Bosch

For Medical Professional only

Clefer

100mg/5ml Injection

(Iron Sucrose U.S.P.)

کلیفر ۱۰۰ ملی گرام/۵ ملی لیٹر انجکشن

DESCRIPTION:

Clefer (iron sucrose injection, USP), an iron replacement product, is a brown, sterile, aqueous, complex of polynuclear iron (III)-hydroxide in sucrose for intravenous use. Iron sucrose injection has a molecular weight of approximately 34,000 to 60,000 daltons and a proposed structural formula: [Na2Fe5O8(OH).3(H2O)]n.m(C12H22O11)

PHARMACOLOGICAL PROPERTIES

Mechansim of action:

Iron sucrose, the active ingredient of **Clefer** is composed of a polynuclear iron(III)-hydroxide core surrounded by a large number of non-covalently bound sucrose molecules. The polynuclear iron core has a structure similar to that of the core of the physiological iron storage protein ferritin. The complex is designed to provide, in a controlled manner, utilizable iron for the iron transport and storage proteins in the body (i.e., transferrin and ferritin, respectively).

Following intravenous administration, the polynuclear iron core from the complex is taken up predominantly by the reticuloendothelial system in the liver, spleen, and bone marrow. In a second step, the iron is used for the synthesis of Hb, myoglobin and other iron-containing enzymes, or stored primarily in the liver in the form of ferritin.

Pharmacokinetic Properties:

Distribution:

In the first 6–8 hours, 52Fe was taken up by the liver, spleen and bone marrow. The radioactive uptake by the macrophage-rich spleen is considered to be representative of the reticuloendothelial iron uptake.maximum total serum iron concentrations were attained 10 minutes after injection and had an average concentration of 538 µmol/l. The volume of distribution of the central compartment corresponded well to the volume of plasma (approximately 3 litres).

Biotransformation:

Upon injection, sucrose largely dissociates and the polynuclear iron core is mainly taken up by the reticuloendothelial system of the liver, spleen, and bone marrow. At 4 weeks after administration, red cell iron utilization ranged from 59 to 97%.

Excretion:

The iron sucrose complex has a weight average molecular weight (Mw) of approximately 43 kDa, which is sufficiently large to prevent renal elimination. Renal elimination of iron, occurring in the first 4 hours after injection of a **Clefer** dose of 100 mg iron, corresponded to less than 5% of the dose. After 24 hours, the total serum iron concentration was reduced to the pre-dose level. Renal elimination of sucrose was about 75% of the administered dose.

CLINICAL PARTICULARS:

Therapeutic indications

Clefer 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 non-compliant,
- In active inflammatory bowel disease where oral iron preparations are ineffective,
- In chronic kidney disease when oral iron preparations are less effective.

DOSAGE AND ADMINISTRATION

Administration:

Clefer 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: Clefer 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 **Clefer** (20mg iron) in max. 20ml 0.9% w/v sodium chloride [5ml (100mg iron) in max. 100ml 0.9% w/v NaCl etc. 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 1½ hours; 400mg iron at 2½ hours and 500mg iron at least 3½ hours. For the administration of the maximum tolerated single dose of 7 mg iron/kg body weight, an infusion time of at least 3½ 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.

Intravenous injection: Clefer can also be administered undiluted by slow intravenous injection at the (normal) recommended rate of 1 ml **Clefer** (20 mg

iron) per minute [5 ml **Clefer** (100 mg iron) in at least 5 minutes]. A maximum of 10 ml Clefer (200 mg iron) can be injected per injection.

Before administration of the therapeutic dose in a new patient a test dose of 1 ml **Clefer** (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.

Injection into dialyser: Clefer 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 35kg body weight: target Hb = 130 g/l resp. depot iron = 15 mg/kg body weight
35kg body weight and above: target Hb=150 g/l resp. 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 / Factor 1000 = conversion from g to mg)

Total amount of **Clefer** to be administered (in ml) = $\frac{\text{Total iron deficit [mg]}}{\text{20 mg/ml}}$
(1 ampoule of **Clefer** corresponds to 5 ml)

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 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 **Clefer** dose to compensate the iron deficit is calculated according the following formulas:
- If the quantity of blood lost is known: The administration of 200mg i.v. Iron (= 10ml **Clefer**) 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 **Clefer** 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 **Clefer** needed

Normal Dosage
Adults and the Elderly
5-10ml **Clefer** (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 0.15ml **Clefer** (3 mg iron) per kg body weight once to three times per week depending on the haemoglobin level.

Maximum tolerated single dose
Adults and the Elderly:
As injection: 10ml Clefer (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. Administration time and dilution ratio see section "Administration".

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 **Clefer** is contra-indicated in cases of:
- Anemia not caused by iron deficiency.
- Iron overload or disturbances in utilisation of iron.
- known hypersensitivity to Clefer or any of its inactive components.
- Pregnancy first trimester.

WARNINGS AND PRECAUTIONS:
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. There have been reports of hypersensitivity reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction). In several studies performed in patients who had a history of a hypersensitivity reaction to iron dextran or ferric gluconate.

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).

Clefer should only be administered when staff trained to evaluate and manage anaphylactic reactions is immediately available, 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 **Clefer** injection. 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 reactions should be available, including an injectable 1:1000 adrenaline solution. Additional treatment with antihistamines and/or corticosteroids should be given as appropriate.

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.

Parenteral iron should be used with caution in the case of acute or chronic infection. It is recommended that the administration of **Clefer** 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 **Clefer** at the injection site can lead to pain, inflammation and brown discoloration of the skin.

DRUG INTERACTIONS:
As with all parenteral iron preparations, **Clefer** 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 **Clefer**.

USE IN PREGNANCY AND LACTATION:
Pregnancy:
A careful risk/benefit evaluation is required before use during pregnancy and **Clefer** should not be used during pregnancy unless clearly necessary. Iron deficiency anaemia occurring in the first trimester of pregnancy can in many cases be treated with oral iron. Treatment with **Clefer** should 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:
Preclinical data do not indicate direct or indirect harmful effects to the nursing child. Non metabolised iron sucrose is unlikely to pass into the mother's milk.

ADVERSE EFFECTS:
The following adverse effects have been observed with iron sucrose therapy.

Common: Dysgeusia, Hypotension, hypertension, Nausea,

Uncommon: Hypersensitivity, Headache, dizziness, paraesthesia, hypoaesthesia, Flushing, phlebitis, Dyspnoea, Vomiting, abdominal pain, diarrhoea, constipation, Pruritus, rash, Muscle spasm, myalgia, arthralgia, pain in extremity, back pain, Chills, asthenia, fatigue, oedema peripheral, pain, Alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, serum ferritin increased.

Not known: Anaphylactoid/anaphylactic reactions, angioedema, Depressed level of consciousness, confusional state, loss of consciousness, anxiety, tremor, Bradycardia, tachycardia, Kounis syndrome, Circulatory collapse, thrombophlebitis, Bronchospasm, Urticaria, erythema, Cold sweat, malaise, pallor, influenza like illness

Rare: Syncope, somnolence, Palpitations, Chromaturia, Chest pain, hyperdrosis, pyrexia, Chest pain, hyperdrosis, pyrexia.

OVERDOSAGE:
Overdose can cause iron overload which may manifest itself as haemosiderosis. Overdose should be treated, as deemed necessary by the treating physician, with an iron chelating agent or according to standard medical practice.

Incompatibilities
Clefer 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.

Nature and contents of container
Type 1 glass ampoules with extractable volumes of 5 ml.

Presentation
Clefer Injection 100mg/5ml: Pack of 5's Ampoules.

Direction:
Protect from light, store below 25°C. Do not freeze
Do not use if solution contains foreign matter.
Keep out of the reach of children.
The expiation date refer to product correctly stored at the required condition.
For suspected adverse drug reaction for BOSCH products, report at ade@bosch-pharma.com.

To be sold on prescription of a registered medical practitioner only.

ہدایات برائے استعمال:

ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
25°C سے کم درجہ حرارت پر روشنی سے محفوظ رکھیں۔
انجکشن میں کوئی غیر حل پذیر شئے نظر آئے تو ہرگز استعمال نہ کریں۔
بچوں کی پہنچ سے دُور رکھیں۔
صرف رجسٹرڈ میڈیکل پریکٹیشنر کے نسخے پر فروخت کے لئے۔

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