

## 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 to TUFAM. See section 4.8 for how to report adverse reactions.

### 1. NAME OF THE MEDICINAL PRODUCT

FERROVEN® 100 mg/5 mL I.V. Solution for Injection

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

#### Active Ingredient:

1754,39 mg ferric hydroxide sucrose complex equivalent to 100 mg Ferric (III) (20 mg/ml).

#### Excipients:

For a full list of excipients, see section 6.1.

### 3. PHARMACEUTICAL FORM

Solution for injection.

Dark brown solution in colorless glass ampoules.

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

It is used in the following conditions:

- Iron deficiency anemia due to impaired gastrointestinal absorption of iron,
- Iron deficiency anemia due to active gastrointestinal bleeding,
- Iron deficiency anemia due to total or subtotal gastrectomy,
- Iron deficiency anemia in patients who are unable to tolerate oral iron replacement,
- Iron deficiency anemia resistant to oral iron supplementation,
- Clinical conditions requiring rapid iron supplementation,
- In the presence of iron deficiency in dialysis dependent or non-dialysis-dependent patients with chronic renal failure receiving erythropoietin (EPO) therapy.

FERROVEN® should not be recommended in the first trimester. In second and third trimesters, it should be used only when the physician deems it necessary.

#### 4.2 Posology and method of administration

##### Posology/frequency and duration of administration

In adults; 1-2 ampoule (100-200 mg iron) of FERROVEN® is administered 1 to 3 times per week according to haemoglobin levels. The total dose in hemodialysis patients is 1000 mg to be administered in 10 divided doses. When required the recommended dose may be repeated. Dosing frequency should not exceed 3 times per week.

##### Method of administration:

FERROVEN® must only be administered by the intravenous route (slow intravenous injection or infusion). It should not be administered by intramuscular or bolus intravenous injection.

FERROVEN® ampoule per minute. Not more than 1 FERROVEN® ampoule should be administered per injection. A test dose should be administered prior to the first dose of

FERROVEN<sup>®</sup> treatment. If any allergic reaction or intolerance occurs in the course of the administration, the treatment should be immediately discontinued.

FERROVEN<sup>®</sup> should only be administered where all resuscitation equipment are available and in the presence of personnel trained to evaluate and manage emergency anaphylactic reactions. After each injection of FERROVEN<sup>®</sup>, the patient should be observed for adverse effects for at least 30 minutes. (See section 4.4).

If any allergic reaction or intolerance occurs during the administration, the treatment must be stopped immediately.

#### **Intravenous injection:**

FERROVEN<sup>®</sup> can also be administered as slow intravenous injection without being diluted. The recommended quantity is to be administered at 1 mL FERROVEN<sup>®</sup> (20 mg iron) per minute (5 mL FERROVEN<sup>®</sup> in at least five minutes). The dose should not exceed 200 mg FERROVEN<sup>®</sup> in one injection, no further administration should be made. Unused FERROVEN<sup>®</sup> ampoule content must be discarded.

#### **Infusion:**

FERROVEN<sup>®</sup> ampoule should preferably be administered as an infusion to reduce the risk of hypotension and paravenous injection. For this purpose, a 5 mL ampoule (100 mg iron) must be diluted with up to 100 mL of 0.9% NaCl. The duration of infusion must be not less than 15 minutes for 100 mg iron, 30 minutes for 200 mg iron, 1.5 hours for 300 mg iron, 2.5 hours for 400 mg iron, 3.5 hours for 500 mg iron. The maximum dose of iron for each administration must not exceed 7 mg/kg body weight, i.e 500 mg iron, and administered during at least 3.5 hours irrespective of the dose.

Any unused contents of FERROVEN<sup>®</sup> ampoule should be discarded.

During haemodialysis, FERROVEN<sup>®</sup> may be administered directly to the venous side of the dialyzer. It should be administered similarly to intravenous administration.

#### **Special populations**

**Renal/hepatic insufficiency:** No dose adjustment is necessary for the patients with renal or hepatic insufficiency.

**Pediatric population:** No data is available for the safety and efficacy in children. Parenteral iron preparations are not recommended for children under 14 years of age due to lack of clinical experience.

**Geriatric population:** No dose adjustment is necessary for the elderly patients.

### **4.3 Contraindications**

The use of FERROVEN<sup>®</sup> is contraindicated in cases of;

- Hypersensitivity to the active substance, to FERROVEN<sup>®</sup> or any of the excipients listed in section 6.1.
- Known hypersensitivity to other parenteral iron drugs.
- In case of hypersensitivity to FERROVEN<sup>®</sup> or inactive substances in its composition,
- In patients with the history of asthma, eczema or other atopic allergy

- Anemias not attributable to iron deficiency,
- Pregnancy first trimester,

#### **4.4 Special warnings and precautions for use**

Although rare, potentially fatal hypersensitivity reactions characterized by anaphylactic shock, loss of consciousness, collapse, hypotension, dyspnea, and convulsions may develop in patients who are receiving parenterally administered ferric-hydroxide-sucrose complex. Such reactions are observed during the use of many preparations including an iron carbohydrate complex. Therefore, as a precaution during the IV administration of a ferric-hydroxide-sucrose complex, the equipment required for cardiopulmonary resuscitation must be available. Although fatal hypersensitivity reactions have not been reported in clinical studies with intravenous ferric-hydroxide-sucrose complex, treating physicians are advised to be cautious during the administration of intravenous ferric-hydroxide-sucrose complex and all IV iron preparations.

Parenterally administered iron drugs can cause hypersensitivity reactions including severe and potentially fatal anaphylactic/anaphylactoid reactions. Hypersensitivity reactions have also been reported after previously uneventful doses of parenteral iron complexes including iron sucrose.

The risk of hypersensitivity reactions increases for patients with known drug allergies, including a history of severe asthma, eczema or other atopic allergy. Hypersensitivity reactions to parenteral iron complexes also increase in cases of immune systems disorders or infection (e.g. systemic lupus erythematosus, rheumatoid arthritis).

FERROVEN® should only be administered where all resuscitation equipment are available and in the presence of personnel trained to evaluate and manage emergency anaphylactic reactions. After each injection of FERROVEN®, the patient should be observed for adverse effects for at least 30 minutes. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately. To manage acute anaphylactic/anaphylactoid reactions, equipment for cardiorespiratory resuscitation and materials including an injectable 1:1000 adrenaline solution should be made available. Additional treatment with antihistamines and/or corticosteroids should be given as appropriate.

Since iron excretion from the body is limited and excess iron in the tissues can be dangerous, periodic blood tests (hemoglobin, hematocrit, serum ferritin and transferrin saturation) should be performed in patients receiving intravenous ferric-hydroxide-sucrose complex. Treatment should be discontinued in patients with suspected iron overload.

FERROVEN® should be administered with caution in patients with liver failure.

FERROVEN® should be administered with caution in patients with acute or chronic infection with high levels of ferritin. Parenteral iron can have undesirable effects in patients with bacterial or viral infection.

If the injection is administered rapidly, hypothermia could develop.

Paravenous injection should be avoided when administering FERROVEN®. Paravenous injection may cause subcutaneous tissue damage and brown discoloration. Such cases should be treated with gel or ointments containing heparin.

FERROVEN<sup>®</sup> contains less than 1 mmol (23 mg) of sodium in each dose; so it basically does not contain any sodium.

FERROVEN<sup>®</sup> should be used at the recommended dose to reduce the possibility of undesirable side effects.

Accidental ingestion of iron-containing products in children can lead to fatal poisoning.

Keep out of reach of children.

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

FERROVEN<sup>®</sup> should not be administered concomitantly with oral iron preparations since the absorption of oral iron is reduced. Oral iron therapy should be started at least 5 days after the last injection of FERROVEN<sup>®</sup>.

#### **4.6 Pregnancy and lactation**

##### **General recommendation**

Pregnancy category B.

Despite this category of pregnancy, the physician should decide on prescribing the drug to a pregnant woman by making a detailed benefit-risk assessment according to the gestational week, the existing/diagnosed disease and other characteristics of the pregnant woman.

Risk categories assist healthcare personnel with the potential risk of the drug in pregnancy, however the physician's assessment is essential

##### **Women of childbearing potential/Contraception**

Patients should be instructed to consult their doctor if they are or want to become pregnant during treatment with FERROVEN<sup>®</sup>.

##### **Pregnancy**

While teratogenic activity has not been observed in animal studies, there are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies do not always demonstrate human response, this drug should not be used during pregnancy unless clearly necessary.

It should not be used during the first trimester of pregnancy.

No adequate and well-controlled studies are available on the use of FERROVEN<sup>®</sup> in pregnant women. Therefore, a careful benefit/risk assessment must be carried out prior to use during pregnancy, and FERROVEN<sup>®</sup> must not be used during pregnancy unless clearly necessary.

Iron deficiency occurring in the first trimester of pregnancy can in many cases be treated with oral iron. Treatment with FERROVEN<sup>®</sup> should be limited to second and third trimester if the benefit is considered to outweigh the potential risk for both the mother and the fetus.

## **Lactation**

Ferric hydroxide sucrose is not excreted in human milk. FERROVEN® may be used in the lactation period.

## **Reproduction / Fertility**

There are no effects on the fertility.

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

Since dizziness, confusion or light headedness develops following the administration of FERROVEN®, patients should not drive or use machinery until these symptoms have ceased.

## **4.8 Undesirable effects**

The adverse reactions accepted as product-related are listed below::

Frequencies are defined as: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), very rare ( $< 1/10,000$ ), or not known (cannot be estimated from the available data).

### **Immune system disorder**

Rare: Anaphylactoid reactions

### **Nervous system disorders**

Common: Transient taste perversions (in particular metallic taste).

Uncommon: Headache, dizziness

Rare: Paraesthesia, syncope, burning sensation

### **Cardiovascular disorders**

Uncommon: Hypotension and collapse; tachicardia and palpitation

Rare: Hypertension

### **Respiratory, thoracic and mediastinal disorders**

Uncommon: Bronchospasm, dyspnoea

### **Gastrointestinal disorders**

Uncommon: Nausea, vomiting, abdominal pain, diarrhea

### **Skin and subcutaneous tissue**

Uncommon: Pruritus, urticaria, rash, erythema and exanthema

### **Musculoskeletal, connective tissue and bone disorders**

Uncommon: Muscle cramps, myalgia

### **General disorders and administration site conditions**

Uncommon: Fever, shivering, flushing, chest pain and tightness. Injection site disorders such as superficial phlebitis, burning, swelling.

Rare: Anaphylactic reactions (along with arthralgia, rarely), peripheral oedema, fatigue, asthenia

Isolated cases: Reduced level of consciousness, confusion, angioedema, swelling of joints

## **Reporting suspected adverse reactions**

Reporting any suspected adverse reactions of drugs is very important after the authorization. Reporting enables tracking the benefit/risk balance of the medicinal product. Health professionals should report any suspected adverse reaction to Turkish Pharmacovigilance Center (TÜFAM) ([www.titck.gov.tr](http://www.titck.gov.tr); e-mail: [tufam@titck.gov.tr](mailto:tufam@titck.gov.tr); tel: 0 800 314 00 08; fax: 0312 218 35 99).

## 4.9 Overdose and management

Overdosage with FERROVEN<sup>®</sup> may lead to accumulation of iron which may manifest itself as haemosiderosis. Periodic monitoring of serum ferritin level and transferrin saturation may assist in recognizing iron accumulation. FERROVEN<sup>®</sup> should not be administered to patients with iron overload and treatment should be discontinued when serum ferritin levels equal or exceed normal values. Particular caution should be exercised to avoid iron overload where anemia unresponsive to treatment has been incorrectly diagnosed as iron deficiency anemia.

Symptoms associated with overdosage or infusing FERROVEN<sup>®</sup> too rapidly include hypotension, headache, vomiting, nausea, dizziness, joint aches, paresthesia, abdominal and muscle pain, edema, and cardiovascular collapse. Most symptoms can be successfully treated with i.v. fluids, hydrocortisone, and/or antihistamines. Infusing FERROVEN<sup>®</sup> as recommended or at a slower rate may also alleviate symptoms.

## 5. PHARMACOLOGICAL PARTICULARS

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antianaemic preparations, iron, parenteral preparations  
ATC code: B03AC

The trivalent iron contained in the composition of FERROVEN<sup>®</sup> is a macromolecular iron (III) hydroxide sucrose complex. Sucrose molecule bound with a large number of non-covalent bonds surrounding the polynuclear ferric (III) hydroxide core forms a mass with about 43 kDalton molecular weight. This is too large leading the obstruction of excretion from kidneys. As a result, this complex is stable in the physiological media and does not release the iron in its structure. Iron in the center of the polynuclear core structurally looks like physiologically available ferritin.

The ferrokinetics of ferric-hydroxide-sucrose complex were assessed in 6 patients with chronic renal failure and anemia by using labelled <sup>59</sup>Fe and <sup>52</sup>Fe. Plasma clearance of <sup>52</sup>Fe was in the range of 60 to 100 minutes. <sup>52</sup>Fe was distributed to the liver, spleen and bone marrow. After 2 – 4 weeks following administration, 68 % - 97 % of <sup>59</sup>Fe was detected in the structure of red blood cell.

### 5.2 Pharmacokinetic properties

#### General properties

##### **Absorption:**

After IV administration of ferric-hydroxide-sucrose complex, the elimination half-life is 6 hours, and the total clearance is 1.2 L/hour.

##### **Distribution:**

After the use of IV ferric-hydroxide-sucrose complex, the unsteady-state volume of distribution is 10.0 L, and the steady-state volume of distribution is 7.9 L.

**Biotransformation:**

Following intravenous administration, the ferric-hydroxide-sucrose complex is dissociated into iron and sucrose by the reticuloendothelial system.

**Elimination:**

The sucrose component is eliminated mainly by urinary excretion. 68% of the sucrose is eliminated in urine in 4 hours and 75% in 24 hours. Maximum 5% of the iron can be eliminated in urine in 24 hours at each dose level.

**Special Patient Groups**

There is no data available yet on the characteristics of iron (III) hydroxide sucrose complex in patients with renal or hepatic dysfunction.

**5.3 Preclinical safety data**

In preclinical data depending on the animal studies, repeated toxicity, no harmful effects of genotoxicity or reproductive toxicity were seen.

**6. PHARMACEUTICAL PARTICULARS****6.1 List of Excipients**

Water for injection

Sodium hydroxide (1 N)

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf Life**

36 months.

**6.4 Special Precautions for Storage**

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

**6.5 Nature and Contents of Container**

5 ampoule (Type I glass, colorless) of 5 ml capacity which has been settled in convenient separator, leaflet, carton box.

**6.6 Special Precautions for Disposal and Other Handling**

Unused products or waste materials should be disposed in accordance with the “Medical Waste Disposal Directive” and “Packaging and Packaging Waste Directive”.

**7. MARKETING AUTHORIZATION HOLDER**

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**8. MARKETING AUTHORIZATION NUMBER**

[To be completed nationally]

**9. DATE OF FIRST AUTHORIZATION / RENEWAL OF AUTHORIZATION**

[To be completed nationally]

**10. DATE OF REVISION OF THE SMPC**

[To be completed nationally]