PRODUCT MONOGRAPH

[Pr] pms-DEFEROXAMINE

(deferoxamine mesylate for injection)

Lyophilized powder

500 mg/vial and 2.0 g/vial

Iron and Aluminum Chelating Agent

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(deferoxamine mesylate for injection)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Parenteral	Lyophilized powder in vials, 500 mg/vial and 2.0 g/vial	None. *For a complete listing see **Dosage Forms, Composition and Packaging** section.*

INDICATIONS AND CLINICAL USE

pms-DEFEROXAMINE (deferoxamine mesylate) is indicated for:

- Acute iron intoxication.
- Chronic iron overload due to transfusion-dependent anemias.
- Diagnosis of aluminum overload (deferoxamine infusion test).
- Chronic aluminum overload in patients with End-Stage Renal Failure (ESRF) under maintenance dialysis.

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

- Induction of emesis.
- Gastric lavage.
- Maintenance of clear airways.
- Control of peripheral vascular failure.
- Correction of acidosis.

Geriatrics (> 65 years of age):

Clinical Studies of deferoxamine mesylate did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently compared to younger subjects. Post marketing reports suggest a possible trend for an increased risk of eye disorders in the geriatric population, specifically the occurrence of color blindness, maculopathy, and scotoma. However, it is unclear if these eye disorders were dose related. Although the number of reports was very

small, certain elderly patients may be predisposed to eye disorders when taking deferoxamine mesylate. Post marketing reports also suggest that there may be an increased risk of deafness and hearing loss in the geriatric population. (see **ADVERSE REACTIONS**). In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Pediatrics (< 16 years of age):

High doses of deferoxamine mesylate 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 dose, growth velocity may resume to pre-treatment levels in some patients.

Pediatric patients receiving pms-DEFEROXAMINE should be monitored for body weight and longitudinal growth every three months.

CONTRAINDICATIONS

Patients who are hypersensitive to deferoxamine mesylate or component of the container, except where desensitization is successful. For a complete listing, see the **DOSAGE FORMS, COMPOSTION AND PACKAGING** section of the product monograph.

WARNINGS AND PRECAUTIONS

General

Therapy with deferoxamine mesylate should be initiated and maintained by physician experienced in the treatment of chronic iron overload due to blood transfusions.

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).

As with all medicines, deferoxamine mesylate should be kept out of reach of children.

Rapid intravenous injection of deferoxamine mesylate exceeding 15 mg/kg/h has produced flushing of the skin, urticaria, hypotension and shock (see **DOSAGE AND ADMINISTRATION**)

Vitamin C supplements should not be given to patients with cardiac failure because impairment of cardiac function may be experienced in patients with severe chronic iron overload receiving combined treatment of deferoxamine mesylate with high doses of vitamin C (more than 500 mg daily) (see DRUG INTERACTIONS).

Ear/Nose/Throat

There have been reports of hearing loss and audiometric abnormalities occurring in patients receiving deferoxamine mesylate treatment, particularly where the doses used were higher than those recommended and/or where the serum ferritin levels were low. The 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.

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

Endocrine and Metabolism

Deferoxamine mesylate may lower blood sugar, serum calcium, and serum sodium, and increase blood coagulability. Therefore, these parameters should be monitored during therapy, if possible.

In addition, aluminum overload treatment may result in hypocalcaemia decrease serum calcium and aggravation of hyperparathyroidism.

Infections and Infestations

In patients with iron overload it has been reported that infections (including septicemia), especially with Yersinia enterocolitica and Yersinia pseudotuberculosis, may be promoted by deferoxamine mesylate. If a patient under treatment with deferoxamine mesylate 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. Treatment with deferoxamine mesylate can be resumed after the infection has cleared.

In patients undergoing maintenance hemodialysis while receiving deferoxamine mesylate for aluminum and/or iron overload, rare cases of mucormycosis, some with a fatal outcome, have been reported. Deferoxamine mesylate abolishes the fungistatic effect of serum and increased the *in vitro* growth of the fungus by potentiating iron uptake by the fungus. If any of the suspected signs or symptoms are observed, 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 therapy, indicating that other factors, e.g. a compromised immune system, may play a role in the development of this infection.

Neurologic

In patients with aluminum-related encephalopathy, high doses of deferoxamine mesylate may exacerbate neurological dysfunction (convulsion), probably due to an increase in circulating aluminum. Deferoxamine mesylate may also precipitate the onset of dialysis dementia. Pretreatment with clonazepam is reported to provide protection against such neurological deterioration.

Ophthalmologic

There have been reports of visual disturbances occurring in patients receiving deferoxamine mesylate treatment, particularly where the doses used were higher than those recommended and/or where the serum ferritin levels were low. The visual disturbances 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.

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

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

Renal

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

Cases of acute renal failure, renal tubular disorder, and blood creatinine increased have been reported (see **ADVERSE REACTIONS**). Monitoring patients for changes in renal function (e.g. increased serum creatinine) should be considered.

Respiratory

Acute 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 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 **DOSAGE AND ADMINISTRATION**).

Sensitivity/Resistance

Patients may develop sensitivity reactions (see **CONTRAINDICATIONS**).

Skin

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

Special Populations

Pregnant Women:

There are no adequate and well-controlled studies conducted in pregnant women.Studies in animals (rabbits) have shown reproductive toxicity/teratogenicity (see **TOXICOLOGY**). The risk to the fetus/mother is unknown. Women of childbearing potential with chronic iron and/or aluminum overload should not receive deferoxamine mesylate 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. During pregnancy, particularly in the first trimester, deferoxamine mesylate should only be used if the hazard of acute iron intoxication is considered to be greater than the potential teratogenic hazard of deferoxamine mesylate.

Nursing Women:

It is not known whether deferoxamine mesylate passes into the breast milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse drug reactions in breast-fed newborns/infants, a decision should be made whether to abstain from breast-feeding or to abstain from using the medicinal product, taking into account the importance of the medicinal product to the mother.

Pediatrics (< 16 years of age):

Pediatric patients receiving deferoxamine mesylate should be monitored for body weight and longitudinal growth every three months.

High doses of deferoxamine mesylate 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 dose, growth velocity may resume to pre-treatment levels in some patients.

Geriatrics (> 65 years of age):

Clinical Studies of deferoxamine mesylate did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from the younger subjects. Post marketing reports suggest a possible trend for an increased risk of eye disorders in the geriatric population, specifically the occurrence of color blindness, maculopathy, and scotoma. However, it is unclear if these eye disorders were dose related. Although the number of reports was very small, certain elderly patients may be predisposed to eye disorders when taking deferoxamine mesylate. Post marketing reports also suggest that there may be an increased risk of deafness and hearing loss in the geriatric population (see **ADVERSE REACTIONS**). In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Hepatic impairment
No studies have been performed in patients with hepatic impairment.

Monitoring and Laboratory Tests
Complete ophthalmological examination, audiological testing and studies of visual evoked potential should be carried out before the start of long-term deferoxamine mesylate treatment as well as at regular intervals preferably every 3 months, during the time that deferoxamine mesylate treatment is continued.

The following parameters (blood sugar, serum calcium, serum sodium, and increase blood coagulability) should be monitored during therapy, if possible.

Pediatric patients receiving deferoxamine mesylate should be monitored for body weight and longitudinal growth every three months.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
Some of the signs and symptoms reported as adverse effects may also be manifestations of the underlying disease (iron and/or aluminum overload).

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

Adverse reactions (Table 1 and section Less Common Clinical Trial Adverse Drug Reactions (<1%)) are ranked under the heading of frequency estimate, the most frequent first, using the

following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10,000 to < 1/1000); very rare (<1/10,000) including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

The following unwanted effects have been observed.
Table 1

Nervous system:	
Common:	Headache
Gastrointestinal:	
Common:	Nausea
Skin and subcutaneous tissue:	
Common:	Urticaria
Musculo-skeletal and connective tissue:	
Very common:	Arthralgia, myalgia
Common:	Growth retardation and bone disorders (e.g. metaphyseal dysplasia) in higher doses and young children (See **WARNINGS AND PRECAUTIONS** and Special remarks below)
General and administration site:	
Very common:	Injection site reaction including pain, swelling, infiltration, erythema, pruritis, eschar, crust (see special remarks below)
Common:	Pyrexia

Special remarks

Musculo-skeletal and connective tissue disorders:
Growth retardation and bone disorders (e.g. metaphyseal dysplasia) are common with doses above 60 mg/kg, especially in patients who begin iron chelation during the first three years of life. The risk is considerably reduced with doses of 40 mg/kg or less.

General disorders and administration site conditions:
At the injection site, reactions including pain, swelling, infiltration, erythema, pruritus, and eschar/crust are very common, while vesicles, local edema and burning are uncommon. Local manifestations may be accompanied by systemic reactions such as arthralgia/myalgia (very

common), headache (common), urticaria (common), nausea (common), pyrexia (common), vomiting (uncommon), abdominal pain (uncommon) or asthma (uncommon).

Renal and urinary

Excretion of the iron complex may cause reddish-brown discoloration of the urine.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Blood and lymphatic system
Very rare: Blood disorder (incl. thrombocytopenia, leucopenia)

Ear and labyrinth
Uncommon: Deafness neurosensory, tinnitus (see **WARNINGS AND PRECAUTIONS** and special remarks below)

Eye
Rare: Loss of vision, scotoma, retinal degeneration, optic neuritis, cataract, visual acuity decreased, blurred vision, night blindness, visual field defects, chromatopsia (impairment of color vision), corneal opacities (see **WARNINGS AND PRECAUTIONS** and special remarks below)

Gastrointestinal
Uncommon: Vomiting, abdominal pain
Very rare: Diarrhea

General and administration site
Uncommon: Injection site reaction including vesicles, edema, burning

Immune system
Very rare: Anaphylactic reaction, anaphylactic shock, angioneurotic oedema

Infections and infestations
Rare: Mucormycosis (See **WARNINGS AND PRECAUTIONS**)
Very rare: Gastroenteritis Yersinia (See **WARNINGS AND PRECAUTIONS**)

Musculo-skeletal and connective tissue
Very rare: Bone pain
Unknown: Muscle spasms

Nervous system
Very rare: Neurological disturbances including dizziness, precipitation or exacerbation of aluminum-related dialysis encephalopathy, neuropathy peripheral, paraesthesia (see **WARNINGS AND PRECAUTIONS**)
Unknown: Convulsion

Renal and urinary
Unknown: Acute renal failure, renal tubular disorder, blood creatinine increased

Respiratory, thoracic and mediastinal:
Uncommon: Asthma
Very rare: Acute respiratory distress, lung infiltration (See **WARNINGS AND PRECAUTIONS**)

Skin and subcutaneous tissue
Very rare: Rash generalized

Vascular
Rare: Hypotension, tachycardia and shock (if precautions for administration are not adhered to)

Special remarks

Ear and labyrinth disorders
Deafness neurosensory and tinnitus are uncommon if doses are kept within guidelines and if doses are reduced when ferritin levels fall (ratio of the mean daily dose of deferoxamine mesylate divided by serum ferritin should be below 0.025).

Eye disorders
The various eye disorders are rare, except if high doses are given (see **WARNINGS AND PRECAUTIONS**).

Hepatic impairment

Rare cases of hepatic impairment have been reported in patients who have been treated with deferoxamine mesylate, however a causality with the drug is not established.

Rare cases of increased transaminases have been reported in patients who have been treated with deferoxamine mesylate, however a causality with the drug is not established.

Nervous system disorders
Convulsions have mainly been reported in dialyzed patients with aluminum overload.

DRUG INTERACTIONS

Drug-Drug Interactions

Concomitant use of Prochlorperazine
Concurrent treatment with deferoxamine mesylate and prochlorperazine, a phenothiazine derivative, may lead to temporary impairment of consciousness.

Concomitant use of Vitamin C
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. Larger doses of Vitamin C fail to produce an additional effect.

In patients with severe chronic iron overload receiving combined treatment of deferoxamine mesylate 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 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 and Vitamin C.
- Vitamin C therapy should be initiated only after an initial month of regular deferoxamine mesylate therapy.
- Vitamin C therapy should be given only if patient is receiving deferoxamine mesylate 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.

Concomitant use of Erythropoietin
There is evidence that aluminum intoxication causes reduced erythropoiesis. In dialysis patients with iron and/or aluminum overload receiving deferoxamine mesylate 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 -bound Gallium-67. Discontinuing deferoxamine mesylate treatment 48 hours prior to scintigraphy is recommended.

DOSAGE AND ADMINISTRATION

Dosing Considerations

pms-DEFEROXAMINE (deferoxamine mesylate) SHOULD ONLY BE GIVEN PARENTERALLY. THE DOSE SHOULD NOT EXCEED 6.0 GRAMS IN A TWENTY-FOUR HOUR PERIOD. Although pms-DEFEROXAMINE 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).

Rapid intravenous injection of deferoxamine mesylate exceeding 15 mg/kg/h has produced flushing of the skin, urticaria, hypotension and shock (see **WARNINGS AND PRECAUTIONS**)

Hepatic impairment
No studies have been performed in patients with hepatic impairment.

Recommended Dose and Dosage Adjustment

Acute Iron Intoxication
pms-DEFEROXAMINE is an adjunct to standard measures generally used in the treatment of 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 of the 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.

pms-DEFEROXAMINE 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. Acute respiratory distress syndrome has been reported following intravenous administration of excessive doses of deferoxamine. Treatment should be interrupted if signs of toxicity occur.

INTRAMUSCULAR ROUTE: The intramuscular route may be used when the patient is normotensive. When administering pms-DEFEROXAMINE 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 pms-DEFEROXAMINE 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 pms-DEFEROXAMINE 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.

The drug should not be given at concentrations higher than 95 mg/mL when given subcutaneously as this increases the risk of local reactions by the subcutaneous route.

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, pms-DEFEROXAMINE should normally 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 pms-DEFEROXAMINE administration. The Deferoxamine 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 pms-DEFEROXAMINE 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 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 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.

pms-DEFEROXAMINE 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 Infusion Test (see above), particularly if bone biopsy findings present evidence of aluminum-related bone disease. pms-DEFEROXAMINE 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 completion of the first 3-month course of pms-DEFEROXAMINE treatment, followed by a 4-week wash out period, the Deferoxamine 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, pms-DEFEROXAMINE 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.

Administration

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. The pms-DEFEROXAMINE solution is clear and colorless to slightly yellow at the recommended concentration of 95 mg/mL, and darker yellow at the recommended concentration of 213 mg/ml. This concentration may produce a stronger yellow-colored solution. The drug should be completely dissolved before the solution is withdrawn.

The final volume (Approximate Available Volume) of the reconstituted Lyophilized Vial is greater than the specified volume of Sterile Water for injection.

a) Reconstitution of Lyophilized Vials for Subcutaneous Administration

Vial Size	**Volume of Sterile Water** for Injection **to be Added to Vial**	**Approximate Available Volume**	**Nominal Concentration per mL**
500 mg	5 mL	5.3 mL	95 mg/mL
2 g	20 mL	21.1 mL	95 mg/mL

b) Reconstitution of Lyophilized Vials for Intravenous Administration (may be further diluted)

Vial Size	**Volume of Sterile Water** for Injection **to be Added to Vial**	**Approximate Available Volume**	**Nominal Concentration per mL**
500 mg	5 mL	5.3 mL	95 mg/mL
2 g	20 mL	21.1 mL	95 mg/mL

c) Reconstitution of Lyophilized Vials for Intramuscular Administration

Vial Size	**Volume of Sterile Water** for Injection **to be Added to Vial**	**Approximate Available Volume**	**Nominal Concentration per mL**
500 mg	2 mL	2.3 mL	213 mg/mL
2 g	8 mL	9.4 mL	213 mg/mL

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.

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

OVERDOSAGE

Since pms-DEFEROXAMINE (deferoxamine mesylate) is available only for parenteral administration, acute intoxication is unlikely to occur.

Tachycardia, hypotension and gastrointestinal symptoms have occasionally developed in patients who received overdoses of deferoxamine mesylate.

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

Acute respiratory distress syndrome including death has been reported following treatment with excessively high intravenous doses of deferoxamine mesylate (see **WARNINGS AND PRECAUTIONS**).

High doses of deferoxamine mesylate for the treatment of chronic iron and/or aluminum overload have resulted in visual disturbances and hearing loss (see **WARNINGS AND PRECAUTIONS).**

Treatment:

There is no specific antidote.
Signs and symptoms of overdosage may be eliminated by reducing the dosage or interrupting treatment.
Deferoxamine mesylate is dialyzable.

For management of a suspected drug overdose, contact your regional Poison Control Centre Immediately.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Deferoxamine mesylate 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 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-metal complexes are also excreted in feces.

Theoretically chelation occurs on a 1:1 molar basis, hence 100 parts by weight of deferoxamine mesylate 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 may also cause a slight increase in the excretion of sodium and calcium.

Pharmacodynamics

Deferoxamine mesylate 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, tissue iron and aluminum are mobilized resulting in a sharp rise in serum iron and/or aluminum concentration(s).

Deferoxamine mesylate chelates iron, either free or bound in ferritin and hemosiderin, forming the complex ferrioxamine. Deferoxamine mesylate can also mobilize and chelate tissue-bound aluminum forming an aluminoxamine complex. Since both ferrioxamine and aluminoxamine are completely excreted, deferoxamine mesylate 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 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 is not capable of removing iron from the bone marrow or from the erythrocytes.

Pharmacokinetics

Absorption: deferoxamine mesylate is very poorly absorbed orally but well absorbed by the intramuscular and subcutaneous routes.

Distribution: The serum protein-binding rate is less than 10%. It is distributed throughout all body fluids.

Metabolism: 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.

Excretion: It is excreted through the kidneys by glomerular filtration and tubular secretion.

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 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 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 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 is absorbed if administered in the dialysis fluid.

STORAGE AND STABILITY

Protect vials from heat (store below $25^{O}C$).

DOSAGE FORMS, COMPOSITION AND PACKAGING

pms-DEFEROXAMINE (deferoxamine mesylate for injection) 500 mg vials:
Each 7.5 mL vial of white to practically white sterile lyophilized powder contains the medicinal ingredient deferoxamine mesylate (500 mg) for injection without non-medicinal ingredients. Available in cartons of 10 vials.

pms-DEFEROXAMINE (deferoxamine mesylate for injection) 2 g vials:
Each 50 mL vial of white to practically white sterile lyophilized powder contains the medicinal ingredient deferoxamine mesylate (2 g) for injection without non-medicinal ingredients. Available in cartons of 1 vial.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

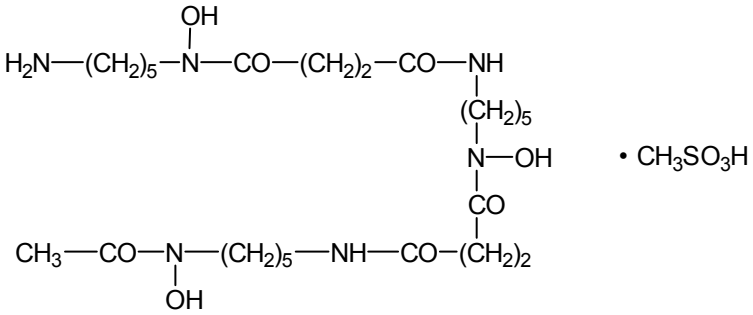
Proper name: Deferoxamine mesylate

Chemical name: N-[5-(3-[(5-Aminopentyl)-hydroxycarbamoyl]-propionamido)-pentyl]-3-([5-(N-hydroxyacetamido)pentyl]-carbamoyl)-propionyl-hydroxam-methansulphonic acid

Molecular formula: $C_{25}H_{48}N_6O_8 \bullet CH_3SO_3H$

Molecular mass: 656.8 (560.7 free base)

Structural formula:



Physicochemical properties: Description: Practically odorless white crystalline powder.

Solubility (at $20^{O}C$): 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 $150^{O}C$

DETAILED PHARMACOLOGY

See ACTION AND CLINICAL PHARMACOLOGY.

TOXICOLOGY

Acute Toxicity Studies

	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 Toxicity Studies

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 Toxicity Studies

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 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.

REFERENCES

1. ACKRILL P, RALSTON AJ, and DAY P. Role of desferrioxamine in the treatment of dialysis encephalopathy. Kidney Int 1986; 29 (Supp 18): S104-S107

2. ALLAIN P, CHALEIL D, MAURAS Y, BEAUDEAU G, VARIN MC, POIGNET JL, CIANCIONI C, ANG KS, CAM G, and SIMON P. Pharmacokinetics of desferrioxamine and of its iron and aluminium chelates in patients on hemodialysis. Clin Chim Acta 1987; 170 (2/3): 331-338

3. ALLAIN P, CHALEIL D, MAURAS Y, VARIN MC, ANG KS, CAM G, and SIMON P. Pharmacokinetics of desferrioxamine and of its iron and aluminium chelates in patients on peritoneal dialysis. Clin Chim Acta 1988; 173 (3): 313-316

4. BOUSQUET J, NAVARRO M, ROBERT G, AYE P, and MICHEL F-B. Rapid desensitisation for desferrioxamine anaphylactoid reactions. Lancet 1983; II (8354): 859-860

5. CAO A, GABUTTI V, MASERA G, MODELL B, SARCHIA G, and VULLO C. 1992 Management protocol for the treatment of thalassemia patients New York: Cooley's Anemia Foundation, 1992.

6. COBURN JW, and NORRIS KC. Diagnosis of aluminium-related bone disease and treatment of aluminium toxicity with deferoxamine. Semin Nephrol 1986; 6 (4) (Suppl 1): 12-21

7. DE BROE ME, D'HAESE PC, COUTTENYE MM, VAN LANDEGHEM GF, and LAMBERTS LV. New insights and strategies in the diagnosis and treatment of aluminum overload in dialysis patients. Nephrol Dial Transplant 1993; 8 (1): 47-50.

8. DE BROE ME, YAWALKAR SJ, and ABREO K. Desferal in dialysis patients with aluminum overload. Ciba-Geigy Limited, Switzerland, 1993

9. DE BROE ME, DRÜEKE TB, and RITZ E. Diagnosis and treatment of aluminum overload in end-stage renal failure patients. Nephrol Dial Transplant 1993; 8 (1): 1-4.

10. FELSENFELD, AJ, RODRIGUEZ M, COLEMAN M, ROSS D, and LLACH F. Desferrioxamine therapy in hemodialysis patients with aluminium-associated bone disease. Kidney Int 1989; 35: 1371-1378

11. HUSSAIN MAM, GREEN N, FLYNN DM, and HOFFBRAND AV. Effect of dose, time and ascorbate on iron excretion after subcutaneous desferrioxamine. Lancet 1977; 1: 977-979

12. IHLE BU, BECKER GJ, and KINCAID-SMITH PS. Clinical and biochemical features of aluminium-related bone disease. Kidney Int 1986; 29 (Suppl 18): S80-S86

13. MILLER KB, ROSENWASSER JL, BESSETTE J-A, BEER DJ, and ROCKLIN RE. Rapid desensitisation for desferrioxamine anaphylactic reaction. Lancet 1981; I (8228): 1059

14. OLIVIERI NF, BUNCIC JR, CHEW E, GALLANT T, HARRISON RV, KEENAN N, LOGAN W, MITCHELL D, RICCI G, SKARF B, TAYLOR M, and FREEDMAN MH. Visual and auditory neurotoxicity in patients receiving subcutaneous deferoxamine infusions. N Eng J Med 1986; 314 (14): 869-873

15. PIPPARD MJ, and CALLENDER ST. The management of iron chelation therapy. Br J Haematol 1983; 54 (4): 503-507

16. PROPPER RD, COOPER B, RUFO RR, NIENHUIS AW, ANDERSON WF, BUNN F, ROSENTHAL A, and NATHAN DG. Continuous subcutaneous administration of deferoxamine in patients with iron overload. N Engl J Med 1977; 297: 418-423

17. ROBOTHAM JL, and LIETMAN PS. Acute Iron Poisoning. A review. Am J Dis Child 1980; 134: 875-897

18. de la SERNA JF, GILSANZ F, RUILOPE LM, PRAGA M, RODICIO JL, and ALCAZAR JM. Improvement in the erythropoiesis of chronic haemodialysis patients with desferrioxamine. Lancet 1988; I: 1009-1011

19. SUMMERS MR, JACOBS A, TUDWAY D, PERERA P, and RICKETTS C. Studies in desferrioxamine and ferrioxamine metabolism in normal and iron-loaded subjects. Br J Haematol 1979; 42: 547-555

20. Product Monograph, DESFERAL, Novartis Pharmaceutical Canada Inc., Revision dated November 21, 2011; Control No: 148289

PART III: CONSUMER INFORMATION

[Pr] pms-DEFEROXAMINE
(deferoxamine mesylate for injection)

This leaflet is part III of a three-part "Product Monograph" published when pms-DEFEROXAMINE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about pms-DEFEROXAMINE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
pms-DEFEROXAMINE is used in the treatment of following conditions:
- acute iron poisoning as an adjunct to the standard treatments,
- chronic iron overload due to frequent blood transfusion,
- chronic aluminum overload in patients with end-stage kidney failure required dialysis.

pms-DEFEROXAMINE is also used to test for aluminum overload.

What it does:

pms-DEFEROXAMINE contains the active substance deferoxamine, which is a so-called "chelator". It works by biding to excess iron or aluminum in the blood and removing them from the body (through the urine and feces).

When it should not be used:

- If you are allergic (hypersensitive) to deferoxamine.

What the medicinal ingredient is:
Deferoxamine mesylate.

What the nonmedicinal ingredients are:
Not applicable. The pms-DEFEROXAMINE vials contain the medicinal ingredient deferoxamine mesylate without non-medicinal ingredients.

What dosage forms it comes in:
pms-DEFEROXAMINE is available as 500 mg and 2 g lyophilized powder for injection in vials.

WARNINGS AND PRECAUTIONS

The treatment with pms-DEFEROXAMINE should be started and followed up by a doctor experienced in the treatment of chronic iron or aluminum overload.

BEFORE you use pms-DEFEROXAMINE talk to your doctor or pharmacist if you:
- have any hearing or eye sight problems. pms-DEFEROXAMINE may cause hearing problems and eye sight problems;
- have high blood sugar (diabetes);
- have blood clotting problems;
- have any neurological problems (convulsion, dementia);
- severe kidney problem that does not required dialysis;
- lung disease or problem breathing;
- are pregnant or planning to become pregnant. pms-DEFEROXAMINE can harm the unborn child, especially if it is used during the first 3 months of pregnancy. If the treatment with pms-DEFEROXAMINE is needed, female patients who can get pregnant should use an effective birth control method before starting, while taking, and for at least one month after the last treatment with pms-DEFEROXAMINE.
- are breastfeeding.

pms-DEFEROXAMINE may reduce growth rate. Patients under 16 years of age should be monitored for body weight and height every three months.

Increased risk of eye disorders have been reported in patients older than 65 years of age.

Effects on ability to drive or use machines:
pms-DEFEROXAMINE may affect your sight or hearing, make you feel dizzy, or cause other disturbances of nervous function. If you experience such effects, you should not drive or use machines.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines in addition to pms-DEFEROXAMINE, including medicines obtained without a prescription. You may need to change the dosage or stop taking one of the medicines.

Drugs that may interact with pms-DEFEROXAMINE include:
- medicines containing prochlorperazine, a neuroleptic drug used to treat neurological disorders
- vitamin C
- erythropoietin
- gallium-67, a medicine given before imaging (scanning, which is used in diagnosis of certain diseases

In patients without heart failure, their doctor may tell them to take vitamin C one month before and during regular treatment with pms-DEFEROXAMINE. The maximum daily dose of vitamin C should not exceed 200 mg for adult patients, 100 mg in older children and 50 mg for children under 10 years of age. However, their doctor also needs to monitor their heart function.

PROPER USE OF THIS MEDICATION

Your doctor has chosen the right dose and method of administration for your particular condition. Follow your doctor's instructions carefully. Make sure you use the medication exactly as your doctor tells you.

Usual dose:

Acute iron poisoning
pms-DEFEROXAMINE can be used in cases of poisoning with iron preparations. This treatment is carried out in hospital.

Chronic iron overload
Daily doses of 20 to 60 mg per kilogram bodyweight. pms-DEFEROXAMINE can be given by slow infusion under the skin (subcutaneously), by infusion into a vein (intravenously), or by injection into a muscle (intramuscularly).

Chronic aluminum overload in patients with severe kidney disease
pms-DEFEROXAMINE is usually given once a week by slow infusion into a vein during the last 60 minutes of a dialysis session, or 5 hours before a dialysis session, depending on the aluminum concentration in your blood.
The dose of pms-DEFEROXAMINE is 5 mg per kilogram of bodyweight.

The duration of treatment and any change in your individual dose of pms-DEFEROXAMINE will depend on the results of the tests carried out by your doctor.

Diagnosis of aluminum overload
If you are receiving dialysis, your doctor will want to test whether you have aluminium overload. You will be given 5 mg of pms-DEFEROXAMINE per kilogram of bodyweight by slow infusion into a vein during the last 60 minutes of a dialysis session. The aluminium content of blood samples taken just before this dialysis session and the next one will be determined.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you have missed a dose of pms-DEFEROXAMINE, tell your doctor at once.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

As with all medicines, pms-DEFEROXAMINE can cause side effects. The following are the possible side effects of pms-DEFEROXAMINE:

Very common side effects: (affecting more than 10 in 100 patients)
- injection site reaction such as pain, swelling, reddening, itching of the skin, eschar (dead tissue that sheds from healthy skin), crust formation, small blisters, burning
- joint or muscle pain

Common side effects: (affecting more than 1 and less than 10 in 100 patients)
- nausea
- headache
- itchy rash
- fever
- reduced growth rate, bone disorders

Uncommon side effects: (affecting between 1and 10 in 1000 patients)
- vomiting
- abdominal pain

Very rare side effects: (affecting less than 1 in 10,0000 patients)
- diarrhea
- skin rash
- sensation of numbness or tingling in fingers and toes

Unknown frequency:
- muscle spasms
- abnormal liver or kidney function test results
- a low blood level of calcium, and worsening hyperparathyroidism in patients treated for aluminum overload
- reddish-brown urine
- low blood pressure, increased heart rate and shock

If any of the side effects gets serious or you experience any other side effects not listed in this leaflet, please tell your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
	Only if severe	**In all cases**	
Uncommon			
Disturbances of hearing such as ringing or noise in the ears, hearing loss		√	
Rare			
Disturbances of vision such as blurred eyesight, abnormal colour vision, night blindness, black spots in the vision, loss of vision, clouding of the lens of the eye, visual field defects or decreased sharpness of vision		√	
Fungal or bacterial infections leading to high fever, shortness of breath, acute diarrhea, abdominal pain, general discomfort or sore throat.		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
	Talk with your doctor or pharmacist		
Dizziness, light-headedness (signs of low blood pressure that can occur when the drug is given too rapidly).		√	
Very rare			
Breathlessness due to lung disorders		√	
Unusual bleeding/bruising (a sign that levels of blood platelets are low)	√		
Fever, sore throat or mouth ulcers due to infections (a sign that levels of white blood cells are low)	√		
Rash, itching, hives, difficulty breathing or swallowing, feeling of tightness in the chest with wheezing or coughing, dizziness, swelling mainly of the face and throat (signs of a severe allergic reaction or asthma)		√	
Disturbances of the nervous system		√	
Unknown			
Severely decreased output of urine (sign of a kidney problem)		√	
Convulsions (mainly in patients on dialysis).		√	

This is not a complete list of side effects. For any unexpected effects while taking pms-DEFEROXAMINE, contact your doctor or pharmacist.

HOW TO STORE IT

- Keep out of reach and sight of children and pets.
- Do not use pms-DEFEROXAMINE after the expiry date shown on the pack.
- Store the vials containing the dry active substance below 25°C.
- One vial is for single use only. The product should be used immediately after the solution has been made up (reconstituted), i.e. treatment should start within 3 hours. When the solution has been prepared under recognized sterile conditions, it may be stored for a maximum period of 24 hours at room temperature before the start of treatment. Opaque or cloudy solutions should be discarded.
- Remember to return any unused vials to your pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**

  - Fax toll-free to 1-866-678-6789, or

  - Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 0701E
  Ottawa, Ontario
  K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting Pharmascience Inc. at1-888-550-6060.

This leaflet was prepared by
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Montréal, Canada
H4P 2T4

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