mOsmol/L. Each 5 mL ampoule contains 20 mg/mL iron as iron sucrose (Iron(III)-hydroxide sucrose complex) corresponding to 100 mg iron per ampoule. The excipients are: Water for injection and sodium hydroxide (for pH adjustment).

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#### **USES**

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##### *Actions*

##### **Pharmacology:**

Pharmacotherapeutic group: Anti-anaemic preparation, iron, parenteral preparation, ATC code: B03AC.

##### **Pharmacodynamics:**

##### Mechanism of action

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 other iron-containing enzymes, or stored primarily in the liver in the form of ferritin.

##### **Pharmacokinetics**

##### Distribution

The ferrokinetics of iron sucrose labelled with <sup>52</sup>Fe and <sup>59</sup>Fe were assessed in 6 patients with anaemia and chronic renal failure. In the first 6–8 hours, <sup>52</sup>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  $\mu\text{mol/L}$ . The volume of distribution of the central compartment corresponded well to the volume of plasma (approximately 3 litres).

#### Biotransformation

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 59 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. 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.

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## **CLINICAL TRIALS**

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### *Nephrology*

#### *Dialysis dependent chronic kidney disease*

Study LU98001 was a prospective, open-label, single arm study to investigate the efficacy and safety of Venofer in hemodialysis patients with iron deficiency anaemia (Hb concentration  $>8$  and  $<11.0$  g/dL, TSAT  $<20\%$ , and serum ferritin  $<300$   $\mu\text{g/L}$ ) who were receiving rHuEPO therapy. A total of 77 patients [44 (57%) male; mean age 62.5 (range: 24-85 years)] participated in the study and received 100 mg of iron as Venofer administered via the dialysis line for up to 10 sessions over 3 to 4 weeks. A mean total dose of  $983.1 \pm 105.63$  mg of iron as Venofer was administered over a mean of  $9.8 \pm 1.06$  dialysis sessions. A Hb  $\geq 11$  g/dL was attained in 39/45 (87%; 95% CI 76.5, 96.9) of evaluable patients. Similar results were observed in the ITT population 60/77 (78%; 95% CI 68.5, 87.3). The maximum increase in serum ferritin from  $83.6 \pm 11.69$   $\mu\text{g/L}$  to  $360.3 \pm 36.81$   $\mu\text{g/L}$  (n=41) was seen at the completion of treatment with Venofer. The maximum increase in TSAT from  $17.1 \pm 1.5\%$  to  $27.6 \pm 2.7\%$  (n=41) was seen at the 5-week follow-up visit.

#### *Non-dialysis dependent chronic kidney disease*

Study 1VEN03027 was an open-label, randomised study comparing Venofer and oral ferrous sulfate in adult patients with renal insufficiency and iron deficiency anaemia (Hb  $\leq 11.0$  g/dL, serum ferritin  $\leq 300$   $\mu\text{g/L}$ , and TSAT  $\leq 25\%$ ) with or without rHuEPO therapy. Patients were randomized to 1000 mg of iron as Venofer (500 mg infusion over 3.5 to 4 hours on Days 0 and 14, or 200 mg injections administered over 2 to 5 minutes on 5 different occasions from Day 0 to Day 14) or oral ferrous sulfate 325 mg (65 mg iron), 3 times daily for 56 days. A total of 91 patients were included in each treatment group. A

statistically significant greater proportion of patients in the Venofer group (35/79; 44.3%) compared to the oral iron group (23/82; 28.0%) had an increase in Hb  $\geq$ 1.0 g/dL during the study (p=0.0344). A clinical response (defined as Hb increase  $\geq$ 1.0 g/dL and serum ferritin increase  $\geq$ 160  $\mu$ g/L) was more frequently observed in patients treated with Venofer (31/79; 39.2%) compared to oral iron (1/82; 1.2%); p<0.0001.

### Gastroenterology

A randomised, controlled study compared Venofer with oral iron in 91 patients with irritable bowel disease and anaemia (Hb <11.5 g/dL). Patients were randomised to receive either oral ferrous sulfate tablets 200 mg twice daily (n=46) or Venofer (n=45) given as either a single I.V. dose of 200 mg of iron once per week or every second week for 20 weeks. Forty-three patients in the Venofer group completed the study compared to 35 patients in the oral iron group (p=0.0009). At the end of treatment, 66% of patients in the Venofer group had an increase in Hb  $\geq$ 2.0 g/dL compared to 47% in the oral iron group (p=0.07). In the oral iron group, 41% of patients had anaemia at the end of study compared to 16% in the Venofer group (p=0.007). Forty-two percent of patients in the Venofer group reached their reference Hb (15 g/dL in males and 13 g/dL in females) compared to 22% in the oral iron group (p=0.04).

### Post partum

A prospective, randomised, controlled trial in 43 women with postpartum iron deficiency anaemia (Hb <9 g/dL and serum ferritin <15  $\mu$ g/L at 24-48 hours post-delivery) compared 2 x 200 mg of iron as Venofer given on Days 2 and 4 (n=22) to 200 mg of oral iron as ferrous sulfate given twice daily for 6 weeks (n=21). Significantly higher Hb levels were observed in the Venofer group compared to the oral iron group on Days 5 and 14 (p <0.01). The mean increase in Hb from baseline at Day 5 was 2.5 g/dL in the Venofer group and 0.7 g/dL in the oral iron group. By Day 40 there was no significant difference in Hb levels between the treatment groups. There was a significant increase in serum ferritin in the Venofer group by Day 5 and the serum ferritin remained significantly higher in the Venofer group compared to the oral iron group throughout the study (p<0.01 at Days 5 and 14 and p<0.05 at Day 40).

### Pregnancy

In a randomised, open label study 90 women in their third trimester of pregnancy with iron deficiency anaemia (Hb 8 to 10.5 g/dL and serum ferritin <13  $\mu$ g/L) were randomized to Venofer (n=45) or oral iron polymaltose complex (n=45). The individually calculated total dose of iron as Venofer was administered over 5 days with a maximum single dose of 200 mg given as an infusion and a maximum daily dose of 400 mg iron. The oral iron group received 100 mg iron as tablets thrice daily until delivery. The change in Hb from baseline was significantly greater in the Venofer group compared to the oral iron group at day 28 and at delivery (p<0.01). At delivery the number of patients reaching Hb target was 43 (95.6%) and 28 (62.2%) in the Venofer and oral iron groups, respectively (p<0.001). Serum ferritin values increased significantly over time in both the Venofer (p<0.05) and oral iron (p<0.05) groups.

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## INDICATIONS

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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).

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## DOSAGE AND ADMINISTRATION

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### POSODOLOGY

The cumulative dose of Venofer must be calculated for each patient individually and must not be exceeded.

#### **Calculation of dosage**

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, for example:

**Total iron deficit [mg] = BW [kg] x (target Hb-actual Hb) [g/L] x 0.24\* + storage iron [mg]**

Below 35 kg BW: Target Hb = 130 g/L and storage iron = 15 mg/kg BW

35 kg BW and above: Target Hb = 150 g/L and storage iron = 500 mg

\* Factor 0.24 = 0.0034 (iron content of Hb = 0.34%) x 0.07 (blood volume = 7% of BW) x 1000 (conversion of [g] to [mg])

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

Total amount of Venofer to be administered according to body weight, actual Hb level and target Hb level\*:

BW	Total number of Venofer ampoules (20mg iron per mL) to be administered (1 ampoule of Venofer corresponds to 5mL)			
	Hb 60 g/L	Hb 75 g/L	Hb 90 g/L	Hb 105 g/L
5 kg	1.5	1.5	1.5	1
10 kg	3	3	2.5	2
15 kg	5	4.5	3.5	3
20 kg	6.5	5.5	5	4
25 kg	8	7	6	5.5
30 kg	9.5	8.5	7.5	6.5
35 kg	12.5	11.5	10	9
40 kg	13.5	12	11	9.5
45 kg	15	13	11.5	10
50 kg	16	14	12	10.5
55 kg	17	15	13	11
60 kg	18	16	13.5	11.5
65 kg	19	16.5	14.5	12
70 kg	20	17.5	15	12.5
75 kg	21	18.5	16	13
80 kg	22.5	19.5	16.5	13.5
85 kg	23.5	20.5	17	14
90 kg	24.5	21.5	18	14.5

\* Below 35 kg BW: Target Hb = 130 g/L  
 35 kg BW and above: Target Hb = 150 g/L

To convert Hb (mM) to Hb (g/L), multiply the former by 16.1145.

If the total necessary dose exceeds the maximum allowed single dose, then the administration must be divided.

## **Calculation of dosage for iron replacement secondary to blood loss and to support autologous blood donation:**

The required Venofer dose to compensate for the iron deficit may be calculated according to the following formulas:

If the quantity of blood lost is known:

The administration of 200 mg iron ( 10 mL of Venofer) should result in an increase in Hb approximately equivalent to 1 unit blood (= 400 mL with Hb = 150 g/L).

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

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

If the Hb level is less than desired:

Formula assumes that the storage iron does not need to be restored. Iron to be replaced [mg] = BW [kg] x 0.24 (target Hb -actual Hb) [g/L]

Example: For BW = 60 kg and Hb decrease = 10 g/L       $\Rightarrow \cong 150$  mg iron to be replaced  
 $\Rightarrow 7.5$  mL Venofer needed

For the maximum tolerated single and weekly dose, see “Normal posology” and “Maximum tolerated single and weekly doses”.

### **Normal posology:**

#### ***Adults***

5 - 10 mL of Venofer (100 - 200 mg iron) 1 to 3 times a week. For administration time and dilution ratio see “Method of administration”.

#### ***Paediatric population***

There is moderate 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 “Method of administration”.

#### ***Maximum tolerated single and weekly doses***

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 single 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 given in “Method of administration” should be strictly adhered to, even if the patient does not receive the maximum tolerated single dose.

#### Method of administration

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

#### 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:

<b>Venofer dose (mg of iron)</b>	<b>Venofer dose (mL of Venofer)</b>	<b>Maximum dilution volume of sterile 0.9% m/V NaCl solution</b>	<b>Minimum Infusion Time</b>
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

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

#### 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.

#### Injection into venous line of 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.

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## CONTRAINDICATIONS

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The use of Venofer is contraindicated in of the following conditions:

- Anaemia not caused by iron deficiency.
- Iron overload or disturbances in utilisation of iron.
- Known hypersensitivity to iron sucrose, Venofer or any of its excipients listed in section “Presentation”.
- Pregnancy first Trimester.

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## WARNINGS AND PRECAUTIONS

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Parenterally administered iron preparations can cause allergic or anaphylactoid reactions, which can be potentially fatal. Therefore Venofer should only be used in those patients in whom a clearly established indication for parenteral iron therapy exists, confirmed by appropriate laboratory test.

Venofer should only be administered when personnel trained to evaluate and manage anaphylactic reactions, and resuscitative interventions, are immediately available. Each patient should be monitored for signs and symptoms of hypersensitivity during and after **each** administration of intravenous iron for at least 30 minutes. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately.

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. However it was shown in a study with a limited number of iron dextran sensitive patients that Venofer could be administered with no complications.

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.

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*).

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)***

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***

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.

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## **ADVERSE EFFECTS**

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The most frequently reported adverse drug reactions (ADRs) of Venofer in clinical trials were transient taste perversion (dysgeusia), hypotension, fever (pyrexia) and shivering (chills), 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").

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:

<b>System Organ Class</b>	<b>Common (≥1/100, &lt;1/10)</b>	<b>Uncommon (≥1/1,000, &lt;1/100)</b>	<b>Rare (≥1/10,000, &lt;1/1,000)</b>	<b>Frequency not known<sup>1)</sup></b>
<b>Infections and infestations</b>			Pneumonia	
<b>Blood and lymphatic system disorders</b>		Polycythemia <sup>2)</sup>		
<b>Immune system disorders</b>		Hypersensitivity		Angioedema, anaphylactoid reactions (rarely involving arthralgia)
<b>Metabolism and nutrition disorders</b>			Iron overload	
<b>Nervous system disorders</b>	Dysgeusia	Headache, dizziness, burning sensation, paraesthesia, hypoaesthesia	Syncope, migraine, somnolence	Depressed level of consciousness, confusional state, loss of consciousness, light headed feeling, anxiety, tremor
<b>Cardiac disorders</b>		Palpitations		Bradycardia, tachycardia
<b>Vascular disorders</b>	Hypotension, hypertension	Thrombophlebitis, phlebitis, flushing		Circulatory collapse, superficial vein thrombosis
<b>Respiratory, thoracic and mediastinal disorders</b>		Dyspnoea, bronchospasm		
<b>Renal and urinary disorders</b>		Chromaturia		
<b>Gastrointestinal disorders</b>	Nausea	Vomiting, abdominal pain, diarrhoea, constipation	Dry mouth	
<b>Skin and subcutaneous tissue disorders</b>		Pruritus, rash, exanthema, urticaria, erythema		
<b>Musculoskeletal and connective tissue disorders</b>		Muscle cramps, myalgia, arthralgia, pain in extremity, back pain	Limb discomfort, muscle spasms	Hypotonia, joint swelling

<b>System Organ Class</b>	<b>Common (≥1/100, &lt;1/10)</b>	<b>Uncommon (≥1/1,000, &lt;1/100)</b>	<b>Rare (≥1/10,000, &lt;1/1,000)</b>	<b>Frequency not known<sup>1)</sup></b>
<b>General disorders and administration site conditions</b>	Injection site pain	Chills, injection site reactions, injection site irritation, injection site extravasation, injection site discoloration, injection site burning, injection site swelling, asthenia, fatigue, pain, chest pain, pyrexia	Feeling hot, injection site pruritis, injection site bruising, peripheral oedema	Hyperhidrosis, cold sweat, malaise, pallor
<b>Investigations</b>		Gamma-glutamyltransferase increased, alanine aminotransferase increased, aspartate aminotransferase increased, liver function tests abnormal	Serum ferritin increased <sup>2)</sup> , blood creatinine increased, blood lactate dehydrogenase increased	

<sup>1)</sup> Spontaneous reports from the post-marketing setting

<sup>2)</sup> Possibly as a consequence of iron overdose or iron overload

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## **INTERACTIONS**

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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.

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## **OVERDOSAGE**

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

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## **Pharmaceutical Precautions**

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### ***Instructions for use / handling***

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

The diluted solution must appear as brown and clear.

Each ampoule of Venofer is intended for single use only.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

### ***Incompatibilities***

Venofer must only be mixed with sterile 0.9 % m/M NaCl solution. No other intravenous dilution solutions and therapeutic agent should be used as 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.

### ***Shelf life***

Shelf-life in the product as packaged for sale:

3 years.

Shelf-life after first opening of the container:

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

Shelf-life after dilution with sterile 0.9% m/V sodium chloride (NaCl) 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**

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

For storage conditions after dilution or first opening of the medicinal product, see section "Shelf life".

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**MEDICINE CLASSIFICATION**

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Pharmacy only

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**Package quantities**

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5 mL solution in one ampoule (type I glass) in pack sizes of 5. Each 5 mL ampoule contains 20 mg/mL iron as iron sucrose corresponding to 100 mg iron per ampoule.

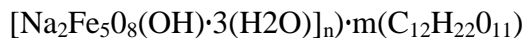
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**Further information**

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*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.

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**NAME AND ADDRESS**

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