Summary of product characteristics

1. Name of the medicinal product:

Venofer, solution for injection

2. Qualitative and quantitative composition

One millilitre of solution contains 20 mg of iron as iron sucrose (iron(III)-hydroxide sucrose complex).

Each 5 ml ampoule of Venofer contains 100 mg iron as iron sucrose (iron(III)-hydroxide sucrose complex).

Excipient with known effect
Venofer contains up to 7 mg sodium per ml.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Solution for injection

Venofer is a dark brown, non-transparent, aqueous solution.

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,
- In active inflammatory bowel disease where oral iron preparations are ineffective,
- In chronic kidney disease when oral iron preparations are less effective.

The diagnosis of iron deficiency must be based on appropriate laboratory tests (e.g. Hb, serum ferritin, TSAT, serum iron, etc.).

(Hb haemoglobin, TSAT transferrin saturation)

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 administration (see section 4.4).

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 (ml) to be administered according to body weight, actual Hb level and target Hb level*:

BW	**Total amount of Venofer (20mg iron per ml) to be administered:**			
	Hb 6.0 g/dl	Hb 7.5 g/dl	Hb 9.0 g/dl	Hb 10.5 g/dl
30 kg	47.5 ml	42.5 ml	37.5 ml	32.5 ml
35 kg	62.5 ml	57.5 ml	50 ml	45 ml
40 kg	67.5 ml	60 ml	55 ml	47.5 ml
45 kg	75 ml	65 ml	57.5 ml	50 ml
50 kg	80 ml	70 ml	60 ml	52.5 ml
55 kg	85 ml	75 ml	65 ml	55 ml
60 kg	90 ml	80 ml	67.5 ml	57.5 ml
65 kg	95 ml	82.5 ml	72.5 ml	60 ml
70 kg	100 ml	87.5 ml	75 ml	62.5 ml
75 kg	105 ml	92.5 ml	80 ml	65 ml
80 kg	112.5 ml	97.5 ml	82.5 ml	67.5 ml
85 kg	117.5 ml	102.5 ml	85 ml	70 ml
90 kg	122.5 ml	107.5 ml	90 ml	72.5 ml

* 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.

<u>Posology</u>

Adults

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

Paediatric population

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

Method of administration

Venofer must only be administered by the intravenous route. This may be by a slow intravenous injection, by an intravenous drip infusion 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**
50 mg	2.5 ml	50 ml	8 minutes
100 mg	5 ml	100 ml	15 minutes
200 mg	10 ml	200 ml	30 minutes

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 Venofer (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 the active substance, to Venofer or any of its excipients listed in section 6.1
- Known serious hypersensitivity to other parenteral iron products
- Anaemia not caused by iron deficiency
- Evidence of iron overload or hereditary disturbances in utilization of iron.

4.4 Special warnings and precautions for use

Parenterally administered iron preparations can cause hypersensitivity reactions including serious and potentially fatal anaphylactic/anaphylactoid reactions. Hypersensitivity reactions have also been reported after previously uneventful doses of parenteral iron complexes including iron sucrose. 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 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. For known serious hypersensitivity to other parenteral iron product see section 4.3.

The risk of hypersensitivity reactions is enhanced for patients with known allergies including drug allergies, including patients with a history of severe asthma, eczema or other atopic allergy.

There is also an increased risk of hypersensitivity reactions to parenteral iron complexes in patients with immune or inflammatory conditions (e.g. systemic lupus erythematosus, rheumatoid arthritis).

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. Each patient should be observed for adverse effects for at least 30 minutes following each Venofer injection. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately. Facilities for cardio respiratory resuscitation and equipment for handling acute anaphylactic/anaphylactoid reactions should be available, including an injectable 1:1000 adrenaline solution. Additional treatment with antihistamines and/or corticosteroids should be given as appropriate.

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, in particular Porphyria Cutanea Tarda (PCT). 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 and brown discoloration of the skin.

Venofer contains up to 7 mg sodium per mL, equivalent to 0.4% of the WHO

recommended maximum daily intake of 2 g sodium for an adult.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is no data from the use of iron sucrose in pregnant women in the first trimester. Data (303 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.

A careful risk/benefit evaluation is required before use during pregnancy and Venofer should not be used during pregnancy unless clearly necessary (see section 4.4).

Iron deficiency anaemia occurring in the first trimester of pregnancy can in many cases be treated with oral iron. Treatment with Venofer should be confined to second and third trimester if the benefit is judged to outweigh the potential risk for both the mother and the fetus.

Foetal bradycardia may occur following administration of parenteral irons. It is usually transient and a consequence of a hypersensitivity reaction in the mother.

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

Breast-feeding

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 and mating performance in rats.

4.7 Effects on the ability to drive and use machines

In the case of symptoms of dizziness, confusion or light headedness following the administration of Venofer, patients should not drive or use machinery until the symptoms have ceased.

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.
Anaphylactoid/anaphylactic reactions were reported only in the post-marketing setting (estimated as rare); fatalities have been reported. See section 4.4.

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		Anaphylactoid/ anaphylactic reactions, angioedema
Nervous system disorders	Dysgeusia,	Headache, dizziness, paraesthesia, hypoaesthesia	Syncope, somnolence	Depressed level of consciousness, confusional

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)]
				state, loss of 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		
Skin and subcutaneous tissue disorders		Pruritus, rash		Urticaria, erythema
Musculoskeletal and connective tissue disorders		Muscle spasm, myalgia, arthralgia, pain in extremity, back pain		
General disorders and administration site conditions	Injection/ infusion site reaction [2)]	Chills, asthenia, fatigue, oedema peripheral, pain	Chest pain, hyperdrosis, pyrexia	Cold sweat, malaise, pallor, influenza like illness[3)]
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; estimated as rare
[2)] The most frequently reported are: injection/infusion site pain, -extravasation, -irritation, -reaction, -discolouration, -haematoma, -pruritus.
[3)] Onset may vary from a few hours to several days.

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il/

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

Chronic kidney disease

Study LU98001 was a single arm study to investigate the efficacy and safety of 100 mg iron as Venofer for up to 10 sessions over 3–4 weeks in haemodialysis patients with iron deficiency anaemia (Hb >8 and <11.0 g/dL, TSAT <20%, and serum ferritin ≤300 µg/L) who were receiving rHuEPO therapy. A Hb ≥11 g/dL was attained in 60/77 patients. The mean increase in serum ferritin and TSAT was significant from baseline to the end of treatment (Day 24) as well as to the 2 and 5 weeks follow-up visit.

Study 1VEN03027 was a randomised study comparing Venofer (1000 mg in divided doses over 14 days) and oral ferrous sulphate (325 mg 3 times daily for 56 days) in non-dialysis dependent chronic kidney disease patients (Hb ≤11.0 g/dL, serum ferritin ≤300 µg/L, and TSAT ≤25%) with or without rHuEPO. 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.

Inflammatory Bowel Disease

A randomised, controlled t compared Venofer (single IV dose of 200 mg iron once per week or every second week until the cumulative dose was reached) with oral iron (200 mg twice daily for 20 weeks) in patients with inflammatory bowel disease and anaemia (Hb <11.5 g/dL). At the end of treatment, 66% of patients in the Venofer group had an increase in Hb ≥2.0 g/dL compared to 47% in the oral iron group (p=0.07).

Postpartum

A randomised, controlled trial in women with postpartum iron deficiency anaemia (Hb <9 g/dl and serum ferritin <15 µg/l at 24–48 hours post-delivery) compared 2 × 200 mg iron given as Venofer on Days 2 and 4 (n=22) and 200 mg of oral iron given as ferrous sulphate twice daily for 6 weeks (n=21). The mean increase in Hb from baseline to Day 5 was 2.5 g/dl in the Venofer group and 0.7 g/dl in the oral iron group (p<0.01).

Pregnancy

In a randomised, controlled study, women in their third trimester of pregnancy with iron deficiency anaemia (Hb 8 to 10.5 g/dl and serum ferritin <13 µg/l) were randomised to Venofer

(individually calculated total dose of iron administered over 5 days) or oral iron polymaltose complex (100 mg 3× daily until delivery). The increase in Hb from baseline was significantly greater in the Venofer group compared to the oral iron group at Day 28 and at delivery ($p<0.01$).

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. Renal elimination of sucrose was about 75% of the administered dose.

5.3 Preclinical safety data

Non-clinical 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

The expiry date of the product is indicated on the packaging materials.

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% m/V sodium chloride solution.

6.4 Special precautions for storage

Prescribed storage conditions: 4 –25 °C. Do not freeze. Store in the original package in order to protect from light.
For storage conditions after dilution or first opening of the medicinal product, see section 6.3.

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 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.

7. Manufacturer:

Vifor (International), Rechenstrasse 37, St. Gallen, 9014, Switzerland

8. License holder and importer:

CTS Ltd.
4 Haharash st.
Hod Hasharon 4524075

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