PRODUCT MONOGRAPH

PrDEFEROXAMINE MESYLATE FOR INJECTION*

500 mg and 2.0 g lyophilized powder in vials

Iron and Aluminum Chelating Agent

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PRODUCT MONOGRAPH

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THERAPEUTIC CLASSIFICATION

Iron and Aluminum chelating agent

ACTIONS AND CLINICAL PHARMACOLOGY

DEFEROXAMINE MESYLATE FOR INJECTION is a chelating agent which forms complexes predominantly with trivalent iron and aluminum ions; it is thus of value in the treatment of acute/chronic iron intoxication, and also chronic aluminum overload in dialysis patients with end-stage renal failure (ESRF).

DEFEROXAMINE MESYLATE FOR INJECTION complexes with iron to form ferrioxamine, a stable chelate, which cannot take part in further chemical reactions. It can also mobilize and chelate tissue-bound aluminum, forming an aluminoxamine complex. Both complexes - ferrioxamine and aluminoxamine - are freely soluble in water and are readily excreted through the kidneys. Excreted ferrioxamine gives the urine a characteristic reddish colour. Some of the DEFEROXAMINE MESYLATE FOR INJECTION-metal complexes are also excreted in feces.

Theoretically chelation occurs on a 1:1 molar basis, hence 100 parts by weight of DEFEROXAMINE MESYLATE FOR INJECTION can bind approximately 8.5 and 4.1 parts by weight of trivalent iron and aluminum respectively.

Although primarily effective in raising iron and aluminum excretion, DEFEROXAMINE MESYLATE FOR INJECTION may also cause a slight increase in the excretion of sodium and calcium.

INDICATIONS AND CLINICAL USE

a) Acute iron intoxication.
b) Chronic iron overload due to transfusion-dependent anemias.
c) Diagnosis of aluminum overload (DEFEROXAMINE MESYLATE FOR INJECTION infusion test).
d) Chronic aluminum overload in patients with End-Stage Renal Failure (ESRF) under maintenance dialysis.

In cases of acute iron intoxication, DEFEROXAMINE MESYLATE FOR INJECTION is an adjunct to, and not a substitute for, standard therapeutic measures which may include:

i) Induction of emesis.
ii) Gastric lavage.
iii) Maintenance of clear airways.
iv) Control of peripheral vascular failure.
v) Correction of acidosis.

CONTRAINDICATIONS

Patients with a known or suspected sensitivity to deferoxamine mesylate, except where desensitization is successful.

WARNINGS

Patients may develop sensitivity reactions (see CONTRAINDICATIONS).

In patients with severe renal failure, caution is indicated as the DEFEROXAMINE MESYLATE FOR INJECTION-metal complexes are excreted mainly via the kidneys. Elimination of chelated iron and aluminum can be increased by dialysis.

In patients suffering from iron overload it has been reported that infections (including septicemia), especially with Yersinia enterocolitica and Yersinia pseudotuberculosis, may be promoted by DEFEROXAMINE MESYLATE FOR INJECTION. If a patient under treatment with DEFEROXAMINE MESYLATE FOR INJECTION develops fever accompanied by acute enteritis / enterocolitis, diffuse abdominal pain, or pharyngitis the treatment should be temporarily withdrawn, appropriate bacteriological tests performed, and suitable antibiotic therapy instituted at once. THIS THERAPY SHOULD INCLUDE SPECIAL COVERAGE FOR YERSINIA ORGANISMS. After the infection has cleared, treatment with DEFEROXAMINE MESYLATE FOR INJECTION can be resumed.

In patients undergoing maintenance hemodialysis while receiving DEFEROXAMINE MESYLATE FOR INJECTION for aluminum and/or iron overload, rare cases of mucormycosis have been reported, a severe fungal infection that can be fatal. However, a causal relationship to the drug has not been established. If any of the suspected signs or symptoms are observed, DEFEROXAMINE MESYLATE FOR INJECTION treatment should be discontinued, mycological tests performed and appropriate treatment instituted immediately. Mucormycosis may also occur in dialysis patients who are not receiving DEFEROXAMINE MESYLATE FOR INJECTION therapy, indicating that other factors, e.g. a compromised immune system, may play a role in the development of this infection.

During chronic toxicity tests in dogs, high doses of DEFEROXAMINE MESYLATE FOR INJECTION (>200 mg/kg daily) were associated with cataracts. However, cataracts have rarely been observed in humans who receive DEFEROXAMINE MESYLATE FOR INJECTION over prolonged periods.

There have been reports of visual disturbances, hearing loss and audiometric abnormalities occurring in patients receiving DEFEROXAMINE MESYLATE FOR INJECTION treatment, particularly where the doses used were higher than those recommended and/or where the serum ferritin levels were low. The visual disturbances and hearing loss returned to normal in several cases when the drug was discontinued. However in some cases, a residual effect remained. Renal failure patients receiving maintenance dialysis having low ferritin levels may be particularly prone to adverse reactions.

Visual symptoms have been reported after single doses of DEFEROXAMINE MESYLATE FOR INJECTION. Complete ophthalmological examination, audiological testing and studies of visual evoked potential should be carried out before the start of long-term DEFEROXAMINE MESYLATE FOR INJECTION treatment as well as at regular intervals preferably every 3 months, during the time that DEFEROXAMINE MESYLATE FOR INJECTION treatment is continued.

When low-dose therapy is used the risk of adverse reactions is reduced. If disturbances of vision and/or hearing occur, treatment with DEFEROXAMINE MESYLATE FOR INJECTION should be discontinued in order to further the chances that disturbances of vision and/or hearing will prove reversible. If treatment with DEFEROXAMINE MESYLATE FOR INJECTION is subsequently resumed using a reduced dosage, ophthalmological and auditory examination/testing should be performed at more frequent intervals. It is always important to reconsider the benefit/risk ratio when DEFEROXAMINE MESYLATE FOR INJECTION treatment is resumed after the occurrence of an adverse reaction.

Respiratory distress syndrome has been reported in patients with acute iron intoxication and also in thalassemic patients treated with excessively high doses of intravenous DEFEROXAMINE MESYLATE FOR INJECTION for more than one day. The daily dose should not exceed

80 mg/kg up to a maximum of 6.0 grams. Treatment should be terminated at the first signs of respiratory complications (see also DOSAGE AND ADMINISTRATION).

In patients with aluminum-related encephalopathy, high doses of DEFEROXAMINE MESYLATE FOR INJECTION may exacerbate neurological dysfunction (seizures), probably due to an increase in circulating aluminum. DEFEROXAMINE MESYLATE FOR INJECTION may also precipitate the onset of dialysis dementia. Pretreatment with clonazepam is reported to provide protection against such neurological deterioration. In addition, aluminum overload treatment may decrease serum calcium and aggravate hyperparathyroidism.

It should be noted that some of the signs and symptoms reported as adverse effects may in fact be manifestations of the underlying disease (iron and/or aluminum overload).

High doses of DEFEROXAMINE MESYLATE FOR INJECTION and concomitant low ferritin levels during the treatment of chronic iron overload in children, have been associated with growth retardation. After reduction of the DEFEROXAMINE MESYLATE FOR INJECTION dose, growth velocity may resume to pre-treatment levels in some patients.

Pregnancy:

In animal experiments, deferoxamine mesylate has proven teratogenic. Women of childbearing potential with chronic iron and/or aluminum overload should not receive DEFEROXAMINE MESYLATE FOR INJECTION unless the use of an effective form of contraception, established before treatment, is continued throughout treatment and for at least the first month after treatment. Those patients reported to have received DEFEROXAMINE MESYLATE FOR INJECTION therapy during pregnancy have born children without any malformations. However, during pregnancy, particularly in the first trimester, DEFEROXAMINE MESYLATE FOR INJECTION should only be used if the hazard of acute iron intoxication is considered to be greater than the potential teratogenic hazard of DEFEROXAMINE MESYLATE FOR INJECTION.

Lactation:

It is not known whether deferoxamine mesylate passes into the breast milk. Therefore, mothers receiving DEFEROXAMINE MESYLATE FOR INJECTION should not breast feed their infants.

PRECAUTIONS

Flushing of the skin, urticaria, hypotension, and shock have occurred in a few patients following the rapid intravenous injection of DEFEROXAMINE MESYLATE FOR INJECTION. Treatment by intravenous route should not exceed 15 mg/kg/h.

Pediatric patients receiving DEFEROXAMINE MESYLATE FOR INJECTION should be monitored for body weight and longitudinal growth every three months (See WARNINGS).

DEFEROXAMINE MESYLATE FOR INJECTION may lower blood sugar, serum calcium, and serum sodium, and increase blood coagulability. Therefore, these parameters should be monitored during therapy, if possible.

As with all medicines, DEFEROXAMINE MESYLATE FOR INJECTION should be kept out of reach of children.

Drug Interactions:

Concurrent treatment with DEFEROXAMINE MESYLATE FOR INJECTION and prochlorperazine, a phenothiazine derivative, may lead to temporary impairment of consciousness.

Where an iron-overload is associated with ascorbic acid deficiency, oral administration of Vitamin C in the standard dosage (150 - 250 mg daily) may serve to enhance excretion of the iron complex in response to DEFEROXAMINE MESYLATE FOR INJECTION. Larger doses of Vitamin C fail to produce an additional effect.

In patients with severe chronic iron overload receiving combined treatment of DEFEROXAMINE MESYLATE FOR INJECTION with high doses of Vitamin C (more than 500 mg daily) impairment of cardiac function may be experienced; the impaired cardiac function

proved reversible when the Vitamin C was withdrawn. Cardiac impairment results from high doses of Vitamin C which increases the labile iron within the tissues to toxic levels.

The following precautions should be taken when DEFEROXAMINE MESYLATE FOR INJECTION and Vitamin C are to be used concomitantly:

- Vitamin C supplements should not be given to patients with cardiac failure.
- Cardiac function should be monitored before commencing and during the combined therapy of DEFEROXAMINE MESYLATE FOR INJECTION and Vitamin C.
- Vitamin C therapy should be initiated only after an initial month of regular DEFEROXAMINE MESYLATE FOR INJECTION therapy.
- Vitamin C therapy should be given only if patient is receiving DEFEROXAMINE MESYLATE FOR INJECTION regularly (ideally soon after setting up the pump).
- Daily doses of approximately 200 mg of Vitamin C in adults, 100 mg of Vitamin C in older children and 50 mg of Vitamin C in children under 10 years, should not be exceeded.

There is evidence that aluminum intoxication causes reduced erythropoiesis. In dialysis patients with iron and/or aluminum overload receiving DEFEROXAMINE MESYLATE FOR INJECTION and erythropoietin, it is important to adjust the dosage of the latter when necessary. Regular monitoring of iron stores should also be conducted. Gallium-67-imaging results may be distorted due to rapid urinary excretion of DEFEROXAMINE MESYLATE FOR INJECTION-bound Gallium-67. Discontinuing DEFEROXAMINE MESYLATE FOR INJECTION treatment 48 hours prior to scintigraphy is recommended.

ADVERSE REACTIONS

Some manifestations mentioned below may also be signs or symptoms of iron and/or aluminum overload.

The following unwanted effects have been observed on rare occasions.

Hypersensitivity / Dermatological:

- Frequent: pain, swelling, induration, erythema, burning, pruritus, wheals and rash (urticaria) at the infusion or injection site, occasionally accompanied by fever, chills and malaise.
- Rare: anaphylactic/anaphylactoid reactions with or without shock, angioedema.
- These reactions occur mainly when the drug is infused S.C. or administered in concentrations higher than those recommended. When signs of local irritation are observed after administration of DEFEROXAMINE MESYLATE FOR INJECTION solution, administration of a lower concentration is recommended.

Cardiovascular:

- Hypotension, shock, tachycardia, arrhythmias.

Respiratory:

- Isolated cases: Adult respiratory distress syndrome with dyspnea, cyanosis and interstitial pulmonary infiltrates (see WARNINGS).

Neurological:

- Dizziness, convulsions, exacerbation of neurological dysfunction in aluminum-related encephalopathy.
- Isolated cases: precipitation of dialysis dementia, peripheral sensory neuropathy, paresthesia (see WARNINGS).

Gastrointestinal:

- Abdominal discomfort, diarrhea, nausea, vomiting.

Hematological:

- Isolated cases: blood dyscrasias (eg. thrombocytopenia).

Ear:

- Auditory disturbances, hearing loss (including high-frequency sensorineural hearing loss), tinnitus (see WARNINGS).

Ophthalmological:

- Retinal pigmentary abnormalities (decreased visual acuity, impaired colour and night vision, vision loss), blurred vision, visual field defects, opacities of the lenses and cornea, optic neuropathy and neuritis, abnormal visual evoked potentials, scotoma.

Endocrine system:

- Growth retardation (see WARNINGS).

Other:

- Impairment of hepatic and renal function, dysuria, pyrexia, leg cramps.
- Isolated cases: malaise, bone pain

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Since DEFEROXAMINE MESYLATE FOR INJECTION is available only for parenteral administration, acute intoxication is unlikely to occur.

Rapid intravenous injection of DEFEROXAMINE MESYLATE FOR INJECTION exceeding 15 mg/kg/h has produced flushing of the skin, urticaria, hypotension and shock (see PRECAUTIONS).

Tachycardia, hypotension and gastrointestinal symptoms have occasionally developed in patients who received overdoses of DEFEROXAMINE MESYLATE FOR INJECTION.

Inadvertent I.V. administration of an overdose of DEFEROXAMINE MESYLATE FOR INJECTION may be associated with acute but transient vision loss, aphasia, agitation, headache, nausea, bradycardia and hypotension.

Respiratory distress syndrome including death has been reported following intravenous administration of excessive doses of DEFEROXAMINE MESYLATE FOR INJECTION (see WARNINGS).

High doses of DEFEROXAMINE MESYLATE FOR INJECTION for the treatment of chronic iron and/or aluminum overload have resulted in visual disturbances and hearing loss (see WARNINGS).

Treatment:

There is no specific antidote.

Signs and symptoms of overdosage may be eliminated by reducing the dosage or interrupting treatment.

DEFEROXAMINE MESYLATE FOR INJECTION is dialyzable.

DOSAGE AND ADMINISTRATION

DEFEROXAMINE MESYLATE FOR INJECTION SHOULD ONLY BE GIVEN PARENTERALLY. THE DOSE SHOULD NOT EXCEED 6.0 GRAMS IN A TWENTY-FOUR HOUR

PERIOD. Although DEFEROXAMINE MESYLATE FOR INJECTION can be given by intramuscular injection, in most cases

it exerts a considerably greater effect when administered by continuous infusion either intravenously (especially in cases of acute iron intoxication) or subcutaneously (especially in patients with chronic iron overload).

Acute Iron Intoxication

DEFEROXAMINE MESYLATE FOR INJECTION is an adjunct to standard measures generally used in treating acute iron intoxication, which may include induction of emesis, gastric lavage, maintenance of clear airways, control of peripheral vascular failure, and correction of acidosis.

Treatment should be adapted to the severity the of intoxication, with reference to serum iron (SI) and total iron binding capacity (TIBC) which should be regularly monitored. In addition, the total amount of iron ingested and remaining in the gastrointestinal tract should be taken into account.

DEFEROXAMINE MESYLATE FOR INJECTION should be instituted I.V. or I.M. in:

a) All patients with SI > TIBC (>500 μg/dL or 89.5 μmol/L),
b) Any patient with SI > 350 μg/dL or 62.6 μmol/L (if TIBC is unavailable) and evidence of free iron, or
c) Any patient where SI is not readily available and the patient demonstrates the signs and symptoms of iron intoxication.

   Note: Leukocytosis (WBC > 15,000/mm^3), hyperglycemia (blood sugar > 150 mg/dL) or diarrhea strongly suggest SI will be in the toxic range.

INTRAVENOUS INFUSION: The intravenous route should be used when the patient is hypotensive, in shock or major clinical findings are present. In general, provided infusion lines can be readily established and maintained, and SI levels and TIBC can be readily monitored, intravenous infusion is the preferred route of administration. Infusion rates should be adapted to the severity of intoxication. The rate of infusion should not exceed 15 mg/kg/h and should be reduced as soon as the situation permits, usually after 4 to 6 hours such that the total intravenous dose does not exceed 80 mg/kg up to a maximum of 6.0 grams in 24 hours. Respiratory distress syndrome has been reported following intravenous administration of excessive doses of DEFEROXAMINE MESYLATE FOR INJECTION. Treatment should be interrupted if signs of toxicity occur.

INTRAMUSCULAR ROUTE: The intramuscular route may be used when the patient is normotensive. When administering DEFEROXAMINE MESYLATE FOR INJECTION in children by the intramuscular route, initially inject 90 mg/kg. This may be followed by 45 mg/kg every four to twelve hours, as necessary, up to a maximum of 6 grams per 24 hours. IN CHILDREN, THE MAXIMUM SINGLE INJECTION SHOULD NOT EXCEED 1.0 GRAM (2.0 GRAMS IN ADULTS). Attention should be given to volume of solution injected and in small children, two injection sites may be required.

Duration of treatment with DEFEROXAMINE MESYLATE FOR INJECTION by either route will depend on the patient's condition and should be based on the SI levels and TIBC.

The effectiveness of treatment is dependent on an adequate output of urine in order to ensure that the iron complex ferrioxamine is excreted from the body. If oliguria or anuria develop, peritoneal dialysis or hemodialysis may become necessary to remove the ferrioxamine.

Chronic Iron Overload

The daily dose of DEFEROXAMINE MESYLATE FOR INJECTION in children and adults should be tailored to the iron burden of the individual patient as reflected by serum ferritin levels and 24-hour urinary iron excretion. These levels should be monitored daily initially and thereafter at longer intervals (but not less than once every 2 weeks).

Intravenous infusions usually prove somewhat more effective than subcutaneous infusions, but the latter are particularly suitable for ambulant patients.

For subcutaneous infusions, a portable light-weight infusion pump is a practical, effective means of promoting sustained and substantial net urinary iron excretion. The usual needle used is a 25-gauge or 27-gauge, butterfly type, placed in the subcutaneous tissues of the anterior abdominal wall.

For the purpose of infusion treatment the average daily dose range is 1.0 - 4.0 g (20 - 60 mg/kg depending upon iron load) administered S.C. or I.V. over a period of approximately 12 hours. In some cases it is possible to achieve a further increase in iron excretion by infusing the same daily dose over a 24-hour period. When administered S.C. by pump, DEFEROXAMINE MESYLATE FOR INJECTION should be given 4 to 7 times per week depending on the severity of the iron overload. Patients with serum ferritin levels less than 2000 ng/mL require approximately 25 mg/kg/day. Doses of 35 mg/kg/day are required when serum ferritin levels are in the range of 2000 ng/mL to 3000 ng/mL. Higher doses should be administered only if tests the benefits outweigh the risks associated with repeated high daily doses.

For intramuscular treatment when more effective subcutaneous infusions are not feasible, the average initial dose is 0.5 - 1 g daily, given in 1 - 2 injections. The maintenance dose will depend on the patient's iron excretion rate.

Since the iron excretion rates obtained with the above-mentioned modes of administration vary from patient to patient, one should first determine which route and dosage will yield the best results for the individual.

Diagnosis of Aluminum Overload

Use in adults with ESRF: Serum aluminum levels should be determined before and after DEFEROXAMINE MESYLATE FOR INJECTION administration. The DEFEROXAMINE MESYLATE FOR INJECTION Infusion Test is recommended in patients with serum aluminum levels exceeding 60 ng/mL (2.22 μmol/L) associated with serum ferritin levels above 100 ng/mL. A blood sample is taken just prior to a hemodialysis session to determine the baseline serum aluminum level. A 5.0 mg/kg dose of DEFEROXAMINE MESYLATE FOR INJECTION is given as a single, slow I.V. infusion at an infusion rate not exceeding 15 mg/kg/h, ideally during post-dialysis to avoid loss of free drug. An acceptable compromise is during the last 60 minutes of the hemodialysis session. A continuous increase in serum aluminum during the 24-48 hour period following administration is suggestive of aluminum overload. The Test is considered positive if the serum aluminum levels increase above baseline by more than 150 ng/mL (5.55 μmol/L) when a second blood sample is taken at the start of the next hemodialysis session.

The diagnostic capability of the DEFEROXAMINE MESYLATE FOR INJECTION Infusion Test is greatly enhanced if performed in conjunction with histological and biochemical examination of a bone biopsy.

Use in children with ESRF: Little clinical experience has been gained to date on use of DEFEROXAMINE MESYLATE FOR INJECTION in aluminum-overloaded children, the condition being rare in the very young. Dosage should be adapted from the adult dose at the discretion of the physician and adjusted for body-weight (15 - 20 mg/kg).

Chronic Aluminum Overload in Patients with ESRF

The precise dosage should be individually determined and adapted during the course of treatment.

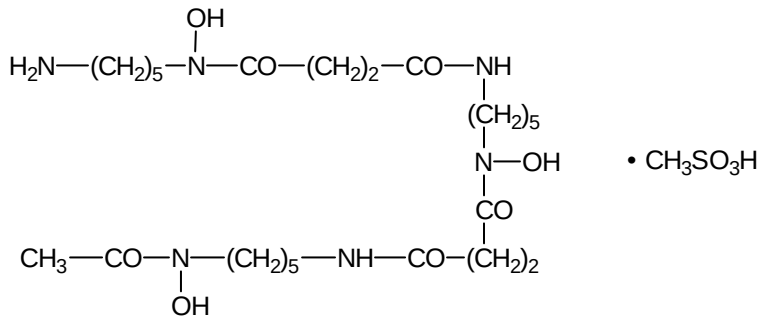
DEFEROXAMINE MESYLATE FOR INJECTION should be used in the treatment of patients having symptoms or evidence of organ dysfunction due to aluminum overload. In addition, treatment should be considered in symptomatic patients if serum aluminum levels are consistently above 60 ng/mL (2.22 μmol/L) and are associated with a positive DEFEROXAMINE MESYLATE FOR INJECTION Infusion Test (see above), particularly if bone biopsy findings present evidence of aluminum-related bone disease. DEFEROXAMINE MESYLATE FOR INJECTION should be given once weekly at a 5.0 mg/kg dose administered as a slow intravenous infusion not exceeding 15 mg/kg/h infusion rate, ideally during post-dialysis to avoid loss of free drug. An acceptable compromise is during the last 60 minutes of the hemodialysis session.

After completing the first 3-month course of DEFEROXAMINE MESYLATE FOR INJECTION treatment, followed by a 4-week wash out period, the DEFEROXAMINE MESYLATE FOR INJECTION Infusion Test should be performed. If two successive performed at 1-month intervals yield an increase in serum aluminum levels of less than 75 ng/mL (2.78 μmol/L) above baseline, further treatment is not recommended.

Patients on continuous ambulatory or cyclic peritoneal dialysis: A 5.0 mg/kg dose once per week prior to the final daily exchange. The intraperitoneal route is recommended in these patients, however, DEFEROXAMINE MESYLATE FOR INJECTION is equally effective when administered I.M., by slow I.V., or S.C. infusion. The mode of administration should be individually determined and the dosage adapted during the course of therapy.

PHARMACEUTICAL INFORMATION

Drug Substance



Deferoxamine mesylate

Chemical Name:	N-[5-(3-[(5-Aminopentyl)-hydroxycarbamoyl]-propionamido)-pentyl]-3-([5-(N-hydroxyacetamido)pentyl]-carbamoyl)-propionyl-hydroxam-methansulphonic acid
Molecular Formula:	$C_{25}H_{48}N_6O_8 \cdot CH_3SO_3H$
Molecular Weight:	656.8 (560.7 free base)
Description:	Practically odorless white crystalline powder.
Solubility (at 20^OC):	Water (>20%), abs. ethanol (0.1%), acetone (0.006%), chloroform (0.007%), dichloromethane (0.007%)
pK_a:	8.30, 9.05, 9.90, >11
Melting point:	about 150^OC

Composition:

DEFEROXAMINE MESYLATE FOR INJECTION (deferoxamine mesylate for injection) 500 mg and 2 g per vial:

Each vial of sterile lyophilized powder contains the medicinal ingredient deferoxamine mesylate for injection without non-medicinal ingredients.

Stability and Storage Recommendations:

Protect vials from heat (store below 25^OC).

Reconstitution of Lyophilized Vials:

The sterile lyophilized powder in each vial should be reconstituted under aseptic conditions just prior to dilution, only with Sterile Water for Injection. DEFEROXAMINE MESYLATE FOR INJECTION is dissolved by adding 5 mL of sterile water for injection to each 500 mg vial or 20 mL of sterile water for injection to each 2 g vial. The DEFEROXAMINE MESYLATE FOR INJECTION solution should appear clear and colorless to slightly yellow at the recommended concentration of 10%.

The final volume of the reconstituted Lyophilized Vial is greater than the specified volume of Sterile Water for injection.

Dilution of Reconstituted Solution for I.V. Infusion:

Reconstituted solutions that have been prepared with Sterile Water for Injection can be further diluted with physiological saline (0.9%), glucose in water or Ringer's lactate for infusion prior to infusion. The use of freshly prepared diluted solutions is recommended. Reconstituted solutions and solutions further diluted for infusion should be used or discarded within 24 hours from reconstitution when protected from heat (i.e., store below $23^{O}C$) due to the possibility of microbial contamination during preparation. Discard any infusion solution found to have particulate matter or discoloration.

For clinical situations requiring a smaller volume of solution (e.g., I.M injection) the reconstitution table below is to be considered.

Vial Size	Diluent volume to be added to vial	Approximate available volume	Actual Concentration
500 mg	2 mL	2.38 mL	210 mg/mL
2 g	8 mL	9.52 mL	210 mg/mL

This concentration may produce a stronger yellow-colored solution. The drug should be completely dissolved before the solution is withdrawn.

Incompatibilities:

Heparin injectable solution or physiological saline (0.9%) should not be used to reconstitute the vials of lyophilized powder.

AVAILABILITY OF DOSAGE FORMS

Pr DEFEROXAMINE MESYLATE FOR INJECTION* 500 mg vials:
Each 7.5 mL vial of white to practically white lyophilized powder contains deferoxamine mesylate (500 mg). Available in cartons of 10 vials.

Pr DEFEROXAMINE MESYLATE FOR INJECTION* 2 g vials:
Each 50 mL vial of white to practically white lyophilized powder contains deferoxamine mesylate (2 g). Available in cartons of 1 vial.

PHARMACOLOGY

Pharmacodynamics

DEFEROXAMINE MESYLATE FOR INJECTION is a chelating agent which forms complexes predominantly with trivalent iron and aluminum ions: the complex formation constants are 10^{31} and 10^{25} respectively. Affinity for divalent ions such as iron, copper, zinc and calcium is substantially lower (complex formation constants $\leq 10^{14}$). It has little influence on the excretion of trace elements.

Following parenteral administration of DEFEROXAMINE MESYLATE FOR INJECTION, tissue iron and aluminum are mobilized resulting in a sharp rise in serum iron and/or aluminum concentration(s).

DEFEROXAMINE MESYLATE FOR INJECTION chelates iron, either free or bound in ferritin and hemosiderin, forming the complex ferrioxamine. DEFEROXAMINE MESYLATE FOR INJECTION can also mobilize and chelate tissue-bound aluminum forming an aluminoxamine complex. Since both ferrioxamine and aluminoxamine are completely excreted, DEFEROXAMINE MESYLATE FOR INJECTION promotes iron and aluminum excretion in the urine and feces, thereby reducing pathological iron and/or aluminum deposits in the organs.

Clinical studies have shown that ascorbic acid, when taken orally at least 3 days before DEFEROXAMINE MESYLATE FOR INJECTION is given, considerably enhances (by an average of 96%) the iron excretion. This action of ascorbic acid is probably due to its reducing property which facilitates the mobilization of iron from ferritin by producing a dissociable pool of ferrous ions that are then available for binding to transferrin or a chelating agent such as deferoxamine. DEFEROXAMINE MESYLATE FOR INJECTION is not capable of removing iron from the bone marrow or from the erythrocytes.

Pharmacokinetics

DEFEROXAMINE MESYLATE FOR INJECTION is very poorly absorbed orally but well absorbed by the intramuscular and subcutaneous routes. The serum protein-binding rate is less than 10%. It is distributed throughout all body fluids and is excreted through the kidneys by glomerular filtration and tubular secretion. Metabolites were isolated and identified from the urine of patients being treated for iron overload. The metabolism reactions to occur were transamination and oxidation yielding an acid metabolite, beta-oxidation also yielding an acid metabolite, decarboxylation and N-hydroxylation yielding natural metabolites.

In healthy subjects and in patients with transfusion-induced iron overload, plasma concentrations of between 80 and 130 μmol/L were recorded 3 minutes after an intravenous injection of deferoxamine (10 mg/kg), these concentrations falling to one-half within 5-10 minutes and thereafter declining more slowly. This rapid fall in the concentration is due not only to distribution and excretion of the active substance but also both to formation of the iron complex ferrioxamine (which commences within a few minutes and the extent of which depends on the individual's iron status) and to metabolic transformation.

During continuous subcutaneous or intravenous infusion of deferoxamine (100 mg/kg in 24 mL sterile water at a rate of 1 mL per hour), the plasma concentrations of deferoxamine and ferrioxamine in healthy subjects rose - depending on the subject's individual iron status (serum ferritin concentration) - to a plateau after 6 or, more frequently, after 12 hours, i.e. to maximum levels of 20 μmol/L for deferoxamine and 2.75 μmol/L for ferrioxamine. The corresponding values in patients were 8.3 μmol/L for deferoxamine and 12.9 μmol/L for ferrioxamine. The 48-hour urinary excretion averaged 118 μmol in the healthy subjects and 836 μmol in the patients.

In patients with hemochromatosis, the increase in iron excretion occurring in response to deferoxamine was roughly just as high in the feces as in the urine.

Within 12 hours after deferoxamine had been administered to 20 volunteers, 33.1% of the dose was excreted in the urine (the bulk of it in the first 3 hours) in the form of deferoxamine and ferrioxamine and the remainder in the form of metabolites; the corresponding figure in a patient with hemochromatosis was 60.5% of the dose. There are reported cases where deferoxamine was diluted with water and given by mouth or stomach tube after gastric aspiration and lavage in the treatment of acute iron overload. The aqueous deferoxamine solution was left in the stomach to bind unabsorbed iron in the gastrointestinal tract to prevent further absorption. Note however, that the efficacy of oral deferoxamine for this purpose is not clearly established.

In ESRF dialysis patients who received 40 mg/kg DEFEROXAMINE MESYLATE FOR INJECTION infused I.V. over 1 hour, plasma concentration at the end of infusion was 152 μmol/L (85.2 μg/mL) when the infusion was given between dialysis sessions. Plasma concentrations of DEFEROXAMINE MESYLATE FOR INJECTION were between 13 and 27% lower when the infusion was administered during dialysis. In all cases, concentrations of ferrioxamine were approximately 7.0 μmol/L (4.3 μg/mL); and for aluminoxamine 2.0-3.0 μmol/L (1.2-1.8 μg/mL). After infusion was discontinued, plasma concentration of DEFEROXAMINE MESYLATE FOR INJECTION decreased rapidly with a half-life of 20 minutes. A smaller fraction of the dose was eliminated with a longer half-life of 14 hours. The plasma concentrations of aluminoxamine continued to increase for up to 48 hours after infusion and reached values of approximately 7.0 μmol/L (4.0 μg/mL). Following dialysis the plasma concentration of aluminoxamine dropped to 2.2 μmol/L (1.3 μg/mL).

During peritoneal dialysis DEFEROXAMINE MESYLATE FOR INJECTION is absorbed if administered in the dialysis fluid.

TOXICOLOGY

Acute:

	I.V.	SUBCUTANEOUS	ORAL
Mouse	340 mg/kg	1600 mg/kg	>3000 mg/kg
Rat	520 mg/kg	>1000 mg/kg	>1000 mg/kg
Rabbit	600 mg/kg	-	-

The signs of acute intoxication in the animal species tested were nonspecific paralysis, ataxia and acute respiratory failure.

Subacute:

500 mg/kg of deferoxamine was given to rats for 28 days by the subcutaneous route. There was a slight reduction in the white blood cell count and some inhibition of growth. There was no evidence of any damage to parenchymal organs or to bone marrow.

Chronic:

Subcutaneous doses of up to 400 mg/kg of deferoxamine were given to rats for three months. There was no alteration in growth rate, renal function, blood picture, or resistance to intercurrent disease in the animals so treated.

In rabbit, cat and dog, intravenous injection of doses of 10 to 30 mg/kg produced an acute fall in blood pressure. If smaller doses were given previously the reaction was attenuated or abolished.

Reproduction Studies:

Skeletal anomalies have been observed in the fetuses of two animal species at doses just above those recommended for human use. DEFEROXAMINE MESYLATE FOR INJECTION should therefore not be used in women of childbearing potential unless the use of an effective form of contraception, established before treatment, is continued throughout treatment and for at least the first month after treatment.

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