ARTWORK SIZE:
80 mm x 220 mm

For the use of a registered medical practitioner or
a hospital or a laboratory only

For Intravenous use only

IRON SUCROSE INJECTION USP 100 mg/5 mL

Referis

Description
A sterile homogeneous brown liquid filled in 5 mL clear USP Type-I ampoules with purple color snap off.

Composition
Each mL injection ampoule contains 20mg of Iron Sucrose Complex.

Pharmacodynamics
The polynuclear iron (III)-hydroxide cores are superficially surrounded by a large number of non-covalently bound sucrose molecules resulting in an overall complex molecular mass (M_w) of approximately 43 kD. This is sufficiently large to prohibit renal elimination. The resulting complex is stable and does not release ionic iron under physiological conditions. The iron in the polynuclear core is bound in a structure similar to ferritin.

Pharmacokinetics

Absorption-After administering a single intravenous dose of 100 mg iron in the form of iron (III) hydroxide sucrose complex in healthy volunteers, a maximum mean iron level of 538 µmol/l was reached after 10 minutes. The volume of distribution of the central compartment corresponds to the volume of plasma (approximately 3 liters).

Distribution-The iron injected is quickly cleared from the plasma; the terminal half life is approximately 6 hours. The volume of distribution at steady state is about 8 liters, which indicates a low iron distribution in the body fluid. Due to the lower stability of Iron (III) - hydroxide sucrose complex in comparison to transferring, a competitive exchange of iron to transferring was observed. This results in an iron transport of approximately 31 mg iron/24 hours.

Elimination- Renal elimination of iron, occurring in the first 4 hours after injection, corresponds to less than 5 % of the total body clearance (approximately 20 mL/minute). After 24 hours the plasma levels of an iron are reduced to the pre dose iron levels and about 75% of the dosage of sucrose is excreted.

Indications
Referis 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 cannot tolerate oral iron therapy or who are noncompliant,
• In active inflammatory bowel disease where oral iron preparations are ineffective,
• In chronic Kidney disease when oral iron preparations are less effective.
The diagnosis of iron deficiency must be based on appropriate laboratory test (e.g. HB, serum ferritin, TSAT, serum iron, etc) (Hb haemoglobin, TSAT transferring saturation)

Recommended Dosage

The dosage of Referis is determined by the haemoglobin level and body weight, and must be calculated individually based on a calculation of the total iron deficit:

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

*Factor 0.24 = 0.0034 x 0.07 x 1000 (Iron content of haemoglobin is equal to 0.34%; Blood volume is equal to 7% of body weight; Factor 1000 = conversion from g to 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

Alternatively, the total amount of Referis required in mL is determined from the following formula or dosage table given below.

$$\text{Total amount of Iron Sucrose required (mL)} = \frac{\text{Total iron deficit (mg)}}{20\ \text{mg/mL}}$$

Total amount of Iron Sucrose injection to be administered				
Body Weight	**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

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.

For Intravenous drip infusion:

Referis must be diluted to sterile 0.9% w/v Sodium Chloride Injection. Dilution must take place immediately prior to infusion and the solution should be administered as follows:

100 mg iron (5 mL Iron Sucrose Injection) in at least 15 minutes

200 mg iron (10 mL Iron Sucrose 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.

For Intravenous Injection:

Referis may be administered by slow intravenous injection at a rate of 1 mL undiluted solution per minute and not exceeding 10 mL Iron Sucrose Injection USP 100 mg/5 mL (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 can be given.

For Injection into Dialyser

Referis 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.

Children

The use of Referis has not been adequately studied /documented in children and therefore, Referis is not recommended for use in children.

Route of Administration
Referis should only be administered by the Intravenous route.

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Contraindications
The use of Referis is contraindicated in cases of:
• Iron overload or disturbances in utilization of iron (e.g. haemochromatosis, haemosiderosis)
• Anemic conditions not caused by iron deficiency (e.g. haemolytic anaemias)
• Known hypersensitivity to Iron mono-, disaccharide complexes, Iron Sucrose Injection or any of its components.
• Hypersensitivity to the active substance, to Referis or any of its excipients.

Warnings & Precautions
Referis is a strong alkaline solution, hence never be administrated by the subcutaneous or intramuscular route. Paravenous leakage must be avoided because leakage of Referis at the injection site may lead to pain, inflammation, tissue necrosis and brown discoloration of the skin. In case of inadvertent paravenous leakage, while the needle is still inserted, rinse with a small amount of 0.9% w/v Sodium chloride Injection.

Injection of Referis parenterally can cause allergic or anaphylactic reactions, which may be potentially fatal. In the event of allergic reaction, administration of Referis must be stopped and antihistamines and/or corticosteroids should be administered immediately. Referis should only be administered when staff trained to evaluate and manage anaphylactic reactions is immediately available and in an environment where full resuscitation facilities can be assured. Each patient should be observed for adverse effects for at least 30 minutes following each injection.

Hypotensive episodes may occur if the injection is administered too rapidly. Allergic reactions, sometimes involving arthralgia, have been more commonly observed when the recommended dose is exceeded. The risk is enhanced for patients with known allergies including patients with a history of severe asthma, eczema or other atopic allergy. Patients with low iron binding capacity and/or folic acid deficiency are particularly at risk of an allergic or anaphylactic reaction.

Referis should not be administrated in combination with oral iron preparations and must not be mixed with other medicines for simultaneous administration.

Ampoules should be visually inspected for physical damage before use and only a sediment free solution can be used. Referis is intended for single use only. After first opening of the ampoule/ container as well as after dilution with sterile 0.9%w/v Sodium Chloride Injection, the remaining or unused portion of Referis should be discarded.
Porphyria: Safety has not been established.

Interactions with other medicaments
Referis should not be administered concomitantly with oral iron preparations, since the absorption of oral iron is reduced. Therefore, if required oral iron therapy should be started at least 5 days after the last injection of Referis.

Statement on usage during pregnancy and lactation

Pregnancy:
There are no adequate and well-controlled trials of Referis in pregnant women. Treatment with Referis should only be confined to second and third trimester if the benefit is judged to outweigh the potential risk for both the mother and the foetus.

Lactation:
Safety during lactation has not been established.

Adverse Effects/Undesirable effects
Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10000, <1/1000); very rare (≤1/10000) including isolated cases

Nervous system disorders
Common: transient taste perversions (in particular metallic taste)
Uncommon: headache, dizziness
Rare: Paraesthesia, syncope, loss of consciousness, burning sensation.

Cardiovascular disorder
Uncommon: hypotension and collapse, tachycardia and palpitations.
Rare: hypertension.

Respiratory, thoracic and mediastinal disorders
Uncommon: bronchospasm, dyspnoea

Gastrointestinal disorders
Uncommon: nausea, vomiting, abdominal pain, diarrhea.

Skin and Subcutaneous tissue disorders
Uncommon: pruritus, urticaria, rash, exanthema, erythema.

Musculoskeletal, connective tissue and bone disorders
Uncommon: Muscle cramps, myalgia

General Disorder and administration site disorders
Uncommon: Fever, shivering, flushing, chest pain and tightness. Injection site disorders such as superficial phlebitis, burning, swelling.
Rare: arthralgia, peripheral oedema, fatigue, asthenia, malaise, feeling hot, oedema.

Immune system disorders
Rare: anaphylactic reactions.

Overdose & treatment
Over dosage can cause acute iron overloading which may manifest itself as haemosiderosis. Particular caution should be exercised to avoid iron overload where anaemia, non response to treatment, has been incorrectly diagnosed as iron deficiency anaemia. Over dosage should be treated, if required, with an iron chelating agent.

Incompatibilities
Referis must only be mixed with sterile 0.9% w/v sodium chloride solution. No other solutions and therapeutic agents should be used as there is the potential for precipitation and/or interaction. The compatibility with containers other than glass, polyethylene and PVC is not known.

Storage Conditions
Store below 30° C. Do not freeze. Keep out of reach of children.

CONTROLLED MEDICINE

Dosage form and Packing available
5mL Referis is filled in sealed glass ampoule and 5 labelled ampoules are placed in one PVC Plastic Tray.

Shelf-life
Referis can be used within 36 months from the manufacturing date if kept as recommended.

Registration Number
Referis Iron Sucrose Injection USP 100mg/5mL- MAL17085002AZ

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