# SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 1. NAME OF THE MEDICINAL PRODUCT

VENIRO 100 mg/5 ml Solution for IV Injection or Concentrate for Solution for Infusion, Ampoule Sterile

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

**Active substance(s):** Each ampule contains 540 mg iron (III) hydroxide sucrose complex equivalent to 20 mg iron per ml, and 2700 mg iron (III) hydroxide sucrose complex equivalent to 100 mg elemental iron in each 5 ml (total volume).
**Excipient(s) with known effect:** Sodium hydroxide (for pH adjustment to 10–11.1)
For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Ampule containing solution for IV injection and infusion.
Homogeneous, brown-colored, particle-free solution.

## 4. CLINICAL PARTICULARS

### 4.1. Therapeutic indications

VENIRO is indicated for the treatment of:

- Iron deficiency anemia due to iron malabsorption from the gastrointestinal tract,
- Iron deficiency anemia in patients with active gastrointestinal bleeding,
- Iron deficiency anemia in patients with total or subtotal gastrectomy,
- Iron deficiency anemia in patients with intolerance to oral iron therapy,
- Iron deficiency anemia in patients with resistance to oral iron therapy,
- Iron deficiency anemia, where there is a clinical need for a rapid iron supply,
- Iron deficiency anemia in chronic renal failure patients with or without dialysis who receive erythropoietin (EPO) therapy.

VENIRO should not be prescribed in the first trimester of pregnancy. During the second and third trimesters of pregnancy, it should be used when deemed necessary by the physician.

VENIRO should be administered after all essential and relevant blood tests (such as hematocrit, hemoglobin, ferritin level, and erythrocyte count analysis) have been conducted.

### 4.2. Posology and method of administration

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

VENIRO 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 VENIRO administration (see section 4.4).

**Posology**

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

Calculation of dosage
The total cumulative dose of VENIRO, equivalent to the total iron deficit (mg), is determined by the hemoglobin level (Hb) and body weight (BW). The dose of VENIRO 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

Total amount of VENIRO to be administered (in ml) = Total iron deficit [mg] / 20 mg iron per ml

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

| BW | Total amount of VENIRO (20 mg iron/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.

**Posology/frequency and duration of administration**
In adults, 1-2 ampules (100-200 mg iron) of VENIRO is administered 1-3 times a week, depending on hemoglobin levels. In hemodialysis patients, the total dose is 1000 mg to be administered in 10 doses. The recommended dose can be repeated if necessary. Dose administration frequency should not be more than 3 times per week.

Oral iron intake should be discontinued during the course of treatment.

**Method of administration**
VENIRO 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. It should not be administered by intramuscular or bolus intravenous injection.

**Intravenous drip infusion**
VENIRO must only be diluted in a 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:

| VENIRO dose (mg of iron) | VENIRO dose (mL of VENIRO) | 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 VENIRO concentrations are not permissible.

**Intravenous injection**
VENIRO may be administered by slow intravenous injection at a rate of 1 ml undiluted solution per minute (5 ml of VENIRO should be administered over a period of at least 5 minutes) and not exceeding 10 ml VENIRO (200 mg iron) per injection.

**Injection into the venous line of the dialysis machine**
VENIRO may be administered during a hemodialysis session directly into the venous line of the dialysis machine under the same conditions as for intravenous injection.

**Additional information on special populations**
Renal/Hepatic impairment
No dose adjustment is required in those with renal and hepatic impairment. For patients with hepatic dysfunction, see section 4.4.

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

Elderly
For elderly patients, no adjustment of the usual dose is required.

**4.3. Contraindications**
The use of VENIRO is contraindicated in the following conditions:
- Hypersensitivity to the active substance, to VENIRO or any of its excipients listed in section 6.1,
- Known serious hypersensitivity to other parenteral iron products,
- Anemia 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 that 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, the iron (III) hydroxide sucrose complex was shown to be well tolerated. For known serious hypersensitivity to other parenteral iron products, see section 4.3.

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

VENIRO 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 VENIRO administration. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately. Facilities for cardiorespiratory 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. Careful monitoring of iron status is recommended to avoid iron overload.

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

Paravenous leakage must be avoided when administering VENIRO because leakage of VENIRO at the injection site can lead to pain, inflammation, and brown discoloration of the skin.

Accidental intake of iron-containing products in children may cause fatal poisoning. Keep out of reach of children.

This medicinal product contains less than 1 mmol (23 mg) of sodium per dose, i.e., it is essentially "sodium-free".

**4.5. Interactions with other medicinal products and other forms of interaction**

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

**4.6. Pregnancy and lactation**

**General recommendation**

Pregnancy category is "B".

- Despite this pregnancy category, the physician should make the final decision on whether the pregnant woman should use the medicine upon a detailed benefit-risk assessment taking the gestational week, the existing/diagnosed disease, and other characteristics of the pregnant woman into consideration.
- While the risk categories inform healthcare professionals about the potential risk of the medicine during pregnancy, the assessment of the physician is essential.

**Women of child-bearing potential/Birth control (contraception)**

VENIRO is widely used in clinical trials in women of childbearing potential using contraceptives.

**Pregnancy**

There are no data from the use of iron sucrose in pregnant women in the first trimester. Data (303 pregnancy outcomes) from the use of VENIRO in pregnant women in the second and third trimesters showed no safety concerns for the mother or newborn.

There are no adequate and well-controlled studies on the use of VENIRO in pregnant women. Therefore, a careful risk/benefit evaluation is required before use during pregnancy, and VENIRO should not be used during pregnancy unless clearly necessary (see section 4.4.).

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

Fetal 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 pregnancy, embryonal/fetal development, delivery, and postnatal development (see section 5.3).

**Breastfeeding**

There is limited information on the excretion of iron in human milk following intravenous administration of iron sucrose. In one clinical study, 10 healthy breast-feeding mothers with iron deficiency received 100 mg of iron in the form of iron sucrose. 4 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 fetus or newborns may be exposed to iron derived from VENIRO 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-labeled iron sucrose, low secretion of iron into the milk and semen was observed. Non metabolized 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 lightheadedness following the administration of VENIRO, 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 iron (III) hydroxide sucrose complex was dysgeusia, which occurred with a rate of 4.5 events per 100 subjects. The most important serious adverse drug reactions associated with iron (III) hydroxide sucrose complex 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 iron (III) hydroxide sucrose complex in 4,064 subjects in clinical trials as well as those reported from the post-marketing setting are presented in the table below.

Frequencies are defined as: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (not established by available data).

**Immune system disorders**

Uncommon : Hypersensitivity
Not known[1)] : Anaphylactoid/anaphylactic reactions, angioedema

**Nervous system disorders**

Common : Dysgeusia
Uncommon : Headache, dizziness, hypoesthesia, paresthesia
Rare : Syncope, somnolence
Not known[1)] : Tremor, loss of consciousness, depressed level of consciousness, confusional state, anxiety

**Cardiac disorders**
Rare : Palpitations
Not known[1)] : Tachycardia, bradycardia, Kounis syndrome

**Vascular disorders**
Common : Hypotension, hypertension
Uncommon : Flushing, phlebitis
Not known[1)] : Circulatory collapse, thrombophlebitis

**Respiratory, thoracic and mediastinal disorders**
Uncommon : Dyspnea
Not known[1)] : Bronchospasm

**Renal and urinary disorders**
Rare : Chromaturia

**Gastrointestinal disorders**
Common : Nausea
Uncommon : Vomiting, abdominal pain, diarrhea, constipation

**Skin and subcutaneous tissue disorders**
Uncommon : Pruritus, rash
Not known[1)] : Urticaria, erythema

**Musculoskeletal and connective tissue disorders**
Uncommon : Muscle spasm, myalgia, arthralgia, pain in extremity, back pain

**General disorders and administration site conditions**
Common : Injection/infusion site reaction[2)]
Uncommon : Chills, asthenia, fatigue, edema peripheral, pain
Rare : Chest pain, hyperhydrosis, pyrexia
Not known[1)] : Cold sweat, malaise, pallor, influenza-like illness[3)]

**Investigations**
Uncommon : Alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, serum ferritin increased
Rare : 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, -hematoma, -pruritus.
[3)] Onset may vary from a few hours to several days.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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 via the national reporting system.

**4.9. Overdose and treatment**
Overdose can cause iron overload, which may manifest itself as hemosiderosis. 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:** Iron, parenteral preparations

**ATC code:** B03AC

Mechanism of Action

Iron sucrose, the active ingredient of VENIRO, 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, utilizable 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 of iron as an iron (III) hydroxide sucrose complex for up to 10 sessions over 3–4 weeks in hemodialysis patients with iron deficiency anemia (Hb >8 and <11 g/dL, TSAT <20%, and serum ferritin ≤300 mcg/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 weeks 2 and 5 follow-up visits.

Study 1VEN03027 was a randomized study comparing iron (III) hydroxide sucrose complex (1000 mg in divided doses over 14 days) and oral ferrous sulfate (325 mg 3 times daily for 56 days) in non-dialysis-dependent chronic kidney disease patients (Hb ≤11 g/dL, serum ferritin ≤300 mcg/L, and TSAT ≤25%) with or without rHuEPO. A clinical response (defined as Hb increase ≥1 g/dL and serum ferritin increase ≥160 mcg/L) was more frequently observed in patients treated with iron (III) hydroxide sucrose complex (31/79; 39.2%) compared to oral iron (1/82; 1.2%); p<0.0001.

Inflammatory bowel disease

A randomized, controlled study compared iron (III) hydroxide sucrose complex (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 anemia (Hb <11.5 g/dL). At the end of treatment, 66% of patients in the iron (III) hydroxide sucrose complex group had an increase in Hb ≥2 g/dL compared to 47% in the oral iron group (p=0.07).

Postpartum

A randomized, controlled trial in women with postpartum iron deficiency anemia (Hb <9 g/dL and serum ferritin <15 mcg/L at 24–48 hours post-delivery) compared 2 × 200 mg of iron given as iron (III) hydroxide sucrose complex on Days 2 and 4 (n=22) and 200 mg of oral iron given as ferrous sulfate twice daily for 6 weeks (n=21). The mean increase in Hb from baseline to Day 5 was 2.5 g/dL in the iron (III) hydroxide sucrose complex group and 0.7 g/dL in the oral iron group (p<0.01).

Pregnancy
In a randomized, controlled study, women in their third trimester of pregnancy with iron deficiency anemia (Hb 8 to 10.5 g/dL and serum ferritin <13 mcg/L) were randomized to iron (III) hydroxide sucrose complex (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 iron (III) hydroxide sucrose complex group compared to the oral iron group at Day 28 and at delivery ($p<0.01$).

## 5.2. Pharmacokinetic properties

### General properties

Distribution:

The ferrokinetics of iron sucrose labeled with $^{52}Fe$ and $^{59}Fe$ were assessed in 6 patients with anemia 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 reticuloendothelial iron uptake.

Following intravenous injection of a single 100 mg iron dose of iron sucrose in healthy subjects, 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 liters).

Biotransformation:
Upon IV 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 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

Sodium hydroxide
Water for injection

## 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 interaction if mixed with other medicinal products. The compatibility with containers other than glass, polyethylene, and PVC is not known.

**6.3. Shelf life**
24 months.

Shelf life after first opening of the container:
From a microbiological point of view, the product should be used immediately after opening.

**6.4. Special precautions for storage**
Store at room temperature below 25°C and in a dry place protected from light. Discard any unused medicine within 5 hours. Do not freeze.

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

**6.5. Nature and contents of the container**
Available in a 5-mL colorless Type I auto-pull glass ampoule with a white ring on the neck, supplied as a pack of 5, included in a cardboard box.

**6.6. Special precautions for disposal and other handling**
Ampules should be visually inspected for sediment and damage before use. Use only those containing a sediment-free and homogeneous solution.

VENIRO 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 brown and clear.

Each ampule of VENIRO is intended for single use only.

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

**7. MARKETING AUTHORIZATION HOLDER**
DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No:1
34303 Küçükçekmece – İSTANBUL / TÜRKİYE

**8. MARKETING AUTHORIZATION NUMBER(S)**
2015/470

**9. DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION**
Date of first authorization : 26.05.2015
Date of renewal of authorization :

**10. DATE OF REVISION OF THE TEXT**