Defiron®

Iron Sucrose Injection USP

Composition

Defiron® Injection: Each ml injection contains Iron Sucrose Injection USP equivalent to 20 mg elemental Iron.

Pharmacology

The therapeutic class of Iron Sucrose is haematinic. Iron Sucrose Injection USP is a brown, sterile, aqueous, complex of Polynuclear Iron (III) Hydroxide in Sucrose for Intravenous use. The drug product contains approximately 30% Sucrose w/v (300 mg/ml) and has a pH of 10.5-11.1. Following intravenous administration, **Defiron®** is dissociated into Iron and Sucrose by the reticuloendothelial system, and Iron is transferred from the blood to a pool of Iron in the liver and bone marrow. Ferritin, an Iron storage protein, binds and sequesters Iron in a nontoxic form, from which Iron is easily available. Iron binds to plasma transferrin, which carries Iron within the plasma and the extracellular fluid to supply the tissues. The transferrin receptor, located in the cell, and the transferrin-receptor complex is returned to the cell membrane. Transferrin without Iron (apotransferrin) is then released to the plasma. The intracellular Iron becomes (mostly) haemoglobin in circulating red blood cells (RBCs). Transferrin synthesis is increased and ferritin production reduced in Iron deficiency. The converse is true when Iron is plentiful. Its elimination half-life is 6 h, total clearance is 1.2 L/h, non-steady state apparent volume of distribution is 10.0 L and steady state apparent volume of distribution is 7.9 L. In Iron Sucrose, its Iron component appears to distribute mainly in blood and to some extent in extravascular fluid. 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 distribution. The sucrose component is eliminated mainly through urinary excretion.

Indication

Defiron® 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 can not tolerate oral Iron therapy or who are non-compliant
- In active inflammatory bowel disease where oral Iron preparations are ineffective
- Non-dialysis dependent-chronic kidney disease (NDD-CKD) patients receiving an erythropoietin
- Non-dialysis dependent-chronic kidney disease (NDD-CKD) patients not receiving an erythropoietin
- Hemodialysis dependent-chronic kidney disease (HDD-CKD) patients receiving an erythropoietin
- Peritoneal dialysis dependent-chronic kidney disease (PDD-CKD) patients receiving an erythropoietin

It is also indicated in the treatment of Iron deficiency anaemia in patients undergoing surgical procedures, patients donating blood, postpartum patients.

Dosage and Administration

Administration: **Defiron®** is exclusively to be administered intravenously by drip infusion, by slow injection or directly into the venous limb of the dialyser and is not suitable for intramuscular use and for total dose infusion (TDI), where the full dose of Iron required, representing the patient's total Iron deficit is administered in one complete infusion. Before administration of the first therapeutic dose, a test dose should be given. If any allergic reactions or intolerance occurs during administration, the therapy must be stopped immediately.

Intravenous injection: **Defiron®** can also be administered undiluted by slow intravenous injection at the (normal) recommended rate of 1 ml **Defiron®** (20 mg Iron) per minute [5 ml **Defiron®** (100 mg Iron) in 2 to 5 minutes]. A maximum of 10 ml **Defiron®** (200 mg Iron) can be injected per injection. Before administration of the therapeutic dose in a new patient, a test dose of 1 ml **Defiron®** (20 mg Iron) in adults and in children with a body weight greater than 14 kg and half the daily dose (1.5 mg Iron/kg) in children with a body weight less than 14 kg should be injected over 1 to 2 minutes. If no adverse reactions occur within a waiting period of 15 minutes, the remaining portion of the injection can be administered at recommended speed. After an injection the arm of the patient should be extended.

Infusion: **Defiron®** should preferably be administered by drip infusion (in order to reduce the risk of hypotensive episodes and paravenous injection) in a dilution of 1 ml **Defiron®** (20 mg Iron) in max. 20 ml 0.9% w/v Sodium Chloride [5 ml (100 mg Iron) in max. 100 ml 0.9% w/v NaCl etc. up to 25 ml (500 mg Iron) in max. 500 ml 0.9% w/v NaCl]. Dilution must take place immediately prior to infusion and the solution should be administered as follows: 100 mg Iron in at least 15 minutes; 200 mg Iron in at least 30 minutes; 400 mg Iron In at least 1.5 hours, and 500 mg Iron in at least 3.5 hours. Further of the maximum tolerated single dose of 7 mg Iron/kg body weight, an Infusion time of at least 3.5 hours has to be respected, independently of the total dose.

Before administration of the therapeutic dose in a new patient the first 20 mg Iron in adults and in children with a body weight greater than 14 kg and half the daily dose (1.5 mg Iron/kg) in children with a body weight less than 14 kg should be infused over 15 minutes as a test dose. If no adverse reactions occur, the remaining portion of the infusion can be administered at recommended speed.

Injection into dialyser: **Defiron®** may be administered directly into the venous limb of the dialyser under the same conditions as for intravenous injection.

Hemodialysis Dependent-Chronic Kidney Disease Patients (HDD-CKD): **Defiron®** may be administered undiluted as a 100 mg slow intravenous injection over 2 to 5 minutes or as an infusion of 100 mg, diluted in a maximum of 100 ml of 0.9% NaCl over a period of at least 15 minutes per consecutive hemodialysis session for a total cumulative dose of 1,000 mg.

Non-Dialysis Dependent-Chronic Kidney Disease Patient (NDD-CKD): **Defiron®** is administered as a total cumulative dose 1000 mg over a 14 day period as a 200 mg slow IV injection undiluted over 2 to 5 minutes on 5 different occasions within the 14 day period.

Calculation of Dosage:

The dosage has to be individually adapted 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]

Up to 35 kg body weight: target Hb = 130 g/L resp. depot Iron = 15 mg/kg body weight.

Above 35 kg body weight: target Hb = 150 g/L resp. depot Iron = 500 mg.

*Factor 0.24=0.0034 x 0.07 x 1,000 (Iron content of hemoglobin ≅ 0.34%/Blood volume ≅ 7% of body weight/Factor 1000 = conversion from gm to mg)

$$\text{Total amount of Defiron® to be administered (in ml)} = \frac{\text{Total Iron deficit [mg]}}{20 \text{ mg/ml}}$$

Calculation of no. of ampoules required for different body weight and different haemoglobin level

Hb Level	5 kg	10 kg	15 kg	20 kg	25 kg	30 kg	35 kg	40 kg	45 kg	50 kg	55 kg	60 kg	65 kg	70 kg	75 kg	80 kg	85 kg	90 kg
Hb 60 g/L	1.5	3	5	6.5	8	9.5	12.5	13.5	15	16	17	18	19	20	21	22.5	23.5	**24.5**
Hb 75 g/L	1.5	3	4.5	5.5	7	8.5	11.5	12	13	14	15	16	16.5	17.5	18.5	19.5	20.5	**21.5**
Hb 90 g/L	1.5	2.5	3.5	5	6	7.5	10	11	11.5	12	13	13.5	14.5	15	16	16.5	17	**18**
Hb 105 g/L	1	2	3	4	5.5	6.5	9	9.5	10	10.5	11	11.5	12	12.5	13	13.5	14	**14.5**

If the total necessary dose exceeds the maximum allowed single dose, then the administration has to be splitted. If no response of the hematological parameters is observed after 1 to 2 weeks the original diagnosis should be reconsidered.

Calculation of dosage for Iron replacement secondary to blood loss and to support autologous blood donation: The required **Defiron®** *dose to compensate the Iron deficit is calculated according the following formulas: If the quantity of blood lost is known:* The administration of 200 mg IV Iron (=10 ml **Defiron®**) results in an increase in hemoglobin which is equivalent to 1 unit blood (= 400 ml with 150 g/L Hb content). Iron to be replaced [mg] = number of blood units lost x 200 or Amount of **Defiron®** needed (ml) = number of blood units lost x 10.

If the Hb level is reduced: Use the previous formula considering that the depot Iron does not need to be restored.

Iron to be replaced [mg] = body weight [kg] x 0.24 x (target Hb – actual Hb) [g/L]

e.g.: body weight 60 kg, Hb deficit = 10 [g/L] => Iron to be replaced 150 mg => 7.5 ml **Defiron®** needed.

Normal Dosage

Adults and Elderly: 5-10 ml **Defiron®** (100-200 mg Iron) once to three times a week depending on the hemoglobin level.

Children: There is limited data on children under study conditions. If there is a clinical need, it is recommended not to exceed 0.15 ml **Defiron®** (3 mg Iron) per kg body weight once to three times per week depending on the haemoglobin level.

Side Effect

Adverse reactions, whether or not related to Iron Sucrose injection are as follows: hypotension, cramps/leg cramps, nausea, headache, vomiting, and diarrhea. Some of these symptoms may be seen in patients with chronic renal failure or on hemodialysis not receiving intravenous iron. *Body as a Whole*: headache, fever, pain, asthenia, unwell, malaise, accidental injury. *Cardiovascular Disorders, General*: hypotension, chest pain, hypertension, hypervolemia. *Gastrointestinal Disorders*: nausea, vomiting, abdominal pain, elevated liver enzymes. *Central and Peripheral Nervous System*: dizziness. Musculoskeletal System: cramps/leg cramps, musculoskeletal pain. *Respiratory System*: dyspnea pneumonia, cough. Skin and appendages: pruritus, application site reaction. *Hypersensitivity reactions:* In safety studies, several patients experienced mild or moderate hypersensitivity reactions presenting with wheezing, dyspnea, hypotension, rashes, or pruritus. Anaphylactoid reactions including patients who experienced serious or life-threatening reactions (anaphylactic shock, loss of consciousness or collapse, bronchospasm with dyspnea, or convulsion) associated with Iron Sucrose administration can occur. So, patients should be given a small test dose initially.

Contraindication

The use of Iron Sucrose is contraindicated in patients with evidence of Iron overload, in patients with known hypersensitivity to Iron Sucrose or any of its inactive components, and in patients with anaemia not caused by Iron deficiency. It is also contraindicated in patients with history of allergic disorders including asthma, eczema and anaphylaxis, liver disease and infections.

Drug Interaction

Drug-drug interactions involving Iron Sucrose have not been studied. Iron Sucrose Injection should not be administered concomitantly with oral iron preparations since the absorption of oral Iron is reduced. Even oral Iron therapy should not be given until 5 days after last injection.

Precautions

General: Because body Iron excretion is limited and excess tissue Iron can be hazardous, caution should be exercised to withhold Iron administration in the presence of evidence of tissue Iron overload. Patients receiving Iron Sucrose require periodic monitoring of hematologic and haematinic parameters (hemoglobin, hematocrit, serum ferritin and transferrin saturation). 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. *Hypersensitivity Reactions:* Serious hypersensitivity reactions have been rarely reported in patients receiving Iron Sucrose. Several cases of mild or moderate hypersensitivity reactions were observed in these studies. *Hypotension:* Hypotension has been reported frequently in hemodialysis patients receiving intravenous Iron. Hypotension following administration of Iron Sucrose may be related to rate of administration and total dose administered. Caution should be taken to administer Iron Sucrose according to recommended guidelines. *Use in Pregnancy*: Pregnancy Category-B. No adequate and well controlled studies in pregnant women. This drug should be used during pregnancy only if clearly needed. *Use in Lactation:* It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Iron Sucrose is administered to a nursing woman. *Pediatric Use*: Safety and effectiveness of Iron Sucrose in pediatric patients have not been established. *Geriatric Use:* No overall differences in safety were observed between the elder 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.

Overdosage

Dosages of Iron Sucrose Injection in excess of Iron needs may lead to accumulation of Iron in storage sites leading to hemosiderosis. Periodic monitoring of Iron parameters such as serum ferritin and transferrin saturation may assist in recognizing Iron accumulation. Iron Sucrose should not be administered to patients with Iron overload and should be discontinued when serum ferritin levels equal or exceed established guidelines. Particular caution should be exercised to avoid Iron overload where anaemia unresponsive to treatment has been incorrectly diagnosed as Iron deficiency anaemia. Symptoms associated with overdosage or infusing Iron Sucrose too rapidly included hypotension, headache, vomiting, nausea, dizziness, joint aches, paresthesia, abdominal and muscle pain, edema. and cardiovascular collapse. Most symptoms have been successfully treated with IV fluids, hydrocortisone, and/or antihistamines. Infusing the solution as recommended or at a slower rate may also alleviate symptoms.

Storage

Store in a cool (15°C- 30°C) & dry place, protected from light. Keep out of the reach of children. Do not freeze.

How supplied

Defiron® Injection: Each pack contains one ampoule of Iron Sucrose Injection USP (5 ml), one sterile disposable syringe (5 ml), one alcohol prep. pad and one band aid.

Manufactured by :

SQUARE

PHARMACEUTICALS LTD.

BANGLADESH

Revision No.: 00