FREGURD INJECTION

FOR I.V. INJ. ONLY

Composition:

Each ml contains:
Ferric Hydroxide in complex with Sucrose
Eq. to Elemental Iron 20mg.
Water for Injections I.P q.s.

DESCRIPTION :

Iron sucrose injection is a brown, sterile, aqueous complex of poly-nuclear iron (III)-hydroxide in sucrose.
Iron sucrose is a form of the mineral iron. It is approved for use in patients receiving erythropoietin (a hormone that stimulates red blood cell production) and undergoing chronic hemodialysis, which involves filtering the blood in order to remove waste products. In these patients, an iron deficiency is caused by blood replenishing iron loss during the dialysis procedure, increased erythropoiesis (red blood cell production), and insufficient absorption of iron from the gastrointestinal tract. Iron is essential for the synthesis of hemoglobin, which is responsible for the transport of oxygen throughout the body.
Iron sucrose injection has a molecular weight of approximately 34,000 to 60,000 daltons and a proposed structural formula: **$[Na_2Fe_5O_8(OH)•3(H_2O)]n •m(C_{12}H_{22}O_{11})$.**
where: **n** is the degree of iron polymerization and **m** is the number of sucrose molecules associated with the iron (III)-hydroxide.

It is a type 2 complex which limits the maximum dose that can be given to 200mg/day which requires several administrations. Iron sucrose is primarily used to treat anemia or other iron deficiencies.
Iron is a mineral that the body needs to produce red blood cells. When the body does not get enough iron, it cannot produce the number of normal red blood cells needed to keep a patient in good health. This condition is called iron deficiency (iron shortage) or iron deficiency anemia.

MECHANISM OF ACTION :

Fregurd Injection is an aqueous complex of poly-nuclear iron (III)-hydroxide in sucrose. Following intravenous administration, Fregurd Injection 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, Fregurd Injection is dissociated into iron and sucrose. The sucrose component is eliminated mainly by urinary excretion. 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.

Pharmacokinetics :

In healthy adults administered intravenous doses of Fregurd Inj., its iron component exhibit first order kinetics with an elimination half-life of 6 h, total clearance of 1.2 L/h, and steady state apparent volume of

distribution of 7.9 L. The iron component appeared to distribute mainly in blood and to some extent in extra vascular fluid. A study evaluating iron sucrose containing 100 mg of iron in patients with iron deficiency showed that a significant amount of the administered iron distributed to the liver, spleen and bone marrow and that the bone marrow is an irreversible iron trapping compartment.

DISTRIBUTION :

In healthy adults receiving intravenous doses of Iron Sucrose Injection, its iron component appears to distribute mainly in blood and to some extent in the extra vascular fluid. A study evaluating in patients with iron deficiency shows that a significant amount of the administered iron distributes in the liver, spleen and bone marrow.

Elimination Metabolism : Following intravenous administration of iron Sucrose Injection, iron sucrose is dissociated into iron and sucrose by the reticulo-endothelial system. The sucrose component is eliminated mainly by urinary excretion.

Therapeutic indications : Iron Sucrose Injection is indicated for prophylaxis of iron deficiency anemia in pregnancy, for the treatment of iron deficiency anemia in pregnancy, post partum and gynecological surgery. Parenteral irons are frequently used to treat functional iron deficiency, where requirements for iron are greater than the body's ability to supply iron such as in inflammatory states. Iron sucrose injection is also use to treat anemia due to Hemodialysis Dependent Chronic Kidney Disease (HDD-CKD, Non- Dialysis Dependent Chronic Kidney Disease (NDD-CKD) and Peritoneal Dialysis Dependent Chronic Kidney Disease (PDD-CKD).

Usual Adult Dose for Iron Deficiency Anemia : The total cumulative dose of Fregurd Inj., equivalent to the total iron deficit (mg), is determined by the haemoglobin level (Hb) and body weight (BW). The dose of Fregurd Inj. 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]
(*** 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**).

For the prophylaxis and treatment of iron deficiency anemia in pregnancy :
5 - 10 ml of Fregurd Inj. (100 - 200 mg iron) 1 to 3 times a week.
400mg. in 16th weeks or 400mg. in 28th weeks (Given as 200mg. per day and the next dose to be administered after a gape of 48 hours).

Hemodialysis Dependent Chronic Kidney (HDD-CKD) : 5ml (100 mg elemental iron) undiluted slow IV over 2 to 5 minutes. Alternatively, 5 ml (100 mg elemental iron) diluted in a maximum of 100 ml of 0.9% sodium chloride IV over at least 15 minutes. Repeat at consecutive hemodialysis sessions for a total cumulative dose of 1000 mg.

Non- Dialysis Dependent Chronic Kidney Disease (NDD-CKD): Alternatively, 25 ml (500 mg elemental iron), diluted in a maximum of 250 ml sodium chloride 0.9%, IV over 210 to 240 minutes administered on day 1 and day 14 to give a cumulative dose of 1000 mg within a 14- day period. However, there is limited experience with this dosage regimen. A clinical trial (n=30) reported hypotension in 2 patients following administration of this dosage regimen.

Peritoneal Dialysis Dependent Chronic Kidney Disease (PDD-CKD): Two infusions of 15 ml (300 mg elemental iron) each diluted in a maximum of 250 ml of 0.9% sodium chloride administered IV over 90 minutes 14 days apart, followed by one infusion of 20 ml (400 mg elemental iron) diluted in a maximum of 250 ml of 0.9% sodium chloride administered over 150 minutes 14 days after second dose for a total cumulative dose of 1000 mg infused within a 28 day period.

Renal Dose Adjustments : No adjustment recommended

Liver Dose Adjustments : Data not available

Method of administration : Fregurd Inj. 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.
Monitor carefully patients for signs and symptoms of hypersensitivity reactions during and following each administration of Fregurd Inj.
Fregurd Inj. should only be administered when staff trained to evaluate and manage anaphylactic (**A serious allergic reaction that is rapid in onset and may cause death**) 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 Fregurd Inj.

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

Intravenous drip infusion : Fregurd Inj. must only be diluted in sterile 0.9% sodium chloride (NaCl) solution. Dilution must take place immediately prior to infusion and the solution should be administered as follows:

Fregurd Inj. dose (mg of iron)	**Fregurd Inj. dose (ml of Fregurd Inj.)**	**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 Fregurd Inj. concentrations are not permissible.

Intravenous injection : Fregurd Inj. may be administered by slow intravenous injection at a rate of 1 ml undiluted solution per minute and not exceeding 10 ml Fregurd Inj. (200 mg iron) per injection.

Injection into venous line of dialysis machine : Fregurd Inj. may be administered during a hemo dialysis session directly into the venous line of the dialysis machine under the same conditions as for intravenous injection.

Side effects : Commonly reported side effects of iron sucrose include hypotension. In addition to its needed effects, some unwanted effects may be caused 0.5% to 1.5% patients by iron sucrose, like nausea and vomiting, rashes, fever, shivering and giddiness following first dose of iron sucrose. In the event that any of these side effects do occur, they may require medical attention.

WARNINGS AND PRECAUTIONS :

(a). Rare potentially fatal hypersensitivity reactions have been reported in patients receiving iron sucrose injection.
(b). Hypotension may occur if injected too rapidly.
(c). There are no data on the excretion of iron sucrose into human milk. Caution is recommended when administering iron sucrose to nursing women.

Administer with caution in acute or chronic infection or patient with a history of asthma, eczema or other atopic conditions or allergic to other parenteral iron preparations and liver dysfunction.

Paediatric population :
Safety and effectiveness have not been established in pediatric patients and therefore is not recommended in children under 14 years.

Fertility, pregnancy and lactation :

Pregnancy: There is no data from the use of iron sucrose in pregnant women in the first trimester. There are no safety concerns for the mother or newborn.
A careful risk/benefit evaluation is required before use during pregnancy and Fregurd Injection should not be used during pregnancy unless clearly necessary.
Iron deficiency anemia occurring in the first trimester of pregnancy can in many cases be treated with oral iron. Treatment with Fregurd Inj. 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.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

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 iron sucrose inj.via the mother's milk; therefore the risk/benefit should be assessed.
Pre-clinical data do not indicate direct or indirect harmful effects to the nursing child. In lactating rats treated with iron sucrose, low secretion of iron into the milk and transfer of iron into the offspring was observed. Non metabolized iron sucrose is unlikely to pass into the mother's milk.

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. However, in several studies performed in patients who had a history of a hypersensitivity reaction to iron dextran or ferric gluconate, Fregurd Inj. was shown to be well tolerated.
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).
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 reaction should be available, including an injectable 1:1000 adrenaline solution. Additional treatment with antihistamines and/or corticosteroids should be given as appropriate.

Hepatic or renal impairment : 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 should be used with caution in the case of acute or chronic infection. It is recommended that the administration of Fregurd Inj. 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 Fregurd Inj. at the injection site can lead to pain, inflammation, tissue necrosis and brown discoloration of the skin. In case of paravenous leakage, the administration of Fregurd Inj. must be stopped immediately.

CONTRAINDICATIONS :

The use of Fregurd Inj. is contraindicated in the following conditions:
• Hypersensitivity to the active substance to Fregurd Inj. or any of its excipients.
• 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.

Interaction with other medicinal products and other forms of interaction : As with all parenteral iron preparations, Fregurd Inj. 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 Fregurd.

Incompatibilities : This Iron Sucrose Inj. must not be mixed with other medicinal products. Inspect ampoule visually for sediment and damage before use. Use only those containing sediment-free, homogeneous solution. Each ampoule of Fregurd Inj. is intended for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

The compatibility with containers other than polyethylene and glass is not known.

STABILITY AND STORAGE :

Contains no preservatives. Store in original carton at 20°C to 25°C (68° F to 77° F).

PRESENTATION:

1x5ml. ampoule in a mono carton.