Axifer® 100mg Injection

(IRON SUCROSE COMPLEX)

ایکسی فر® انجیکشن

(آئرن سکروز کمپلیکس)

COMPOSITION

Each 5ml ampoule contains:

Iron sucrose complex equivalent to elemental Iron..... 100mg

(USP Specs.)

DESCRIPTION

AXIFER (Iron sucrose complex injection USP) belongs to therapeutic class Hematinic, which is a complex of polynuclear iron (III)-hydroxide in sucrose administered intravenously. The molecular formula of Iron sucrose complex is $[Na_2Fe_5O_8\ (OH)\ .\ 3(H_2O)]n\ .\ m(C_{12}H_{22}O_{11})$ where: n is the degree of iron polymerization and m is the number of sucrose molecules associated with the iron (III)-hydroxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

Iron sucrose complex is an aqueous complex of poly-nuclear iron (III)-hydroxide in sucrose. Following intravenous administration, Iron sucrose complex is dissociated into iron and sucrose and the iron is transported as a complex with transferrin to target cells including erythroid precursor cells. The iron in the precursor cells is incorporated into hemoglobin as the cells mature into red blood cells.

Pharmacokinetics

Distribution

In healthy adults, Iron sucrose complex treated with intravenous doses, iron component of it exhibits first order kinetics, non-steady state apparent volume of distribution of 10.0 L and steady state apparent volume of distribution of 7.9 L. The effects of age and gender on the pharmacokinetics of Iron sucrose complex have not been studied. In in-vitro studies, the amount of Iron sucrose complex in the dialysate fluid was below the levels of detection of the assay (less than 2 parts per million).

Metabolism

When injection is administered, 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%.

Elimination

The average molecular weight (Mw) of Iron sucrose complex has approximately 43 kDa, which is sufficiently large to prevent renal elimination. Renal elimination of iron, occurring in the first 4 hours after injection of an Iron sucrose complex 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. Elimination half-life is 6 hours and total clearance of 1.2 L/hr.

Renal elimination of sucrose was about 75% of the administered dose. Serum clearance of iron is expected to be more rapid in iron deficient patients treated with Iron sucrose complex as compared to healthy individuals.

INDICATIONS

AXIFER (Iron sucrose complex) is indicated for the treatment of iron deficiency anemia of Chronic Kidney Disease (CKD) in the following patients:

- Non-dialysis dependent-chronic kidney disease (NDD-CKD) adult patients receiving an erythropoietin.
- Non-dialysis dependent-chronic kidney disease (NDD-CKD) adult patients not receiving an erythropoietin.
- Hemodialysis dependent-chronic kidney disease (HDD-CKD) adult patients receiving an erythropoietin.
- Peritoneal dialysis dependent-chronic kidney disease (PDD-CKD) adult patients receiving an erythropoietin.
- Non-Dialysis Dependent Chronic Kidney Disease (NDD-CKD), Hemodialysis Dependent Chronic Kidney Disease (HDD-CKD) or Peritoneal Dialysis Dependent Chronic Kidney Disease (PDD-CKD) pediatric patients (2 years of age or older) for iron maintenance treatment with erythropoietin therapy.
- AXIFER (Iron sucrose complex) is also indicated for the treatment of iron-deficiency anemia in the following patients:
  - Adult patients having a clinical need for rapid iron supply.
  - Adult patients who cannot take oral-iron therapy.

DOSAGE AND ADMINISTRATION

Adult Patients with Hemodialysis Dependent-Chronic Kidney Disease (HDD-CKD)

Iron sucrose complex 100 mg undiluted administer as a 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. Iron sucrose complex should be administered early during the dialysis session. The usual total treatment course of Iron sucrose complex is 1000 mg. Iron sucrose complex treatment may be repeated if iron deficiency reoccurs.

Adult Patients with Non-Dialysis Dependent-Chronic Kidney Disease (NDD-CKD)

Iron sucrose complex 200 mg undiluted administer as a slow intravenous injection over 2 to 5 minutes or as an infusion of 200 mg in a maximum of 100 mL of 0.9% NaCl over a period of 15 minutes. Administer on 5 different occasions over a 14 day period. There is limited experience with administration of an infusion of 500 mg of Iron sucrose complex, diluted in a maximum of 250 mL of 0.9% NaCl, over a period of 3.5 to 4 hours on Day 1 and Day 14. Iron sucrose complex treatment may be repeated if iron deficiency reoccurs.

Adult Patients with Peritoneal Dialysis Dependent-Chronic Kidney Disease (PDD-CKD)

Iron sucrose complex administer in 3 divided doses, given by slow intravenous infusion, within a 28 days period: 2 infusions each of 300 mg over 1.5 hours 14 days apart followed by one 400 mg infusion over 2.5 hours 14 days later. Dilute Iron sucrose complex in a maximum of 250 mL of 0.9% NaCl. Iron sucrose complex treatment may be repeated if iron deficiency reoccurs.

Pediatric Patients (2 years of age and older) with HDD-CKD for iron maintenance treatment

The dosing for iron replacement treatment in pediatric patients with HDD-CKD has not been established. For iron maintenance treatment: Iron sucrose complex administer at a dose of 0.5 mg/kg, not to exceed 100 mg per dose, every two weeks for 12 weeks given undiluted by slow intravenous injection over 5 minutes or diluted in 25 mL of 0.9% NaCl and administered over 5 to 60 minutes. Iron sucrose complex treatment may be repeated if necessary.

Pediatric Patients (2 years of age and older) with NDD-CKD or PDD-CKD who are on erythropoietin therapy for iron maintenance treatment

The dosing for iron replacement treatment in pediatric patients with NDD-CKD or PDD CKD has not been established. For iron maintenance treatment: Iron sucrose complex administer at a dose of 0.5 mg/kg, not to exceed 100 mg per dose, every four weeks for 12 weeks given undiluted by slow intravenous injection over 5 minutes or diluted in 25 mL of 0.9% NaCl and administered over 5 to 60 minutes. Iron sucrose complex treatment may be repeated if necessary.

Iron deficiency anemia in adult patients requiring rapid iron supply or those intolerant to oral iron / Alternative individualized dosing for adult patients with Chronic Kidney Disease

Calculation of AXIFER (iron sucrose) cumulative dosage over entire course of therapy:

The total cumulative dose of iron sucrose, equivalent to the total iron deficit (mg) can determined by the hemoglobin level (Hb) and body weight (BW). In this case, the dose of iron sucrose should be individually calculated for each patient according to the total iron deficit calculated with the following formula:

Total iron deficit [mg] = BW [kg] x (target Hb - actual Hb) [g/dl] x 2.4* + storage iron [mg]

Below 35 kg BW:
Target Hb = 13 g/dl and storage iron = 15 mg/kg BW

35 kg BW and above:
Target Hb = 15 g/dl and storage iron = 500 mg

Total AXIFER (Iron sucrose) to be administered (in ml) = Total iron deficit / 20

The cumulative dosage calculated by above formula can be given as single doses of 5-10 ml of AXIFER (100-200 mg) 1 to 3 times per week.

The following table can also be used for cumulative dose selection:

Total amount of Iron sucrose complex (ml) to be administered according to body weight (BW), actual Hb level and target Hb level*

BW	Total amount of Iron sucrose complex (20 mg iron per ml) to be administered			
	Hb 6.0 g/dl	Hb 7.5 g/dl	Hb 9.0 g/dl	Hb 10.5 g/dl
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

* Below 35 kg BW: Target Hb = 13 g/dl
3 5 kg BW and above: Target Hb = 15 g/dl

To convert Hb (mM) to Hb (g/dl), multiply the former by 1.6.
If the total necessary dose exceeds the maximum allowed single dose, then the administration must be divided.

Dosing Consideration in Special populations

Hepatic impairment

No data available regarding the dosage adjustment in hepatic impairment patients

Renal impairment

No data available regarding the dosage adjustment in renal impairment patients

Administration Requirements

Iron sucrose complex must only be administered by the 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

Iron sucrose complex must only be diluted in sterile 0.9% m/V sodium chloride (NaCl) solution. Dilution must take place immediately prior to infusion.

Intravenous injection

Iron sucrose complex may be administered by slow intravenous injection at a rate of 1 ml undiluted solution per minute and not exceeding 10 ml Iron sucrose complex (200 mg iron) per injection.

Injection into venous line of dialysis machine

Iron sucrose complex may be administered during a hemodialysis session directly into the venous line of the dialysis machine under the same conditions as for intravenous injection.

CONTRAINDICATIONS

The use of Iron sucrose complex is contraindicated in:

- Hypersensitivity to the active substance, to Iron sucrose complex
- Known serious hypersensitivity to other parenteral iron products
- Anemia not caused by iron deficiency.
- Evidence of iron overload or hereditary disturbances in utilization of iron

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions
Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-threatening and fatal, have been reported in patients receiving Iron sucrose complex. Patients may present with shock, clinically significant hypotension, loss of consciousness, and/or collapse. If hypersensitivity reactions or signs of intolerance occur during administration, stop Iron sucrose complex immediately. Monitor patients for signs and symptoms of hypersensitivity during and after Iron sucrose complex administration for at least 30 minutes and until clinically stable following completion of the infusion. Only administer Iron sucrose complex when personnel and therapies are immediately available for the treatment of serious hypersensitivity reactions. Most reactions associated with intravenous iron preparations occur within 30 minutes of the completion of the infusion.

Hypotension
Iron sucrose complex may cause clinically significant hypotension. Each administration of Iron sucrose complex requires monitoring for the signs and symptoms of hypotension. Hypotension following administration of Iron sucrose complex may be related to the rate of administration and/or total dose administered.

Iron Overload
The excessive therapy with parenteral iron can lead to excess storage of iron with the possibility of iatrogenic hemosiderosis. All adult and pediatric patients receiving Iron sucrose complex require periodic monitoring of hematologic and iron parameters (hemoglobin, hematocrit, and serum ferritin and transferrin saturation). Do not administer Iron sucrose complex to patients with evidence of iron overload. Transferrin saturation (TSAT) values increase rapidly after intravenous administration of Iron sucrose complex; do not perform serum iron measurements for at least 48 hours after intravenous dosing.

Effects on ability to drive and use machines
In the case of symptoms of dizziness, confusion or light headedness following the administration of Iron sucrose complex, patients should not drive or use machinery until the symptoms have ceased.

ADVERSE REACTIONS

Immune system disorder
Uncommon: hypersensitivity
Frequency not known: Anaphylactoid reaction, angioedema
Nervous system disorder
Common: Dysgeusia
Uncommon: headache, dizziness, paraesthesia, hypoaesthesia
Rare: syncope, somnolence
Frequency not known: Depressed level of consciousness, Delirium (confusional state), loss of consciousness, anxiety, tremor
Cardiac disorder
Rare: palpitations
Frequency not known: Bradycardia, tachycardia
Vascular disorder
Common: Hypotension, hypertension
Uncommon: Flushing, phlebitis
Frequency not known: circulatory collapse, thrombophlebitis
Respiratory, thoracic and mediastinal disorder
Uncommon: Dyspnea
Frequency not known: Bronchospasm
Renal and urinary disorder
Rare: Chromaturia
Gastrointestinal disorder
Common: Nausea
Uncommon: Vomiting, abdominal pain, diarrhea, constipation
Skin and subcutaneous tissue disorder
Uncommon: pruritus, rash
Frequency not known: urticarial (Urticarial rash, urticarial vasculitis), erythema
Musculoskeletal and connective tissue disorders
Uncommon: Muscle spasm, myalgia, arthralgia, pain in extremity, back pain
General disorders and administration site conditions
Common: Injection/ infusion site reaction
Uncommon: Chills, asthenia, Fatigue, edema peripheral, pain
Rare: chest pain, hyperdrosis
Frequency not known: Cold sweat, malaise, pallor
Investigation
Uncommon: Alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, serum ferritin increased
Rare: Blood lactate dehydrogenase increased

DRUG INTERACTIONS
Drug-drug interactions involving Iron sucrose complex have not been studied. However, like other parenteral iron preparations, Iron sucrose complex may be expected to reduce the absorption of concomitantly administered oral iron preparations.

USE IN SPECIAL POPULATIONS

Pregnancy
Pregnancy Category B. There is no data from the use of Iron sucrose complex in pregnant women in the first trimester. The use of Iron sucrose complex in pregnant women in the second and third trimester showed no safety concerns for the mother or newborn.
A careful risk/benefit evaluation is required before use during pregnancy and Iron sucrose complex should not be used during pregnancy unless clearly necessary. Iron deficiency anemia occurring in the first trimester of pregnancy can in many cases be treated with oral iron. Treatment with Iron sucrose complex should be confined to second and third trimester if the benefit is judged to outweigh the potential risk for both the mother and the fetus.

Nursing mother
It is not known whether Iron sucrose complex is excreted in human milk. Iron sucrose complex is secreted into the milk of lactating rats. Because many drugs are excreted in human milk, caution should be exercised when Iron sucrose complex is administered to a nursing woman.

Pediatrics
In pediatric patients, Safety and effectiveness of Iron sucrose complex for iron replacement treatment with dialysis-dependent or non-dialysis-dependent CKD have not been established.
Safety and effectiveness of Iron sucrose complex for iron maintenance treatment in pediatric patients 2 years of age and older with dialysis-dependent or non-dialysis dependent CKD receiving erythropoietin therapy were studied. Iron sucrose complex at doses of 0.5 mg/kg, 1.0 mg/kg, and 2.0 mg/kg was administered. All three doses maintained hemoglobin between 10.5 g/dL and 14.0 g/dL in about 50% of subjects over the 12-week treatment period with stable EPO dosing.
Iron sucrose complex has not been studied in patients younger than 2 years of age.

Elderly
The overall difference in safety between elderly and young patient were not observed, 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. In general, dose administration to an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

OVER DOSAGE
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.

PRESENTATION
Pack of 5 ampoules (5ml).

INSTRUCTIONS
Dosage as advised by the physician
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.
Store below 25 °C.
Do not freeze

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