For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only 8029971-9093

HERFEM-S

(Iron Sucrose Injection USP)

COMPOSITION

HERFEM - S 50

Each ml contains :

Ferric Hydroxide in Complex with Sucrose equivalent to Elemental Iron	20 mg
Water for Injections I.P.	q.s.

HERFEM - S 100

Each ml contains :

Ferric Hydroxide in Complex with Sucrose equivalent to Elemental Iron	20 mg
Water for Injections I.P.	q.s.

DESCRIPTION

Herfem-S (Iron Sucrose injection, USP) is a brown, sterile, aqueous, complex of polynuclear Iron (III)-hydroxide in Sucrose for intravenous use. Iron Sucrose injection has a molecular weight of approximately 34,000 - 60,000 daltons. Each ml contains 20 mg elemental Iron as Iron Sucrose in water for injection. Herfem-S is available in 2.5 ml single dose ampoule (50 mg elemental Iron per 2.5 ml) and also available in 5 ml single dose ampoule (100 mg elemental Iron per 5 ml). The drug product contains approximately 30% sucrose w/v (300 mg/ml) and has a pH of 10.5-11.1. The product contains no preservatives. The osmolarity of the injection is not less than 1150 & not more than 1350 mOsmol/L.

CLINICAL PHARMACOLOGY

Mechanism of Action

Iron sucrose injection is an aqueous complex of poly-nuclear iron (III)-hydroxide in sucrose. Following intravenous administration, iron sucrose is dissociated into iron and sucrose and the iron is transported as a complex with transferrin to target cells including erythroid precursor cells. The iron in the precursor cells is incorporated into hemoglobin as the cells mature into red blood cells.

Pharmacodynamics

Following intravenous administration, iron sucrose is dissociated into iron and sucrose. In 22 patients undergoing hemodialysis and receiving erythropoietin (recombinant human erythropoietin) therapy treated with iron sucrose containing 100 mg of iron, three times weekly for three weeks, significant increases in serum iron and serum ferritin and significant decreases in total iron binding capacity occurred four weeks from the initiation of iron sucrose treatment.

Pharmacokinetic

Following intravenous doses of Iron Sucrose, its Iron component exhibits first order kinetics with an elimination half-life of 6 h, total clearance of 1.2 L/h, non-steady state apparent volume of distribution of 10.0L and steady state apparent volume of distribution of 7.9 L. Since Iron disappearance from serum depends on the need for Iron in the Iron stores and Iron utilizing tissues of the body, serum clearance of Iron is expected to be more rapid in Iron deficient patients treated with Herfem-S as compared to healthy individuals. Following intravenous doses of Iron Sucrose, its Iron component appears to distribute mainly in blood and to some extent in extra vascular fluid. A study evaluating Herfem-S containing 100 mg of Iron labeled with 52Fe/59Fe in patients with Iron deficiency shows that a significant amount of the administered Iron distributes in the liver, spleen and bone marrow and that the bone marrow is an Iron trapping compartment and not a reversible volume of distribution.Following intravenous doses of Iron Sucrose, its Iron component dissociated into Iron and Sucrose by the reticuloendothelial system. The Sucrose component is eliminated mainly by urinary excretion.

INDICATIONS

Iron deficiency anemia in which rapid and reliable substitution of iron is required.

CONTRAINDICATION

- The use of Herfem-S is contraindicated in patients with evidence of Iron overload, in patients with known hypersensitivity to Iron preparations or any of its inactive components, and in patients with anemia not caused by Iron deficiency.
- Anaemias not attributable to iron deficiency
- Iron overload or disturbances in utilization of iron
- Patients with a history of asthma, eczema, or other atopic allergy, because they are more susceptible to experience allergic reaction
- Pregnancy first trimester

WARNINGS AND PRECAUTIONS

Hypersensitivity reaction

Hypersensitivity reactions have been reported with injectable Iron products. Serious hypersensitivity reactions have been rarely reported in patients receiving Iron Sucrose. In the event of an allergic or anaphylactoid reactions administration of Iron Sucrose must be stopped, intramuscular adrenaline should be administered immediately and other supportive measures initiated in line with the established cardio-pulmonary resuscitation procedures of the clinic or hospital.

Hypotension

Hypotension has been reported in patients receiving intravenous Iron. Hypotension following administration of Iron Sucrose may be related to rate of administration and/or total dose administered.

Iron overload

Excessive therapy with parenteral iron can lead to excess storage of iron with the possibility of iatrogenic hemosiderosis. Because body Iron excretion is limited and excess tissues Iron can be hazardous, caution should be exercised to with hold Iron administration in the presence of evidence of tissue Iron overload. Patients receiving Iron Sucrose require periodic monitoring of hematologic and hematinic parameters Iron therapy should be withheld in patients with evidence of Iron overload. Transferrin saturation values increase rapidly after IV administration of Iron Sucrose, thus, serum Iron values may be reliably obtained 48 hours after IV dosing.

Liver dysfunction

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.

Infection

Parenteral iron must be used with caution in case of acute or chronic infection. It is recommended that the administration of iron sucrose is stopped in patients with ongoing bacteraemia. In patients with chronic infection a risk/benefit evaluation has to be performed, taking into account the suppression of erythropoiesis. Paravenous leakage must be avoided because leakage of iron at the injection site may lead to pain, inflammation, tissue necrosis and brown discoloration of the skin. In the case of symptoms of dizziness, confusion or light headedness following the administration of iron sucrose, patients should not drive or use machinery until the symptoms have ceased.

DRUG INTERACTION

Iron Sucrose should not be administered concomitantly with oral Iron preparations since the absorption of oral Iron is reduced.

ADVERSE EFECTS

The most frequently reported adverse drug reactions (ADRs) of iron sucrose injection in clinical trials were transient taste perversion, hypotension, fever and shivering, 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. In clinical trials, the following adverse drug reactions have been reported in temporal relationship with the administration of iron sucrose injection, with at least a possible causal relationship:

Nervous system disorders

Common (≥1/100, < 1/10): transient taste perversions (in particular metallic taste).
Uncommon (≥1/1000, < 1/100): headache, dizziness.
Rare (≥1/10000, < 1/1000): paraesthesia, syncope, loss of consciousness, burning sensation.

Cardio-vascular disorders

Uncommon (≥1/1000, < 1/100): hypotension and collapse, tachycardia and palpitations.
Rare (≥1/10000, < 1/1000): hypertension.

Respiratory, thoracic and mediastinal disorders

Uncommon (≥1/1000, < 1/100): bronchospasm, dyspnoea, cough, nasal congestion

Gastrointestinal disorders

Uncommon (≥1/1000, < 1/100): nausea; vomiting, abdominal pain, diarrhoea, Dysgeusia.

Skin and subcutaneous tissue disorders

Uncommon (≥1/1000, < 1/100): pruritus, urticaria, rash, exanthema, erythema.

Musculoskeletal, connective tissue and bone disorders

Uncommon (≥1/1000, < 1/100): muscle cramps, myalgia.

General disorders and administration site disorders

Uncommon (≥1/1000, < 1/100): fever, shivering, flushing, chest pain, tightness, Injection site disorders such as superficial phlebitis, burning, swelling.
Rare (≥1/10000, < 1/1000): arthralgia, peripheral oedema, fatigue, asthenia, malaise, feeling hot, oedema, ear pain, feeling abnormal, infusion site pain/burning, injection site extravasations, peripheral edema, pyrexia, back pain, pain extremities

Immune system disorders

Rare (≥1/10000, < 1/1000): anaphylactoid reactions, anaphylactic type reaction

Moreover, in spontaneous reports the following adverse reactions have been reported:
Isolated cases: reduced level of consciousness, light-headed feeling, confusion, angio-oedema, swelling of joints, hyperhidrosis, back pain, bradycardia, chromaturia, conjunctivitis, fluid overload, gout, hyperglycemia, hypoglycemia, hypertension, shock, convulsion.

150 mm

Infections and Infestation

Nasopharyngitis, sinusitis, upper respiratory tract infections, pharyngitis, graft complications. Symptoms associated with iron sucrose injection total dosage or infusing too rapidly included hypotension, dyspnea, headache, vomiting, nausea, dizziness, joint aches, paresthesia, abdominal and muscle pain, edema, and cardiovascular collapse. These adverse reactions have occurred up to 30 minutes after the administration of iron sucrose injection. Reactions have occurred following the first dose or subsequent doses of iron sucrose injection. Symptoms may respond to IV fluids, hydrocortisone, and/or antihistamines. Slowing the infusion rate may alleviate symptoms.

OVERDOSAGE

No data are available regarding overdosage of iron sucrose in humans. Excessive dosages of iron sucrose may lead to accumulation of iron in storage sites potentially leading to hemosiderosis. Do not administer iron sucrose injection to patients with iron overload.Toxicities in single-dose studies in mice and rats, at intravenous iron sucrose doses up to 8 times the maximum recommended human dose based on body surface area, included sedation, hypoactivity, pale eyes, bleeding in the gastrointestinal tract and lungs, and mortality.

DOSAGES AND ADMINISTRATION

Administration: Herfem-S injection must only be administered by the intravenous route. This may be by a slow intravenous injection or by an intravenous drip infusion. Before administering the first dose to a new patient, a test dose of Herfem-S injection should be given. Herfem-S injection must not be used for intramuscular injection.

Adults and the elderly: The total cumulative dose of Herfem-S injection, equivalent to the total iron deficit (mg), is determined by the haemoglobin level and body weight. The dose for Herfem-S injection must be individually determined for each patient according to the total iron deficit calculated with the following formula:

Total iron deficit [mg] = body weight [kg] x (target Hb - actual Hb) [g/l] x 0.24* + depot iron [mg]

- Below 35 kg body weight: target Hb = 130 g/l and depot iron = 15 mg/kg body weight
- 35 kg body weight and above: target Hb = 150 g/l and depot iron = 500 mg
- Factor 0.24 = 0.0034 x 0.07 x 1000 (Iron content of haemoglobin 0.34%; Blood volume 7% of body weight; Factor 1000 = conversion from g to mg)

The total amount of Herfem-S injection required in mg is determined from above calculation. Alternatively, the total amount of Herfem-S injection required in ml is determined from the following formula or dosage table.

$$\text{Total amount of Herfem S injection required [ml]} = \frac{\text{Total iron deficit [mg]}}{\text{20 mg / ml}}$$

Dosage table stating the total amount of Herfem S injection in ml				
Body Weight	**Total amount of Herfem S injection to be administered**			
	Hb 60 g/l	Hb 75 g/l	Hb 90 g/l	Hb 105 g/l
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

To convert Hb (mM) to Hb (g/l), multiply the former by 16.1145.
Example: For a patient of 60 kg body weight with an actual Hb of 60 g/l 90 ml should be administered. (Alternatively 18 ampoules/vials of 5 ml or 36 vials of 2.5 ml should be administered.)

Dosage: The total single dose must not exceed 200 mg of iron given not more than three times per week. If the total necessary dose exceeds the maximum allowed single dose, then the administration has to be split.

Children: The use of Herfem-S injection has not been adequately studied in children and, therefore, Herfem-S injection is not recommended for use in children.

Intravenous drip infusion:

Herfem-S injection must be diluted with 0.9% w/v Sodium chloride injection I.P.

- 2.5 ml Herfem-S injection (50 mg iron) in max. 50 ml 0.9% w/v Sodium chloride injection I.P.
- 5 ml Herfem-S injection (100 mg iron) in max. 100 ml 0.9% w/v Sodium chloride injection I.P.
- 10 ml Herfem-S injection (200 mg iron) in max. 200 ml 0.9% w/v Sodium chloride injection I.P.

For stability reasons, dilutions to lower Herfem-S injection concentrations are not permissible.
Dilution must take place immediately prior to infusion and the solution should be administered as follows:

- 50 mg iron (2.5 ml Herfem-S injection) in at least 15 minutes
- 100 mg iron (5 ml Herfem-S injection) in at least 15 minutes
- 200 mg iron (10 ml Herfem-S injection) in at least 30 minutes

The first 25 mg of iron (i.e. 25 ml of solution) should be infused as a test dose over a period of 15 minutes. If no adverse reactions occur during this time then the remaining portion of the infusion should be given at an infusion rate of not more than 50 ml in 15 minutes.

Intravenous injection: Herfem-S injection may be administered by slow intravenous injection at a rate of 1 ml undiluted solution per minute and not exceeding 10 ml Herfem-S injection (200 mg iron) per injection. Before administering a slow intravenous injection, a test dose of 1 ml (20 mg of iron) should be injected slowly over a period of 1 to 2 minutes. If no adverse events occur within 15 minutes of completing the test dose, then the remaining portion of the injection may be given.

Injection into dialyser: Herfem-S injection may be administered during a haemodialysis session directly into the venous limb of the dialyser under the same procedures as those outlined for intravenous injection.

USE IN PREGNANCY, NURSING MOTHER, USE IN CHILDREN AND OLDER PATIENTS

Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. In animal reproduction studies, iron sucrose was administered intravenously to rats and rabbits during the period of organogenesis at doses up to 13 mg/kg/day of elemental iron (half or equivalent to the maximum recommended human dose based on body surface area, respectively) and revealed no evidence of harm to the fetus due to iron sucrose. Because animal reproductive studies are not always predictive of human response, iron sucrose injection should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether iron sucrose is excreted in human milk. Iron sucrose is secreted into the milk of lactating rats. Because many drugs are excreted in human milk, caution should be exercised when iron sucrose injection is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of iron sucrose in pediatric patients have not been established. In a country where iron sucrose is available for use in children, at a single site, five premature infants (weight less than 1,250 g) developed necrotizing enterocolitis and two of the five died during or following a period when they received iron sucrose injection, several other medications and erythropoietin. Necrotizing enterocolitis may be a complication of prematurity in very low birth weight infants. No causal relationship to iron sucrose injection or any other drugs could be established.

Geriatric Use

No overall differences in safety were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. In general, dose admini - stration to an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

EXPIRY DATE

Do not use later than the date of expiry.

STORAGE

Store at controlled room temperature. Do not freeze. Keep out of reach of children.

PRESENTATION

Herfem-S 50 and Herfem-S 100 are available in 2.5 ml and 5 ml ampoule.

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Marketed by :
TORRENT PHARMACEUTICALS LTD.
Indrad-382 721, Dist. Mehsana, INDIA.

Manufactured by :
BDR PHARMACEUTICALS INT'L PVT LTD.
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