Pharmacokinetic properties:
Following intravenous injection of a single dose of Hadid containing 100 mg iron in healthy volunteers, maximum iron levels, averaging 538 µmol/l, were obtained 10 min after injection. The volume of distribution of the central compartment corresponded well to the volume of plasma (approx. 3L). The iron injected was rapidly cleared from the plasma, the terminal half-life being approx. 6 h. The volume of distribution at steady state was about 8L, indicating a low iron distribution in the 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 approx.31mg iron/24 h.

Renal elimination of iron, occurring in the first 4 h after injection, corresponds to less than 5% of the total body clearance. After 24 h the plasma levels of iron were reduced to the pre-dose iron level and about 75% of the dosage of sucrose was excreted.

Preclinical safety data:
Preclinical data showed no special hazards based on conventional studies of repeated toxicity, genotoxicity and toxicity to reproduction in animals.

PHARMACEUTICAL PARTICULARS:
List of excipients
Water for injection and sodium hydroxide.

Incompatibilities
Hadid must only be mixed with 0.9%w/v NaCl solution.
No other intravenous dilution 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.

Shelf life
Shelf-life in the product as packaged for sale:
2 years.

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

Shelf-life after dilution with 0.9% sodium chloride solution:
Chemical and physical in-use stability has been demonstrated for 12 hours at room temperature.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 3 hours at room temperature unless dilution has taken place in controlled and validated aseptic conditions.
Special precautions for storage:
Store in original carton. Store at 15-30°C.

Nature and contents of container
Type I glass ampoules with extractable volumes of 5ml.

Instructions for use/handling:
Ampoules should be visually inspected for sediment and damage before use. Only those with sediment free and homogenous solutions must be used.
See also "Shelf life".

Package form:
Ampoules (5 ml) containing 100 mg of iron: 5

حدید انجیکشن
آئرن سکروز

خوراک: دوا ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
ہدایات: دوا کو **15-30°** سینٹی گریڈ پر رکھیں۔
گرمی، روشنی اور نمی سے محفوظ رکھیں۔ تمام دوائیں بچوں کی پہنچ سے دُور رکھیں۔
صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

Manufactured by:
STANDPHARM PAKISTAN (PVT) LTD
20 Km Ferozepur Road Lahore, Pakistan.
0622-00

Hadid
Iron Sucrose

INJECTION

QUALITATIVE AND QUANTITATIVE COMPOSITION:
Each 5ml ampoule contains 20mg/ml iron as iron sucrose corresponding to 100 mg iron per ampoule.

PHARMACEUTICAL FORM:
Solution for injection or concentrate for solution for infusion. Hadid is a dark brown, non-transparent, aqueous solution with a pH of 10.5-11.0 and an osmolarity of 1250 mOsmol/l.

CLINICAL PARTICULARS
Therapeutic indications
Hadid 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.

Posology and method of administration:
Administration:
Hadid has 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.

Infusion:
Hadid should preferably be administered by drip infusion (in order to reduce the risk of hypotensive episodes and paravenous injection) in a dilution of 1ml Hadid (20mg iron) in max. 20ml 0.9% w/v sodium chloride [5ml (100mg iron) in max. 100ml 0.9% w/v NaCl e.t.c up to 25ml (500mg iron) in max. 500ml 0.9% w/v NaCl]. Dilution must take place immediately prior to infusion and the solution should be administered as follows: 100mg iron in at least 15 minutes; 200mg iron in at least 30 minutes; 300mg iron in at least 1.5 hours; 400mg iron in at least 2.5 hours and 500 mg iron in at least 3.5 hours. For the administration of the maximum tolerated single dose of 7mg iron/kg body weight, an infusion time of at least 3.5 hours has to be respected, independently of the total dose.

Total number of Hadid ampoules to be administered

	Body weight																		
	5kg	10kg	15kg	20kg	25kg	30kg	35kg	40kg	45kg	50kg	55kg	60kg	65kg	70kg	75kg	80kg	85kg	90kg
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 split. If no response of the haematological parameters is observed after l 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 Hadid dose to compensate the iron deficit is calculated according to the following formulas:

- If the quantity of blood lost is known: The administration of 200 mg I.V iron (=10 ml Hadid) results in an increase in haemoglobin which is equivalent to 1 unit blood (= 400ml with 150 g/L Hb content).
Iron to be replaced [mg] = number of blood units lost x 200 or
Amount of Hadid 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 60kg, Hb deficit = 10 g/L = iron to be replaced ≅ 150mg => 7.5ml Hadid needed.

Normal posology
Adults and the Elderly:
5-10 ml Hadid (100-200mg iron) once 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 Hadid (3mg iron) per kg bw once to three times per week depending on the haemoglobin level.

Maximum tolerated single dose Adults and the Elderly:
As injection: 10ml Hadid (200mg iron) injected over at least 10 minutes.

As infusion:
When the clinical situation demanded, doses of up to 500mg have been administered. The maximum tolerated single dose is 7mg iron per kg body weight given once per week, but not exceeding 500mg iron. For administration time and dilution ratio see section

"Administration".
Before administration of the therapeutic dose in a new patient the first 20mg iron in adults and in children with a body weight greater than 14 kg and half the daily dose (1.5mg 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.

Intravenous injection:
Hadid can also be administered undiluted by slow intravenous injection at the (normal) recommended rate of 1 ml Hadid (20mg iron) per minute [5ml Hadid (100 mg iron) in at least 5 minutes]. A maximum of 10 ml Hadid (200mg iron) can be injected per injection.

Before administration of the therapeutic dose in a new patient a test dose of 1 ml Hadid (20mg 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.

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

Dosage
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]
Below to 35 kg body weight target Hb = 130g/L resp. depot iron = 15mg/kg body weight 35kg body weight and above: target Hb = 150g/L resp.depot iron = 500mg
*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")
Total amount of Hadid to be administered (in ml) =

$$\frac{\text{Total iron deficit [mg]}}{20\ \text{mg/ml.}}$$

(1 ampoule of Hadid corresponds to 5ml)
A higher incidence of adverse reactions (in particular hypotension, which can also be more severe, is associated with higher dosages.
Therefore the infusion times given in section "Administration" must be strictly adhered to, even if the patient does not receive the maximum tolerated single dose.

Contra-indications:
The use of Hadid is contra-indicated in cases of:
-anaemia not caused by iron deficiency,
-Iron overload or disturbances in utilization of iron,
-known hypersensitivity to Hadid or any of its inactive components,
- Pregnancy first Trimester.

Special warnings and special precautions for use:
Hadid should only be administered where the indication is confirmed by appropriate investigations (e.g. serum ferritin, or haemoglobin (Hb) or haematocrit or erythrocyte count. Or red cell indices — MCV, MCH, MCHC.

Parenterally administered iron preparations can cause allergic or anaphylactoid reactions, which can be potentially lethal. In the case of a mild allergic reaction, antihistamines should be administered; in the case of a serious anaphylactoid reaction adrenaline should be administered immediately. Facilities for cardio-pulmonary resuscitation must be available.

In patients with a history of asthma, eczema, other atopic allergies or allergic reactions to other parenteral iron preparations and patients with low iron binding capacity and/or folic acid deficiency Hadid should be administered with care as they are particularly at risk of an allergic reaction. However it was shown in a study with a limited number of iron dextran sensitive patients that Hadid could be administered with no complications.

Hadid should be administered with care in patients with liver dysfunction.

Hadid must be used with care in patients with acute or chronic infection who have excessive ferritin values as parenterally administered iron can unfavourably influence a bacterial or viral infection.

Hypotensive episodes may occur if injection is administered too rapidly.

Paravenous leakage must be avoided because leakage of Hadid at the injection site may lead to pain, inflammation, tissue necrosis, sterile abscess and brown discoloration of the skin.

Interaction with other medicaments and other forms of interaction:
As with all parenteral iron preparations, Hadid should not be administered concomitantly with oral iron preparations since the absorption of oral iron is reduced. Therefore an oral iron therapy should at least be started 5 days after the last injection.

Pregnancy and Lactation:
Data on a limited number of exposed pregnancies indicated no adverse effects of Iron Sucrose on pregnancy or on the health of the foetus/newborn child. No well-controlled studies in pregnant women are available to date. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development.
Nevertheless, risk/benefit evaluation is required.

Non metabolised Iron Sucrose is unlikely to pass into the mother's milk. Therefore, Hadid should not present a risk to the suckling child.

Effects on ability to drive and use machines:
It is unlikely that Hadid has an influence on the ability to drive and use machines.

Undesirable effects:
The most frequently reported adverse drug reactions (ADRs) of Hadid 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 (see "Special warnings and Precautions for use").

In clinical trials, the following adverse drug reactions have been reported in temporal relationship with the administration of Hadid, with at least a possible causal relationship:

Nervous system disorders:
Common (greater than or equal to 1% and less than 10%): transient taste perversions (in particular metallic taste).

Uncommon (greater than or equal to 0.1% and less than 1%): headache; dizziness. Rare (greater than or equal to 0.01% and less than 0.1%): paraesthesia.

Cardio-vascular disorders:
Uncommon: hypotension and collapse; tachycardia and palpitations.

Respiratory, thoracic and mediastinal disorders
Uncommon: bronchospasm, dyspnoea.

Gastrointestinal disorders:
Uncommon: nausea; vomiting; abdominal pain; diarrhoea.

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

Musculoskeletal, connective tissue and bone disorders:
Uncommon: muscle cramps, myalgia.

General disorders and administration site disorders
Uncommon: fever, shivering, flushing; chest pain and tightness. Injection site disorders such as superficial phlebitis, burning, swelling.
Rare: anaphylactoid reactions (rarely involving arthralgia); peripheral oedema; fatigue, asthenia; malaise.

Moreover, in spontaneous reports the following adverse reactions have been reported:
Isolated cases: reduced level of consciousness, light-headed feeling, confusion, angioedema and swelling of joints.

Paravenous leakage must be avoided because leakage of Hadid at the injection site may lead to pain, inflammation, tissue necrosis, sterile abscess and brown discoloration of the skin.

Overdose:
Overdosage can cause acute iron overloading which may manifest itself as haemosiderosis.
Overdosage should be treated with supportive measures and, if required, an iron chelating agent.

PHARMACOLOGICAL PROPERTIES:
The polynuclear iron(III)-hydroxide cores are superficially surrounded by a large number of non-covalently bound sucrose molecules resulting in a complex whose molecular mass MW is approx. 43 kDa. This is sufiiciently large to prohibit renal elimination. The resulting complex is stable and does not release ionic iron under physiological conditions.

The iron in the polynuclear cores is bound in a similar structure as in the case of physiologically occurring ferritin.

Pharmacodynamic properties:
The ferrokinetics of Hadid labelled with ^{59}Fe and ^{52}Fe were assessed in 6 patients with anaemia and chronic renal failure. Plasma clearance of ^{52}Fe was in the range of 60 to 100 minutes. ^{52}Fe was distributed to the liver, spleen and bone marrow. At two to four weeks after administration, the maximum red blood cell utilisation of ^{59}Fe ranged from 68% to 97%.