RANOFER INJECTION 100 MG/ 5 ML

DESCRIPTION:
RANOFER INJECTION 100 MG/ 5 ML: A dark brown, non-transparent, sterile aqueous solution in 5 ml amber ampoule.

COMPOSITION:
Each 5 ml amber ampoule of Ranofer contains 100 mg iron as iron sucrose [iron (III)-hydroxide sucrose complex], corresponding to 20 mg iron per ml.

PHARMACODYNAMICS:
Plasma clearance of 52Fe was in the range of 60 to 100 minutes. 52Fe was distributed to the liver, spleen and bone marrow. At two to four weeks after administration, the maximum red blood cell utilization of 59Fe ranged from 68% to 97%.

PHARMACOKINETICS:
Following intravenous injection of a single dose of Ranofer containing 100 mg iron, maximum iron levels, averaging 538 mmol/l, were obtained 10 minutes after injection. The volume of distribution of the central compartment corresponded well to the volume of plasma (Approximately 3 L).
The iron injected was rapidly cleared from the plasma, the terminal half-life being approximately 6 hours. The volume of distribution at steady state was about 8 L, indicating a low iron distribution in body fluid. Due to the lower stability of iron sucrose in comparison to transferrin, a competitive exchange of iron to transferrin was observed. This resulted in iron transport of approximately 31 mg iron/24 hours.
Renal elimination of iron, occurring in the first 4 hours after injection, corresponds to less than 5% of the total body clearance. After 24 hours the plasma levels of iron were reduced to the pre-dose iron level and about 75% of the dosage of sucrose was excreted.

INDICATIONS:
Ranofer is indicated for the treatment of iron deficiency anaemia 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 non-compliant,
- In active inflammatory bowel disease where oral iron preparations are ineffective.

Ranofer should only be administered where the indication is confirmed by appropriate investigations (e.g. Hb, serum ferritin, serum iron)

RECOMMENDED DOSAGE:
Calculation of dosage
The total cumulative dose of Ranofer, equivalent to the total iron deficit (mg), is determined by the haemoglobin level and body weight. The dose of Ranofer 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
Conversion from g/L to mg/L = Factor 1000
Total amount of Ranofer to be administered (in ml) = $\frac{\text{Total iron deficit (mg)}}{\text{20mg/ml}}$

Body Weight (kg)	Total number of ampoules Ranofer to be administered (1 ampoule of Ranofer corresponds to 5 ml)			
	Hb 60 g/l	Hb 75 g/l	Hb 90 g/l	Hb 105 g/l
5	1.5	1.5	1.5	1
10	3	3	2.5	2
15	5	4.5	3.5	3
20	6.5	5.5	5	4
25	8	7	6	5.5
30	9.5	8.5	7.5	6.5
35	12.5	11.5	10	9
40	13.5	12	11	9.5
45	15	13	11.5	10
50	16	14	12	10.5
55	17	15	13	11
60	18	16	13.5	11.5
65	19	16.5	14.5	12
70	20	17.5	15	12.5
75	21	18.5	16	13
80	22.5	19.5	16.5	13.5
85	23.5	20.5	17	14
90	24.5	21.5	18	14.5

To convert Hb (mM) to Hb (g/l), multiply the former by 16.1145
If the total necessary dose exceeds the maximum allowed single dose, then the administration has to be split, please refer to Route of Administration

Calculation of dosage for iron replacement secondary to blood loss and to support autologous blood donation
The required Ranofer dose to compensate the iron deficit is calculated according to the following formulas:
If quantity of blood lost is known:
The administration of 200 mg i.v. iron (=10 ml Ranofer) results in an increase in haemoglobin 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 Ranofer needed [ml] = number of blood units lost x 10

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If the Hb level is reduced:
Use the following 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
≈ 150 mg iron to be replaced
→ 7.5 ml Ranofer needed

Normal posology
Adults and the elderly:
5 – 10 mL Ranofer (100 – 200 mg iron) one to three times a week depending on the haemoglobin 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 Ranofer (3 mg iron) per kg body weight one to three time per week depending on the haemoglobin level.

Maximum Tolerated Dose
As injection, maximum tolerated dose per day given not more than three times per week:
- 200 mg iron (10 ml Ranofer) injected over at least 10 minutes

As infusion, maximum tolerated single dose per day given not more than once per week:
- Patients above 70 kg: 500 mg iron (25 ml Ranofer) in at least 3.5 hours.
- Patients of 70 kg and below: 7 mg iron/kg body weight in at least 3.5 hours

The maximum tolerated single dose is 7 mg iron per kg body weight given once per week, but not exceeding 500 mg iron. Administration time and dilution ratio, please refer to Route of Administration. The infusion times given in sections under Route of Administration must be strictly adhered to, even if the patient does not receive maximum tolerated single dose.

ROUTE OF ADMINISTRATION :
Ranofer must only be administered by 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.

Intravenous drip infusion
Ranofer must be diluted only in 0.9% m/V sodium chloride solution. Dilution must take place immediately prior to infusion and the solution should be administered as follows:

Ranofer Dose (mg of iron)	Ranofer Dose (ml of Ranofer)	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 Ranofer concentrations are not permissible.

Intravenous injection
Ranofer can be administered by slow intravenous injection at a rate of 1 ml undiluted solution per minutes and not exceeding 10 ml Ranofer (200 mg iron) per injection

Injection into dialyser
Ranofer may be administered during a haemodialysis session directly into the venous line of the dialysis machine under the same conditions as for intravenous injection.

CONTRAINDICATIONS:
The use of Ranofer is contra-indicated in cases of:
- Anaemia not caused by iron deficiency,
- Iron overload or disturbances in utilization of iron,
- Known hypersensitivity to Ranofer or any of its inactive components,

WARNINGS AND PRECAUTIONS:
Parentally administered iron preparations can cause allergic or anaphylactoid reactions, which can be potentially fatal. Therefore, antiallergic treatment should be in place with the established cardio-pulmonary resuscitation procedures.
In patients with history of asthma, eczema, other atopic allergies or allergic reactions to other parenteral iron preparations, Ranofer should be administered with care as they are particularly at risk of an allergic reaction.
Ranofer should be administered with care in patients with liver dysfunction.
Ranofer must be used with care in patients with acute or chronic infection who have excessive ferritin values as parenterally administered iron can unfavourably influence bacterial or viral infection.
Paravenous leakage must be avoided because leakage of Ranofer at the injection site may lead to pain, inflammation, tissue necrosis and brown discoloration of the skin.

INTERACTIONS WITH OTHERS MEDICAMENTS:
As with all parenteral iron preparations, Ranofer should not be administered concomitantly with oral iron preparations since the absorption of oral iron is reduced.

USE IN PREGNANCY AND LACTATION:
No well-controlled studies in pregnant women are available to date. Nevertheless, risk/benefit evaluation is required.
Non metabolised Ranofer is unlikely to pass into the mother's milk. No well-controlled clinical studies are available to date.

SIDE EFFECTS:
The most frequently reported adverse drug reaction (ADRs) was dysgeusia. Hypersensitivity reaction was the most significant serious adverse drug reaction associated with this product. The adverse drug reactions reported after administration are presented below.

Common (≥1/100, <1/10)
Nervous system disorders: Dysgeusia
Vascular disorders: Hypotension, hypertension
Gastrointestinal Disorders: Nausea
General disorders and administration site conditions: Injection/infusion site reaction (extravasation, -irritation, -reaction, -discolouration, -haematoma, -pruritus).

Uncommon (≥1/1,000, <1/100)
Immune system disorders: Hypersensitivity
Nervous system disorders: Headache, dizziness, paraesthesia, hypoaesthesia
Vascular disorders: Flushing, phlebitis
Respiratory, thoracic and mediastinal disorders: Dyspnoea
Gastrointestinal Disorders: Vomiting, abdominal pain, diarrhoea, Constipation
Skin and subcutaneous tissue disorders: Pruritus, rash
Musculoskeletal and connective tissue disorders: Muscle spasm, myalgia, arthralgia, pain in extremity, back pain
General disorders and administration site conditions: Chills, asthenia, fatigue, oedema peripheral, pain
Investigations: Alanine aminotransferase increased, aspartate aminotransferase increased, gammaglutamyltransferase increased, serum ferritin increased

Rare (≥1/10,000, <1/1,000)
Nervous system disorders: Syncope, somnolence
Cardiac disorders: Palpitations
Renal and urinary disorders: Chromaturia
General disorders and administration site conditions: Chest pain, hyperdrosis, pyrexia
Investigations: Blood lactate dehydrogenase increased

Frequency not known
Immune system disorders: Anaphylactoid reactions, Angioedema
Nervous system disorders: Depressed level of consciousness, confusional state, loss of consciousness, anxiety, tremor
Cardiac disorders: Bradycardia, tachycardia
Vascular disorders: Circulatory collapse, thrombophlebitis
Respiratory, thoracic and mediastinal disorders: Bronchospasm
Skin and subcutaneous tissue disorders: Urticaria, erythema
General disorders and administration site conditions: Cold sweat, malaise, pallor

SYMPTOMS AND TREATMENT OF OVERDOSE:
Overdosage can cause acute iron overloading which may manifest itself as haemosiderosis. Overdosage should be treated, if required, with an iron chelating agent.

INCOMPATIBILITIES:

Ranofer must only be mixed with sterile 0.9% m/V sodium chloride solution. No other solutions and therapeutic agent 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:
Unopened Ampoule : Store in original carton. Do not store above 30°C. Do not freeze. Keep out of reach of children. *Jauhkan daripada kanak-kanak.*

PACK SIZES:
Pack in 5 ampoules of 5 ml / box.

SHELF LIFE:
Please refer to outer package.

Shelf life after first opening the container:
From a microbiological point of view, the product should be used immediately.

Shelf life after dilution with sterile 0.9% m/ V sodium chloride solution:
From a microbiological point of view, the product should be used immediately after dilution with sterile 0.9% m/ V sodium chloride.

PRODUCT REGISTRATION HOLDER AND MANUFACTURER:
DUOPHARMA (M) SDN BHD
Lot 2599, Jalan Seruling 59, Kawasan 3,
Taman Klang Jaya, 41200 Klang, Selangor, MALAYSIA

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