℧ NOVARTIS

Prescribing Information

DESFERAL® 0.5 g IM, IV, SC

(Deferoxamine mesylate)

1 Trade name

DESFERAL® 0.5 g

2 Description and composition

Vials containing 0.5 g dry active substance for injection (powder for solution for injection).
Colorless 7.5 mL glass vials, with rubber closures

Active substance(s):
N-[5-(3-[(5-aminopentyl)-hydroxycarbamoyl]-propionamido)pentyl]-3-[(5-[N-hydroxyacetamido]-pentyl)-carbamoyl)-propionohydroxamic acid monoethane sulphonate (= deferrioxamine methane sulphonate).
One vial contains 0.5 g deferoxamine mesylate.

3. Indications

Therapeutic

Treatment of chronic iron overload, e.g.

- transfusional hemosiderosis, especially in thalassemia major, sideroblastic anemia, auto-immune hemolytic anemia, and other chronic anemias.
- idiopathic (primary) hemochromatosis in patients in whom concomitant disorders (e.g. severe anemia, cardiac disease, hypoprotoinemia) preclude phlebotomy.
- iron overload associated with porphyria cutanea tarda.

Treatment for acute iron poisoning.
Treatment for chronic aluminium overload in patients with terminal renal failure (under maintenance dialysis) with

- aluminium-related bone disease,
- and/or dialysis encephalopathy,
- and/or aluminium-related anemia.

Diagnostic

Diagnostic test for iron overload.

4 Dosage and administration

Treatment for chronic iron overload

The main aim of chelation therapy in iron overload in well-controlled patients is to maintain an iron balance and to prevent hemosiderosis, while in overloaded patients a negative iron balance is desirable in order to reduce increased iron stores and prevent the toxic effects of iron .

Children and adults

Desferal therapy should be started after the first 10 to 20 blood transfusions or when there is evidence from clinical monitoring that chronic iron overload is present (e.g. serum ferritin >1,000 ng/mL). Growth retardation may result from iron overload or excessive Desferal doses. If chelation is begun in patients under 3 years of age, growth must be monitored carefully and the mean daily dose should not exceed 40 mg/kg (see section 6 Warnings and precautions).
The dosage and mode of administration may be individually determined and adapted during the course of therapy based on the severity of the patient's iron burden. The lowest effective dosage should be used. To assess the response to chelation therapy, 24-hour urinary iron excretion may initially be monitored daily and the response to increasing doses of Desferal established. Once the appropriate dosage has been established, urinary iron excretion rates may be assessed at intervals of a few weeks. Alternatively, the mean daily dose may be adjusted based on ferritin level in order to keep the therapeutic index below 0.025 (i.e. the mean daily dose (mg/kg) of Desferal divided by the serum ferritin level (nrcograms/L) should be below 0.025). The therapeutic index is a valuable tool in protecting the patient from excess chelation, but it is not a substitute for careful clinical monitoring.
The average daily dose of Desferal is usually between 20 and 60 mg/kg. In general, patients with serum ferritin level below 2,000 ng/mL require about 25 mg/kg/day. Patients with serum ferritin level between 2,000 and 3,000 ng/mL require about 35 mg/kg/day. Patients with higher serum ferritin may require up to 55 mg/kg/day. It is not advisable to regularly exceed an average daily dose of 50 mg/kg/day except when very intensive chelation is needed in patients who have completed growth. If ferritin levels fall below 1,000 ng/mL, the risk of Desferal toxicity increases; it is important to monitor these patients particularly carefully and perhaps to consider lowering the total weekly dose. The doses specified here are the average daily doses. Since most patients use Desferal less than 7 days a week, the actual dose per infusion usually differs from the average daily dose; e.g. if an average daily dose of 40 mg/kg/day is required and the patient wears the pump 5 nights a week, each infusion should contain 56 mg/kg.
Regular chelation with Desferal has been shown to improve life expectancy in patients with thalassemia.

Slow subcutaneous infusion

Slow subcutaneous infusion using a portable, light-weight infusion pump over a period of 8 to 12 hours is regarded as effective and especially convenient for ambulant patients, but may also be given over a 24-hour period. Desferal should normally be used with the pump 5 to 7 times a week. Desferal is not formulated to support subcutaneous bolus injection.

Geriatrics

Clinical studies of Desferal did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently compared to younger subjects. 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 (see section 6 Warnings and precautions and section 7 Adverse drug reactions).

Hepatic impairment

No studies have been performed in patients with hepatic impairment.

Intravenous infusion during blood transfusion

The availability of an intravenous line during blood transfusions makes it possible to administer an intravenous infusion, e.g. in patients who comply poorly with and/or do not tolerate subcutaneous infusions. The Desferal solution should not be put directly into the blood bag but may be added to the blood line by means of a "Y" adaptor located near the venous site of injection. The patient's pump should be used to administer Desferal as usual. Because of the limited amount of drug that can be administered by IV infusion, during blood transfusion, the clinical benefit of this mode of administration is limited. Patients and nurses should be warned against accelerating the infusion, as an intravenous bolus of Desferal may lead to acute collapse (see section 6 Warnings and precautions).

Continuous intravenous infusion

Implanted intravenous systems can be used when intensive chelation is carried out. Continuous intravenous infusion is indicated in patients who are incapable of continuing subcutaneous infusions and in those who have cardiac problems secondary to iron overload. The dose of Desferal depends on the extent of the patient's iron overload. The 24-hour urinary iron excretion should be measured regularly where intensive chelation (i.v.) is required, and the dose adjusted accordingly. Care should be taken when flushing the line in order to avoid a sudden infusion of residual Desferal which may be present in the dead space of the line, as this may lead to circulatory collapse (see section 6 Warnings and precautions).

Intramuscular administration

Since subcutaneous infusions are more effective, intramuscular injections are given only when subcutaneous infusions are not feasible.
Whichever route of administration is chosen, the individual maintenance dose to be selected will depend on the patient's iron excretion rate.

Concomitant use of vitamin C

Patients with iron overload usually develop vitamin C deficiencies, probably because iron oxidizes the vitamin. As an adjuvant to chelation therapy, vitamin C in doses up to 200 mg daily may be given in divided doses, starting after an initial month of regular treatment with Desferal (see section 6 Warnings and precautions). Vitamin C increases the availability of iron for chelation. In general, 50 mg suffices for children under 10 years of age and 100 mg for older children. Larger doses of vitamin C fail to produce any additional increase in the excretion of the iron complex.

Treatment for acute iron poisoning

Desferal is an adjunct to standard measures generally used in the treatment of acute iron poisoning.
Desferal treatment is indicated in any of the following situations:

- all symptomatic patients exhibiting more than transient minor symptoms (e.g., more than one episode of emesis or passage of one soft stool),
- patients with evidence of lethargy, significant abdominal pain, hypovolemia, or acidosis,
- patients with positive abdominal radiograph results demonstrating multiple radiopacities (the great majority of these patients will go on to develop symptomatic iron poisoning),
- any symptomatic patient with a serum iron level greater than 300 to 350 micrograms/dL regardless of total iron binding capacity (TIBC). It has also been suggested that a conservative approach without Desferal therapy or challenge should be considered when serum iron levels are in the 300 to 500 micrograms/dL range in asymptomatic patients, as well as in those with self-limited, non-bloody emesis or diarrhea without other symptoms.

Continuous intravenous administration of Desferal is the preferred route. The recommended infusion rate is 15 mg/kg per hour and should be reduced as soon as circumstances permit, usually after 4 to 6 hours, so that the total intravenous dose does not exceed the recommended 80 mg/kg in any 24-h period.
The following suggested criteria are believed to represent appropriate requirements for cessation of Desferal. Chelation therapy should be continued until all of the following criteria are satisfied:

- The patient must be free of signs or symptoms of systemic iron poisoning (e.g. no acidosis, no worsening hepatotoxicity).
- Ideally, a corrected serum iron level should be normal or low (i.e. below 100 micrograms/dL). Given that laboratories cannot measure serum iron concentrations accurately in the presence of Desferal, it is acceptable to discontinue Desferal when all other criteria are met if measured serum iron level is not elevated.
- Repeat abdominal radiograph test should be obtained in patients who initially demonstrated multiple radiopacities to ensure they have disappeared before Desferal is discontinued because they serve as a marker for continued iron absorption.
- If the patient initially developed vin-rosé colored urine with Desferal therapy, it seems reasonable that urine color should return to normal before Desferal Desferal (absence of vin-rosé urine is not sufficient by itself to warrant discontinuation of Desferal).

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

Treatment for chronic aluminium overload in patients with end-stage renal failure

The iron and aluminium complexes of Desferal are dialyzable. Their elimination will be increased by dialysis in patients with renal failure.
Patients with evidence of symptoms or organ dysfunction due to aluminium overload should receive Desferal treatment. Even in asymptomatic patients, Desferal treatment should be considered if serum aluminium levels are consistently above 60 ng/mL and are associated with a positive Desferal infusion test (see below). This is particularly the case if bone biopsy findings present evidence of aluminium-related bone disease.
Desferal should be administered with a once-weekly 5 mg/kg dose (see section 14 Instructions for use and handling). For patients with post-DFO test serum aluminium levels up to 300 ng/mL Desferal should be given as a slow i.v. infusion during the last 60 minutes of a dialysis session. For patients with a post-DFO test serum aluminium level above 300 ng/mL Desferal should be administered by slow i.v. infusion 5 hours prior to the dialysis session. After completion of the first 3-month course of Desferal treatment, followed by a 4-week wash-out period, a Desferal infusion test should be performed. If two successive Desferal infusion tests performed at 1-month intervals yield serum aluminium levels less than 50 ng/mL, above baseline, further Desferal treatment is not recommended.
In patients on continuous ambulatory peritoneal dialysis (CAPD) or continuous cyclic peritoneal dialysis (CCPD) Desferal should be given once weekly at a 5 mg/kg dose prior to the final exchange of the day. The intraperitoneal route is recommended in these patients, but Desferal can also be given i.m., by slow infusion i.v. or s.c.

Desferal test

This test is based on the principle that in normal subjects Desferal does not raise iron excretion above a certain limit.

Desferal test for iron overload in patients with normal kidney function

0.5 g Desferal should be injected intramuscularly. The urine should then be collected for a period of 6 hours and its iron content determined. An excretion of 1 to 1.5 mg of iron (18 to 27 micromol) during this 6-hour period is suggestive of an iron overload; values of more than 1.5 mg (27 micromol) can be regarded as pathological. The test yields reliable results only in cases where renal function is normal.

5 Contraindications

Known hypersensitivity to the active substance, except where successful desensitization makes treatment possible.

6 Warnings and precautions

Rapid intravenous infusion

Rapid intravenous infusion may lead to hypotension and shock (e.g., flushing, tachycardia, circulatory collapse and cardiac arrest).

Visual and hearing impairment

High doses of Desferal, especially in patients with low ferritin plasma levels, may lead to disturbances of vision and hearing (see section 7 Adverse drug reactions). Patients with renal failure who are on maintenance dialysis and have low ferritin levels may be particularly prone to adverse effects. These symptoms having been reported after single doses of Desferal. The risk of side effects is reduced when low-dose therapy is employed. If visual or auditory disturbances occur, Desferal should be discontinued immediately. The changes induced by Desferal are usually reversible if identified early. Treatment with Desferal may be resumed later at a reduced dose, with close monitoring of audiovisual function.
Specialist ophthalmological and audiological testing are recommended in patients receiving long-term Desferal treatment, and at regular intervals thereafter (every 3 months), particularly if ferritin levels are low. The risk of audiometric abnormalities may be reduced in thalassemia patients if the ratio of the mean daily dose (mg/kg) to the baseline ferritin by the serum ferritin (micrograms/L) is kept below 0.025.

Renal impairment

Approximately half of the metal complex is excreted via the kidneys in iron-overloaded patients with normal renal function. Accordingly, caution is indicated in patients with impaired renal function. The iron and aluminium complexes of deferoxamine are dialyzable; their elimination will be increased by dialysis in patients with renal failure.
Isolated cases of acute renal failure have been reported (see also section 7 Adverse drug reactions). Monitoring patients for changes in renal function (e.g. increased serum creatinine) should be considered.

Pediatrics: growth retardation

Patients with low serum ferritin levels on high doses of Desferal, or patients at young age (< 3 years at commencement) have been reported to have associated with growth retardation (see section 4 Dosage and administration: "Treatment for chronic iron overload").
Growth retardation if associated with excessive doses of Desferal must be distinguished from growth retardation resulting from iron overload. Growth retardation from Desferal use is rare if the dose is kept below 40 mg/kg. If growth retardation has been observed with doses above this value, then reduction of the dose may result in return in growth velocity; however, the predicted adult height will not be attained.
Pediatric patients receiving Desferal should be monitored for body weight and longitudinal growth every 3 months.

Acute respiratory distress syndrome

Acute respiratory distress syndrome has been described following treatment with excessively high i.v. doses of Desferal in patients with acute iron intoxication, and also in thalassemic patients. The recommended daily doses should therefore not be exceeded.

Infections

In patients with iron overload it has been reported that Desferal increases susceptibility to infections, e.g. with *Yersinia enterocolitica* and *Yersinia pseudotuberculosis*. If a patient under treatment with Desferal develops fever accompanied by acute enteritis/enterocolitis, diffuse abdominal pain, or pharyngitis, treatment should be temporarily discontinued, bacteriological tests performed, and suitable antibiotic therapy started at once. Treatment with Desferal can be resumed after the infection has resolved.
Rare cases of mucormycosis, some with a fatal outcome, have been reported in patients receiving Desferal for aluminium overload. In most of the reported cases or symptoms occur, Desferal should be discontinued, mycological tests carried out and appropriate treatment instituted immediately. Mucormycosis may also occur in patients who are not receiving Desferal, indicating that other factors (such as dialysis, diabetes mellitus, disturbance of acid-base balance, hematological malignancies, immunosuppressive drugs, or a compromised immune system) may play a role in the development of this infection.

Cardiac impairment with high doses of vitamin C

In patients with severe chronic iron overload, impairment of cardiac function has been reported following concomitant treatment with Desferal and high doses of vitamin C (more than 0.5 g daily). Cardiac deficiency was reversible when vitamin C was discontinued. The following precautions should be taken when Desferal and vitamin C are used concomitantly:

- Vitamin C supplements should not be given to patients with cardiac failure.
- Start treatment with vitamin C only after an initial month of regular treatment with Desferal
- Give vitamin C only if the patient is receiving Desferal regularly; ideally soon after setting up the pump.
- Do not exceed a daily dose of 200 mg of vitamin C, given in divided doses.
- Monitoring of cardiac function is advisable during such combined therapy.

Patients treated for chronic aluminium overload

In patients with aluminium-related dialysis encephalopathy, high doses of Desferal may exacerbate neurological dysfunction (convulsion), probably owing to an acute increase in circulating aluminum (see section 7 Adverse drug reactions). Desferal may precipitate the onset of dialysis dementia. Pre-treatment with anticonvulsants has been reported to prevent this neurological deterioration. Also, treatment of aluminum-overload patients with Desferal may exacerbate or aggravation of hyperparathyroidism.

Instructions for use and handling

Desferal should not be given in doses higher than recommended. 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 (see section 14 Instructions for use and handling). When intramuscular use is the only option it may be necessary to use higher concentrations to facilitate the injection (see section 14 Pharmaceutical information including incompatibilities).
If the reconstituted concentration of 95 mg/mL the reconstituted solution is clear, and colorless to slightly yellowish. Only clear solutions should be used. Opaque or colored solutions should be discarded. Due care must be taken with the injection technique.
For subcutaneous infusion, the needle should not be inserted too close to the dermis.
Patients experiencing dizziness or other central nervous disturbances, or impairment of vision or hearing, should refrain from driving a vehicle or operating machines (see section 7 Adverse drug reactions).

Urine Discoloration

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

7 Adverse drug reactions

Adverse drug reactions from (Table 7-1) are listed according to system organ classes in MedDRA. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are ranked in order of decreasing seriousness.
In addition, the corresponding frequency category using the following convention (CIOMS III) is also provided for each adverse drug reaction: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (≤1/10,000) including isolated reports; *"unknown"* (when not possible to reliably estimate the frequency of the adverse reactions reported from post-marketing experience because reports are from a population of uncertain size).
Some of the signs and symptoms reported as adverse effects may also be manifestations of the underlying disease (iron and/or aluminum overload).

Table 7-1 Adverse drug reactions

Infections and infestations	
Rare:	Mucormycosis (see section 6 Warnings and precautions).
Very rare:	Gastroenteritis Yersinia (see section 6 Warnings and precautions).
Blood and lymphatic system disorders	
Very rare:	Blood disorder (incl thrombocytopenia, leukopenia).
Immune system disorders	
Very rare:	Anaphylactic shock, anaphylactic reaction, angioneurotic edema.
Nervous system disorders	
Common:	Headache.
Rare:	Neurological disturbances including dizziness, precipitation or exacerbation of aluminum-related dialysis encephalopathy, neuropathy peripheral, paresthesia (see section 6 Warnings and precautions).
Unknown:	Convulsions (see Special remarks below).
Eye disorders	
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 section 6 Warnings and precautions and Special remarks below).
Ear and labyrinth disorders	
Uncommon:	Deafness neurosensory, tinnitus (see section 6 Warnings and precautions and Special remarks below).
Cardiovascular disorders	
Rare:	Hypotension, tachycardia and shock if precautions for administration are not adhered to (see section 4 Dosage and administration and section 6 Warnings and precautions).
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Asthma.
Very rare:	Acute respiratory distress, lung infiltrates (see section 6 Warnings and precautions).
Gastrointestinal disorders	
Common:	Nausea.
Uncommon:	Vomiting, abdominal pain.
Very rare:	Diarrhea.
Skin and subcutaneous tissue disorders	
Common:	Urticaria.
Very rare:	Rash generalized.
Musculoskeletal and connective tissue disorders	
Very common:	Arthralgia, myalgia.
Common:	Growth retardation and bone disorder (e.g. metaphyseal dysplasia) in higher doses and young children (see section 6 Warnings and precautions and Special remarks below).
Unknown	Muscle spasms.
Renal and urinary disorders	
Unknown:	Acute renal failure, renal tubular disorder, blood creatinine increased (see section 6 Warnings and precautions and section 10 Overdosage).
General disorders and administration site conditions	
Very common:	Injection site reaction including pain, swelling, infiltration, erythema, pruritus, eschar, crust (see Special remarks below).
Common:	Pyrexia.
Uncommon:	Injection site reaction including vesicles, edema, burning (see Special remarks below).

Special remarks

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 Desferal divided by serum ferritin should be below 0.025) (see section 6 Warnings and precautions).
The various eye disorders are rare, except if high doses are given (see section 6 Warnings and precautions).
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.
At the injection site: pain, swelling, infiltration, erythema, pruritus, and eschar(rare are very common, and vesicles, local edema and burning are uncommon. Local manifestations may be accompanied or cells thereby forming the complex ferrioxamine (FO). Urinary iron excretion of FO is predominantly a reflection of iron derived from plasma turnover whereas faecal iron reflects mainly intrahepatic iron chelation. Iron may be chelated from ferritin and hemosiderin but is relatively slow at clinically relevant concentrations of DFO. DFO, however, does not remove iron from transferrin or from hemoglobin or from other hemin-containing substances.
DFO also mobilize and chelate aluminium, forming an aluminoxamine (AIO) complex.

Pharmacodynamics (PD)

Since both ferrioxamine, FO and AIO, are completely excreted, DFO promotes the excretion of iron and aluminum in the urine and faeces and thus reduces pathological iron or aluminum deposits in the organs.

Pharmacokinetics (PK)

Absorption

DFO is rapidly absorbed after intramuscular bolus injection or slow subcutaneous infusion, but is only poorly absorbed from the gastrointestinal tract in the presence of intact mucosa. The absolute bioavailability is less than 2 % after oral administration of 1 g DFO.
During peritoneal dialysis DFO is absorbed if administered in the dialysis fluid.

Distribution

In healthy volunteers peak plasma concentrations of 15.5 micromol/L (9.7 micrograms/mL) were measured 30 minutes after an intramuscular injection of 10 mg/kg DFO. One hour after injection the peak concentration of FO was 3.7 micromol/L (2.3 micrograms/mL). After intravenous infusion of 2 g (about 29 mg/kg) of DFO in healthy volunteers over 2 hours mean steady state concentrations of DFO of 30.5 micromol/L were reached, distribution of DFO is very rapid with a mean distribution half-life of 0.4 hours. Less than 10 % of DFO is bound to serum proteins *in vitro*.

Biotransformation

Four metabolites of DFO were isolated and identified from the urine of patients with iron overload. The following biotransformation reactions have been found to occur with DFO: transamination and oxidation yielding an acid metabolite, beta-oxidation also yielding an acid metabolite, decarboxylation and N-hydroxylation yielding neutral metabolites.

Elimination

Both DFO and FO have a biphasic elimination after intramuscular injection in healthy volunteers; for DFO the apparent distribution half-life is 1 hour, and for FO 2.4 hours. The apparent terminal half-life is 6 hours for both. Within six hours of injection, 22 % of the dose appears in the urine as DFO and 1 % as FO.

10 Overdosage

Signs and symptoms

Inadvertent administration of an overdose or inadvertent intravenous bolus administration/rapid intravenous infusion may be associated with hypotension, tachycardia and gastrointestinal disturbances; acute but transient loss of vision, aphasia, agitation, headache, nausea, bradycardia, as well as acute renal failure (see section 7 Adverse drug reactions) have been reported.
Acute respiratory distress syndrome has been described following treatment with excessively high i.v. doses of Desferal in patients with acute iron intoxication, and also in thalassemic patients (see also section 6 Warnings and precautions).

Treatment

There is no specific antidote. Desferal should be discontinued and appropriate symptomatic measures undertaken.
Desferal is dialyzable.

11 Clinical pharmacology

Pharmacotherapeutic group, ATC

Chelating agent (ATC code: V03AC01).

Mechanism of action

Deferoxamine (DFO) forms complexes predominantly with ferric iron and with trivalent aluminium ions; the complex formation constants are 10^{31} and 10^{23}, respectively. The affinity of DFO for divalent ions such as Fe^{2+}, Cu^{2+}, Zn^{2+}, Ca^{2+} is substantially lower (complex formation constants 10^{14} or below). Chelation occurs at a 1:1 molar basis, so that 1 g DFO can theoretically bind 85 mg ferric iron or 41 mg Al^{3+}.
Owing to its chelating properties, DFO is capable of taking up iron from transferrin, either in plasma or in cells thereby forming the complex ferrioxamine (FO). Urinary iron excretion of FO is predominantly a reflection of iron derived from plasma turnover whereas faecal iron reflects mainly intrahepatic iron chelation. Iron may be chelated from ferritin and hemosiderin but is relatively slow at clinically relevant concentrations of DFO. DFO, however, does not remove iron from transferrin or from hemoglobin or from other hemin-containing substances.
DFO also mobilize and chelate aluminium, forming an aluminoxamine (AIO) complex.

Pharmacodynamics (PD)

Since both ferrioxamine, FO and AIO, are completely excreted, DFO promotes the excretion of iron and aluminum in the urine and faeces and thus reduces pathological iron or aluminum deposits in the organs.

Pharmacokinetics (PK)

Absorption

DFO is rapidly absorbed after intramuscular bolus injection or slow subcutaneous infusion, but is only poorly absorbed from the gastrointestinal tract in the presence of intact mucosa. The absolute bioavailability is less than 2 % after oral administration of 1 g DFO.
During peritoneal dialysis DFO is absorbed if administered in the dialysis fluid.

Distribution

In healthy volunteers peak plasma concentrations of 15.5 micromol/L (9.7 micrograms/mL) were measured 30 minutes after an intramuscular injection of 10 mg/kg DFO. One hour after injection the peak concentration of FO was 3.7 micromol/L (2.3 micrograms/mL). After intravenous infusion of 2 g (about 29 mg/kg) of DFO in healthy volunteers over 2 hours mean steady state concentrations of DFO of 30.5 micromol/L were reached, distribution of DFO is very rapid with a mean distribution half-life of 0.4 hours. Less than 10 % of DFO is bound to serum proteins *in vitro*.

Biotransformation

Four metabolites of DFO were isolated and identified from the urine of patients with iron overload. The following biotransformation reactions have been found to occur with DFO: transamination and oxidation yielding an acid metabolite, beta-oxidation also yielding an acid metabolite, decarboxylation and N-hydroxylation yielding neutral metabolites.

Elimination

Both DFO and FO have a biphasic elimination after intramuscular injection in healthy volunteers; for DFO the apparent distribution half-life is 1 hour, and for FO 2.4 hours. The apparent terminal half-life is 6 hours for both. Within six hours of injection, 22 % of the dose appears in the urine as DFO and 1 % as FO.

Characteristics in patients

In **patients with hemochromatosis** peak plasma levels of 7.0 micromol/L (3.9 micrograms/mL) were measured for DFO, and 15.7 micromol/L (9.6 micrograms/mL) for FO. 1 hour after an intramuscular injection of 10 mg/kg DFO. These patients eliminated DFO and FO with half-lives of 5.6 and 4.6 hours, respectively. Six hours after the injection 17 % of the dose was excreted in the urine as DFO and 12 % as FO.
In **patients with thalassemia** continuous intravenous infusion of 50 mg/kg/24 h of DFO resulted in plasma steady state levels of DFO of 7.4 micromol/L (4.1 micrograms/mL). Elimination of DFO from plasma was biphasic with a mean distribution half-life of 0.28 hours and an apparent terminal half-life of 3.0 hours. The total plasma clearance was 0.5 L/h/kg and the volume of distribution at steady state was estimated at 1.35 L/kg. Exposure to the main iron binding metabolite was around 54 % of that of DFO in terms of AUC. The apparent monoexponential elimination half-life of the metabolite was 1.3 hours.
In **patients dialyzed for renal failure** who received 40 mg/kg DFO infused i.v. within 1 hour, the plasma concentration of DFO at the end of infusion was 152 micromol/L (85.2 micrograms/mL) when the infusion was given between dialysis sessions. Plasma concentrations of DFO were between 13 % and 27 % lower when the infusion was administered during dialysis. Concentrations of FO were in all cases approx. 7.3 micromol/L (4.3 micrograms/mL) and for AIO 2-3 micromol/L (1.2-1.8 micrograms/mL). After the infusion was discontinued, the plasma concentration of DFO decreased rapidly with a half-life of 20 minutes. A smaller fraction of the dose was eliminated with a slower half-life of 1 hours. The plasma concentrations of AIO continued to increase for up to 48 hours after the infusion and reached values of approx. 7 micromol/L (4 micrograms/mL). Following dialysis the plasma concentration of AIO dropped to 1.2 micromol/L (1.3 micrograms/mL).

12 Clinical studies

Deferoxamine was used as a comparator in a randomized, one-year clinical trial investigating the use of an oral iron chelator (deferiprone) in patients with beta-thalassemia and transfusional hemosiderosis. A total of 290 patients were treated with subcutaneous deferoxamine at starting doses of 20 to 60 mg/kg for 5 days per week. The study showed a dose-dependent effect of deferoxamine on serum ferritin levels, liver iron concentration and iron excretion rate.
Deferoxamine was also used as a comparator in a second open-label, controlled, one-year trial investigating the use of deferasirox in patients with sickle cell disease and transfusional hemosiderosis. A total of 63 patients were treated with subcutaneous deferoxamine at starting doses of 20 to 60 mg/kg at least 5 days per week. At baseline the patient performance was comparable to the actual body weight of the patient, the appropriate amount of Desferal solution is withdrawn from the vial and added to 150 mL 0.9 % saline (NaCl solution).
Dissolved Desferal can also be added to the dialysis fluid, and given intraperitoneally to patients on CAPD or CCPD .
The use of Desferal in chronic iron overload by means of an infusion pump is described in section 14 Pharmaceutical information as follows (for illustrations see below):

1. Draw the water for injection into a syringe.
2. After cleaning the rubber stopper of the Desferal vial with alcohol, inject the content of the syringe into the vial.
3. Shake the vial thoroughly to dissolve the powder.
4. Draw the solution so obtained into the syringe.
5. Attach the extension tube to the pump, connect the extension tube to the butterfly-type needle, and then fill the empty space in the tube with the solution in the syringe.
6. Place the syringe in the infusion pump.
7. For infusion you may insert the butterfly-type needle under the skin of the abdomen, arm, upper leg or thigh. It is important to first clean the skin very thoroughly with alcohol. Then insert the needle firmly, up to the wings into a fold of the skin formed by your free hand. The tip of the needle should move freely when the needle is wiggled. If it doesn't move freely, the tip of the needle may be too close to the skin. Try again at a new site after cleaning it with alcohol.
8. Then fix the needle and tape it down.

Desferal PL+PHY
SH DES APL 30JUN20
SH DES API 30JUN20
PS

One vial is for single use only. The product should be used immediately after reconstitution (commencement of treatment within 3 hours). When reconstitution is carried out under validated aseptic conditions the product may be stored for a maximum period of 24 hours at room temperature before administration.
Desferal must be kept out of the reach and sight of children.

Instructions for use and handling

When administered parenterally, the drug should be used as a 95 mg/mL solution in water for injection except for i.m. injection where a higher reconstitution may be necessary. Preparation of powder for solution for injection is given in Tables 14-1 and 14-2 for subcutaneous, intravenous and intramuscular administrations, respectively. After the appropriate volume for injection is injected into the vial containing 0.5 g Desferal powder, the vial is shaken well. Only clear and colorless to slightly yellowish solutions should be used (see also section 6 Warnings and precautions).

Table 14-1: Preparation for subcutaneous and intravenous administrations

RECONSTITUTE DESFERAL WITH STERILE WATER FOR INJECTION			
Vial Size	Amount of Sterile Water for Injection Required for Reconstitution	Total Drug Content after Reconstitution	Final Concentration per mL after Reconstitution
0.5 g	5 mL	0.5 g/5.3 mL	95 mg/mL

Table 14-2: Preparation for intramuscular administration

RECONSTITUTE DESFERAL WITH STERILE WATER FOR INJECTION			
Vial Size	Amount of Sterile Water for Injection Required for Reconstitution	Total Drug Content after Reconstitution	Final Concentration per mL after Reconstitution
0.5 g	2 mL	0.5 g/2.35 mL	213 mg/mL

The 95 mg/mL Desferal solution after reconstitution can further diluted with routinely employed infusion solutions (NaCl 0.9 %, glucose 5 %, Ringer's solution, Ringer-Lactate solution, peritoneal dialysis solutions such as Dianeal 137 Glucose 2.27 %, Dianeal PD4 Glucose 2.27 %, and CAPD/DPCA 2 Glucose 1.5 %).
If the Desferal infusion is used for the treatment of chronic aluminium overload, the 5.3 mL Desferal solution in the 0.5 g vial is an adequate dose (5 mg/kg for a patient with 100 kg body weight. According to the actual body weight of the patient, the appropriate amount of Desferal solution is withdrawn from the vial and added to 150 mL 0.9 % saline (NaCl solution).
Dissolved Desferal can also be added to the dialysis fluid, and given intraperitoneally to patients on CAPD or CCPD .
The use of Desferal in chronic iron overload by means of an infusion pump is described in section 14 Pharmaceutical information as follows (for illustrations see below):

1. Draw the water for injection into a syringe.
2. After cleaning the rubber stopper of the Desferal vial with alcohol, inject the content of the syringe into the vial.
3. Shake the vial thoroughly to dissolve the powder.
4. Draw the solution so obtained into the syringe.
5. Attach the extension tube to the pump, connect the extension tube to the butterfly-type needle, and then fill the empty space in the tube with the solution in the syringe.
6. Place the syringe in the infusion pump.
7. For infusion you may insert the butterfly-type needle under the skin of the abdomen, arm, upper leg or thigh. It is important to first clean the skin very thoroughly with alcohol. Then insert the needle firmly, up to the wings into a fold of the skin formed by your free hand. The tip of the needle should move freely when the needle is wiggled. If it doesn't move freely, the tip of the needle may be too close to the skin. Try again at a new site after cleaning it with alcohol.
8. Then fix the needle and tape it down.
9. Patients usually wear the pump on the body using a belt or shoulder holster. Many patients consider overnight use to be most convenient.

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