1. Trade Name of the Medicinal Product

Venofer

2. Qualitative and Quantitative Composition

Each 5 ml ampoule contains 20 mg/ml iron as iron sucrose corresponding to 100 mg iron per ampoule.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Solution for injection or concentrate for solution for infusion.
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 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
- Where oral iron preparations are ineffective (e.g., in active inflammatory bowel disease)

Venofer should only be administered where the indication is confirmed by appropriate investigations.

4.2 Posology and method of administration

Monitor carefully patients for signs and symptoms of hypersensitivity reactions during and following each administration of Venofer.

Venofer should only be administered when staff trained to evaluate and manage anaphylactic reactions is immediately available, in an environment where full resuscitation facilities can be assured. The patient should be observed for adverse effects for at least 30 minutes following each Venofer injection.

Posology

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/dl] x 2.4* + storage iron [mg]

Below 35 kg BW: Target Hb = 13 g/dl and storage iron = 15 mg/kg BW

35 kg BW and above: Target Hb = 15 g/dl and storage iron = 500 mg

* Factor 2.4 = 0.0034 (iron content of Hb = 0.34%) x 0.07 (blood volume = 7% of BW) x 1000 (conversion of [g] to [mg]) x 10

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

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

BW	Total number of ampoules Venofer (20 mg iron per ml) to be administered: (1 ampoule of Venofer corresponds to 5 ml)			
	Hb 6.0g/dl	Hb 7.5 g/dl	Hb 9.0 g/dl	Hb 10.5 g/dl
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 = 13 g/dl
35 kg BW and above: Target Hb = 15 g/dl

To convert Hb (mM) to Hb (g/dl), multiply the former by 1.6.
If the total necessary dose exceeds the maximum allowed single dose, then the administration must be divided. If no response of the haematological parameters is observed after 1 to 2 weeks the original diagnosis should be reconsidered.

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 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 = 15 g/dl).

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 2.4 x (target Hb – actual Hb) [g/dl]

Example: For BW = 60 kg and Hb decrease = 1 g/dl ⇒ ≅ 150 mg iron to be replaced
⇒ 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

Adults

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 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:

Venofer dose (mg of iron)	**Venofer dose (ml of Venofer)**	**Maximum dilution volume of sterile 0.9% m/V NaCl solution**	**Minimum Infusion Time**
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

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.

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
- Anaemia not caused by iron deficiency
- Evidence of iron overload or disturbances in utilisation of iron
- Pregnancy first Trimester

4.4 Special warnings and precautions for use

Parenterally administered iron preparations can cause allergic or anaphylactoid reactions, which can be potentially fatal . 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 have been reports of hypersensitivity reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction, see section 4.8).

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, in several studies performed in patients who had a history of a hypersensitivity reaction to iron dextran or ferric gluconate, Venofer was shown to be well tolerated.

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.

Paravenous leakage must be avoided because leakage of Venofer at the injection site can lead to pain, inflammation, tissue necrosis and brown discoloration of the skin. If this occurs, the administration of Venofer must be stopped immediately. To date, tissue necrosis has not been found to occur in clinical studies using Venofer.

4.5 Interaction with other medicinal products and other forms of interaction

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

4.6 Fertility, pregnancy and lactation

Pregnancy

There is no or only a limited amount of data (less than 300 pregnancy outcomes) from the use of iron sucrose in pregnant women in the first trimester. A moderate amount of data (between 300-1,000 pregnancy outcomes) from the use of Venofer in pregnant women in the second and third trimester showed no safety concerns for the mother or newborn.

Venofer should be used during the second and third trimester pregnancy only if the potential benefit justifies the potential risk to the foetus (see section 4.4). For pregnancy first trimester see section 4.3 contraindications. 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.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Breastfeeding
There is limited information on the excretion of iron in human milk following administration of intravenous iron sucrose. In one clinical study, 10 healthy breast-feeding mothers with iron deficiency received 100 mg iron in the form of iron sucrose. Four days after treatment, the iron content of the breast milk had not increased and there was no difference from the control group (n=5). It cannot be excluded that newborns/infants may be exposed to iron derived from Venofer via the mother's milk, therefore the risk/ benefit should be assessed.

Preclinical data do not indicate direct or indirect harmful effects to the nursing child. In lactating rats treated with ^{59}Fe-labelled iron sucrose, low secretion of iron into the milk and transfer of iron into the offspring was observed. Non metabolised iron sucrose is unlikely to pass into the mother's milk.

Fertility
No effects of iron sucrose treatment were observed on fertility, mating performance and early embryonic development in rats.

4.7 Effects on ability to drive and use machines

Venofer is unlikely to influence the ability to drive and 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 Undesirable effects

The most commonly reported adverse drug reaction in clinical trials with Venofer was dysgeusia, which occurred with a rate of 4.5 events per 100 subjects. The most important serious adverse drug reactions associated with Venofer are hypersensitivity reactions, which occurred with a rate of 0.25 events per 100 subjects in clinical trials.

The adverse drug reactions reported after the administration of Venofer in 4,064 subjects in clinical trials as well as those reported from the post-marketing setting are presented in the table below.

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	Dysgeusia	Headache, dizziness, paraesthesia, hypoaesthesia	Syncope, somnolence	Depressed level of consciousness, confusional state, loss of

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)]
				consciousness, anxiety, tremor
Cardiac disorders			Palpitations	Bradycardia, tachycardia, Kounis syndrome
Vascular disorders	Hypotension, hypertension	Flushing, phlebitis		Circulatory collapse, Thrombophlebitis
Respiratory, thoracic and mediastinal disorders		Dyspnoea		Bronchospasm
Renal and urinary disorders			Chromaturia	
Gastrointestinal disorders	Nausea	Vomiting, abdominal pain, diarrhoea, constipation	Dry mouth	
Skin and subcutaneous tissue disorders		Pruritus, rash		Urticaria, erythema
Musculoskeletal and connective tissue disorders		Muscle spasms , myalgia, arthralgia, pain in extremity, back pain		
General disorders and administration site conditions	Injection/infusion site reactions*	Chills, asthenia, fatigue, oedema peripheral, pain	Chest pain, hyperhidrosis,pyrexia	Cold sweat, malaise, pallor,influenza like illness [2]

Investigations		Alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase 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

2) Onset may vary from a few hours to several days

4.9 Overdose

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

5. Pharmacological Properties

5.1 Pharmacodynamic properties

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

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.

Clinical efficacy and safety

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 µg/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 ± 105.63 mg of iron as Venofer was administered over a mean of 9.8 ± 1.06 dialysis sessions. A Hb ≥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 ± 11.69 µg/l to 360.3 ± 36.81 µg/l (n=41) was seen at the completion of treatment with Venofer. The maximum increase in TSAT from 17.1 ± 1.5% to 27.6 ± 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 anemia (Hb ≤11.0 g/dl, serum ferritin ≤300 µg/l, and TSAT ≤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 ≥1.0 g/dl during the study (p=0.0344). A clinical response (defined as Hb increase ≥1.0 g/dl and serum ferritin increase ≥160 µg/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.

5.2 Pharmacokinetic properties

Distribution
The ferrokinetics of iron sucrose labelled with ^{52}Fe and ^{59}Fe were assessed in 6 patients with anaemia and chronic renal failure. In the first 6–8 hours, ^{52}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 µmol/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, and renal elimination of sucrose was about 75% of the administered dose.

5.3 Preclinical safety data

Nonclinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity and toxicity to reproduction and development.

6. Pharmaceutical Particulars

6.1 List of excipients

Water for injection
Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6. 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

Shelf-life of the product as packaged for sale:
2 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
Chemical and physical in-use stability has been demonstrated for 12 hours at room temperature. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally

be longer than 3 hours at room temperature unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 30°C. Do not freeze. Store in the original package.

For storage conditions after dilution or first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I glass ampoules with extractable volumes of 5 ml.

6.6 Special precautions for disposal and other handling

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

Venofer must not be mixed with other medicinal products except sterile 0.9% m/V sodium chloride solution for dilution. For instructions on dilution of the product before administration, see section 4.2.

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.

Package Form

Ampoules (5 ml) containing 100 mg of iron: 5
Vifor (International) Inc., Rechenstrasse 37 9014 St Gallen Switzerland

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