1. Name of the medicinal product, composition and pharmaceutical form

Desferal 0.5G

POWDER FOR SOLUTION FOR INJ/INF; IV, IM, SC

Composition

Active substance: Deferoxamine mesylate.

Pharmaceutical form and quantity of active substance per unit

Powder for solution for inj/inf 500 mg per vial.

2. Therapeutic Indications

Therapeutic

Treatment of chronic iron overload, e.g.:

- Transfusional haemosiderosis, especially in thalassaemia major, sideroblastic anaemia, autoimmune haemolytic anaemia and other chronic anaemias;
- idiopathic (primary) haemochromatosis in patients in whom concomitant disorders (e.g. severe anaemia, cardiac disease, hypoproteinaemia) preclude phlebotomy;

iron overload associated with porphyria cutanea tarda Treatment of acute iron poisoning.

Treatment of 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 anaemia.

Diagnostic

For the diagnosis of iron overload.

3. Dosage / Administration

Treatment of 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 haemosiderosis, while in overloaded patients a negative iron balance is desirable in order to reduce increased iron stores and prevent the toxic effects of iron.

Treatment of 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 who develop 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, hypovolaemia or acidosis;
- patients with positive abdominal radiograph results demonstrating multiple radiopacities (the great majority of these patients will go on to develop symptoms of iron poisoning);
- any symptomatic patients with a serum iron levels greater than 300 to 350 µg/dl, regardless of total iron binding capacity (TIBC).

It has also been suggested that a conservative approach without Desferal therapy should be considered in asymptomatic patients withserum iron levels are in the 300 to 500 µg/dl range, as well as in patients with self-limited, non-bloody emesis or diarrhoea, but without other symptoms.

Continuous intravenous (I.V) administration of Desferal is the preferred method of administration. The maximum recommended rate for infusion 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 over a 24-hour period.

The following criteria are considered 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, corrected serum iron levels should be normal or low (i.e. < 100 μg/dl). However, since serum iron levels cannot be measured accurately in the presence of Desferal, it is acceptable to discontinue Desferal if all other criteria are met and measured levels are not elevated.
- Multiple radiopacities serve as a marker for continued iron absorption. Abdominal radiography should therefore be repeated to ensure that they have disappeared before discontinuing Desferal in patients in whom these radiopacities had initially been encountered.
- In patients who initially developed vin-rosé coloured urine with Desferal therapy, it seems reasonable not to withdraw Desferal before urine colour returns to normal (absence of vin-rosé urine, however, does not by itselfjustify discontinuation of Desferal).

The efficacy of treatment depends on an adequate urinary output of urine in order to ensure the elimination of the iron complex ferrioxamine (FO). If oliguria or anuria develops, peritoneal dialysis, haemodialysis or haemofiltration may become necessary to remove FO.

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

The iron and aluminium complexes of Desferal are dialyzable. Patients with 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 as a once-weekly 5 mg/kg dose. For patients showing serum aluminium levels up to 300 ng/ml after DFO testing, Desferal should be given as a slow i.v. infusion during the last 60 minutes of a dialysis session. If serum aluminium is above 300 ng/ml, Desferal should be

administered by slow i.v. infusion 5 hours prior to the dialysis session. After the first 3-month course of Desferaltherapy, followed by a 4-week washout period, a Desferal infusion test should be performed. If two successive Desferal infusion tests performed at an interval of 1-month 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 in a single 5 mg/kg dose prior to the final exchange of the day.

It is recommended that the intraperitoneal route be used in these patients, but Desferal can also be given i.m., s.c. or by slow i.v. infusion.

Children and adults

Desferal therapy should be started after the first 10 20 blood transfusions or when there is evidence of iron overload (e.g. serum ferritin ≥1000 ng/ml).

Iron overload or excessive Desferal doses may result in growth retardation. If chelation therapy is begun in children under 3 years of age, growth must be monitored carefully and the mean daily dose should not exceed 40 mg/kg.

Dosage and mode of administration should be individually determined and adapted to the severity of the patient's iron burden during the course of therapy. The lowest effective dose should be given.

To assess the response to chelation therapy, 24-hour urinary iron excretion may initially be monitored daily,thereby determining the response to increasing doses of Desferal. 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 in accordance with ferritin levels to keep the therapeutic index below 0.025 (i.e. the mean daily dose of Desferal in mg/kg, divided by the serum ferritin level in µg/litre, should be below 0.025). The therapeutic index is a useful tool for 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 a serum ferritin level below 2000 ng/ml require about 25

mg/kg/day. Those with a serum ferritin level between 2000 and 3000 ng/ml require about 35 mg/kg/day. Patients with higher serum ferritin may require up to 55 mg/kg/day. It is nevertheless inavisable to regularly exceed an average daily dose of 50 mg/kg unless very intensive chelation therapy is needed in patients who have completed growth. If ferritin values fall below 1000 ng/ml, the risk of Desferal toxicity increases; It is therefore important to monitor these patients particularly closely and perhaps to consider lowering the total weekly dose.

The doses specified here are the average daily doses. Since most patients take Desferal less than 7 days a week, the actual doses per infusion usually differ from the average daily doses (for example, if an average daily dose of 40 mg/kg is required and the patient wears the pump 5 nights a week, each infusion should contain 56 mg/kg).

It has been possible to show that regular chelation therapy with deferoxamine improves life expectancy in patients with thalassaemia.

Higher doses should be given only if the therapeutic benefit to the patient outweighs the risk of adverse effects associated with repeated high daily doses.

Specific populations

Elderly patients

Clinical studies of Desferal did not include enough patients over 65 years old to determine whether they respond differently from younger patients. In general, dose selection for elderly patients should be cautious, and normally at the lower end of the dosing range, reflecting the greater frequency of impaired hepatic, renal or cardiac function, and of concomitant disease or other drug treatment.

Hepatic impairment

No studies have been performed in patients with hepatic impairment.

Patients with Renal impairment

In patients with renal impairment half of the metal complexes are excreted in the urine . Caution is therefore required in patients with severe renal

impairment. The iron and aluminium complexes of deferoxamine are dialyzable;in patients with renal impairment their elimination is increased by dialysis

Isolated cases of acute renal failure have been reported (see also "Adverse effects"). Monitoring patients for changes in renal function (e.g. increased serum creatinine) should be considered.

Method of administration

Desferal should be given by slow subcutaneous infusion over a 8 to 12 hours using a portable, lightweight infusion pump. This is particulary suitable for ambulatory patients. It can also be given over a 24-hour period. Desferal should normally be used 5 to 7 times a week. The use of Desferal for subcutaneous bolus injection cannot be supported.

Desferal should not be administered at concentrations higher than 95 mg/ml because this increases the risk of local skin reactions (see *Instructions for use and handling*).

If there is no option other than intramuscular injection, it may be necessary to use higher concentrations to facilitate the injection (see *Instructions for use and handling* under "Other information").

In subcutaneous injection the needle should not be inserted too close to the dermis.

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 site of injection. as usual, the patient’s pump should be used to administer Desferal. Because of the limited amount of drug that can be administered by i.v. 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 circulatory collapse (see "Warnings and precautions").

Continuous intravenous infusion

Implanted intravenous infusion systems can be used when carrying out intensive chelation is. Continuous intravenous infusion is indicated in patients who are incapable of continuing subcutaneous infusions and in patientswith cardiac problems secondary to iron overload. The dosage of Desferal depends on the extent of iron overload. 24-hour urinary iron excretion should be measured regularly where intensive chelation therapy (i.v.) is required, and the dose should be adjusted accordingly. Care should be taken when flushing the infusion line to avoid rapid infusion of Desferal which may be present in the dead space of the line. This could lead to circulatory collapse (see "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 maintenance dose must be determined individually and will depend on the patient’s iron excretion rate.

Concomitant administration of vitamin C

Patients with iron overload usually develop vitamin C deficiency, probably because iron oxidizes the vitamin. As an adjuvant to chelation therapy, vitamin C in doses up to 200 mg/daymay be given in divided doses, starting after an initial month of regular chelation therapy with Desferal (see "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. Higher doses of vitamin C fail to produce any additional increase in excretion of the iron complex.

Desferal diagnostic test

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

Desferal test for iron overload in patients with normal renal function

500 mg 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 µmol) during this 6-hour period is suggestive of an iron overload; values of more than 1.5 mg (27 µmol) can be regarded as pathological. The test yields reliable results only in cases where renal function is normal.

4. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 13.

5. Warnings and precautions

Paediatrics: Growth retardation

Growth retardation has been associated both with the use of high dose Desferal in patients with low serum ferritin levels and with the commencement of treatment in children under 3 years of age (see *Treatment of chronic iron overload* under "Dosage / Administration").
Growth retardation associated with high doses of Desferal must be distinguished from growth retardationdue to iron overload. Growth retardation in connection with Desferal use is rare if the dose is kept below 40 mg/kg. For growth retardation associated with doses above this value, dose reduction may bring about a return to the original growth rate; but predicted adult height is not attained.
Paediatric patients receiving Desferal should be monitored for body weight and longitudinal growth every three months.

Infections

In patients with iron overload, there have been reports of increased susceptibility to infections, including sepsis (particularly 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, Desferal treatment should be temporarily withdrawn, appropriate bacteriological tests performed and suitable antibiotic therapy instituted immediately. After the infection has resolved Desferal therapy can be resumed.

In patients with iron or aluminium overload who were treated with Desferal, rare cases of mucormycosis, some with a fatal outcome, have been reported in patients being treated with Desferal for iron or aluminium overload. If any of the suspected signs 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 under certain conditions, other factors (such as dialysis, diabetes mellitus, disturbance of acid-base balance, haematological malignancies, immunosuppressive drugs, or a compromised immune system) may play a role

Vision and hearing impairment

High doses of Desferal, especially in patients with low ferritin plasma levels, may lead to disturbances of vision and hearing (see "Adverse effects"). Patients with renal impairment who are on maintenance dialysis and have low ferritin levels may be particularly prone to adverse effects, visual symptoms having been reported after single doses of Desferal. The risk of adverse drug reactions is lower with low-dose therapy.

Specialist ophthalmological and audiological testing are recommended before the start of Desferal treatment, and at regular intervals thereafter (every 3 months), particularly if ferritin levels are low. The risk of audiometric abnormalities in thalassaemia patients can be reduced by keeping thequotient of the mean daily dose (mg/kg) of Desferal divided by serum ferritin (µg) below 0.025.

Desferal should be discontinued immediately if visual or auditory disturbances occur. Changes caused by Desferal are usually reversible if identified early. Treatment with Desferal can be resumed later at a reduced dosage under close monitoring of audiovisual functions and with due regard to the risk-benefit

ratio. In very rare cases, visual disturbances have also been observed after administration of a diagnostic test dose.
In patients with aluminium-related encephalopathy, high doses of Desferal may exacerbate disturbances of neurological function (convulsion), probably on account of an acute increase in circulating aluminium (see "Adverse effects").
Desferal may precipitate the onset of dialysis dementia. Pretreatment with clonazepam has been reported to protect against this.
Treatment of aluminium overload may also result in hypocalcaemia and aggravation of hyperparathyroidism.

Acute respiratory distress syndrome
Acute respiratory distress syndrome has been reported following treatment with very high i.v. doses of Desferal in patients with acute iron poisoning or thalassemia. The recommended daily doses should therefore not be exceeded.

Heart failure with high doses of vitamin C
The following precautions are necessary when diving Desferal concomitantly with vitamin C:
Vitamin C supplements should not be given to patients with heart failure.
Vitamin C therapy should start before the end of the first month of regular Desferal treatment.
Vitamin C should only be given if the patient is receiving Desferal regularly, ideally soon after setting up the pump.
The daily dose of 200 mg vitamin C, given in divided doses should not be exceeded.
Monitoring of cardiac function is advisable during such combination therapy.
In patients with severe chronic iron overload impairment of cardiac function has been reported in connection with concomitant treatment with Desferal and vitamin C (more than 500 mg daily). The cardiac dysfunction was reversible when vitamin C was discontinued.

Rapid i.v. infusion may lead to hypotension and shock (e.g. flushing, tachycardia, collapse and urticaria).
Desferal should not be used at doses exceeding those recommended.

it should not be administrated at concentrations higher than 95mg/ml because as this increases the risk of local skin reactions (see "*Instructions for use and handling*").

If there is no option other than intramuscular injection it may be necessary to use higher concentrations to facilitate the injection.
In subcutaneous injection, the needle should not be inserted too close to the dermis.
Urine discoloration
Excretion of the iron complex may cause reddish-brown discoloration of the urine.

6. Interactions

Concomitant treatment with Desferal and prochlorperazine, a phenothiazine derivative, may lead to transient disturbances of consciousness, pyramidal disorders and coma.
Impairment of cardiac function has been observed in patients with severe chronic iron overload undergoing combined treatment with Desferal and high doses of vitamin C (>500 mg/day); see "Warnings and precautions"). This has proved reversible on withdrawal of vitamin C.
Gallium-67 imaging results may be distorted because of the rapid urinary excretion of Desferal-bound gallium-67. it is therefore recommended that Desferal be discontinued 48 hours prior to scintigraphy.

Pregnancy / Brest-Feeding
Pregnancy

There are a limited data on the use of deferoxamine in pregnant patients. Studies in animals (rabbits) have shown reproductive toxicity / teratogenicity (see "Preclinical data"). The risk to the fetus and mother is unknown.

Desferal may be used during pregnancy only if the expected benefit outweighs the potential risk to the fetus.

Breast-feeding

It is not known whether deferoxamine is excreted in into the breast milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse effects 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.

For this reason, deferoxamine should not be given to women who are breast-feeding.

7. Effects on ability to drive and use machines

Patients experiencing dizziness, other CNS disturbances, or disturbances of vision or hearing should refrain from driving or using machines (see "Adverse effects").

8. Adverse effects

Some of the signs and symptoms reported as adverse effects may also be manifestations of the underlying disease (iron and / or aluminium overload).

Adverse effects are listed according to MedDRA system organ class.
Frequencies were defined as follows: *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).*
Within each frequency grouping, adverse effects are presented in order of decreasing severity.

Infections and infestations
Rare: Mucormycosis (see "Warnings and precautions").
Very rare: Gastroenteritis, Yersinia, enterocolitis.

Blood and lymphatic system disorders
Very rare: Blood disorders (incl. thrombocytopenia, leukopenia).

Immune system disorders
Very rare: Anaphylactic shock, anaphylactic reactions, angioedema.

Nervous system disorders
Common: Headache.
Very rare: Neurological disturbances including dizziness, precipitation or exacerbation of aluminium-related dialysis encephalopathy; peripheral neuropathy; paraesthesia (see "Warnings and precautions").
Unknown: Convulsion (see *Special remarks* below).

Eye disorders
Rare: Loss of vision, scotoma, retinal degeneration, optic neuritis, cataracts, decreased visual acuity, blurred vision, night blindness, visual field defects, impairment of colour vision, corneal opacities.

Ear and labyrinth disorders
Uncommon: Neurosensory deafness, tinnitus.

Vascular disorders

Rare: Hypotension, tachycardia and shock if recommended precautions for dosing Desferal are not adhered to.

Respiratory thoracic and mediastinal *disorders*

Uncommon: Asthma.

Very rare: Acute respiratory distress, lung infiltration.

Gastrointestinal disorders
Common: Nausea.
Uncommon: Vomiting, abdominal pain.
Very rare: Diarrhoea.

Skin and subcutaneous tissue disorders
Common: Urticaria.
Very rare: Generalized rash.

Musculoskeletal and connective tissue disorders
Very common: Arthralgia (13%), myalgia (13%).
Common: Growth retardation and bone changes (e.g. metaphyseal dysplasia) at higher doses and in young children.
Leg cramps, bone pain and spinal and metaphyseal deformation have been observed.
Unknown: Muscle cramps.

Renal and urinary disorders
Unknown: Acute renal failure, renal tubular disorder, increase in blood creatinine (see "Warnings and precautions" and "Overdose").

General disorders and administration site reactions
Very common: Administration site reactions such as pain (48%), swelling (12%), infiltration (38%), erythema (58%), pruritus (53%) and crust (19%).

Common: Pyrexia.

Special remarks

Excretion of the iron complex may cause reddish-brown discoloration of the urine.
Convulsion has mainly been reported primarily in dialysis patients with aluminium overload (see "Warnings and precautions").

Rare cases of increases transaminases and isolated cases of hepatic failure have been reported in patients who have been treated with Desferal, but causality has not been established.

Patients treated for chronic aluminium overload
Desferal chelation therapy for aluminium overload may result in hypocalcaemia and aggravation of hyperparathyroidism (see "Warnings and precautions").

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

9. Overdose

Signs and symptoms

Inadvertent administration of an overdose or of an i.v. bolus/rapid i.v. infusion may be associated with hypotension, tachycardia and gastrointestinal disturbances. Acute but transient loss of vision, aphasia, agitation, headache, nausea, bradycardia and acute renal failure have also been reported (see "Adverse effects").

Acute respiratory distress syndrome has been reported after i.v. administration of excessively high Desferal doses to patients with acute iron intoxication, and also to patients with thalassaemia (see also "Warnings and precautions").

Management

There is no specific antidote. Desferal should be discontinued and appropriate symptomatic treatment should be initiated.

Desferal is dialysable.

10. Properties / Actions

ATC code: V03AC01

Mechanism of action

Deferoxamine (DFO) is a chelating agent which forms complexes predominantly with trivalent iron and aluminium ions: the complex formation constants are 10^{31} and 10^{25}, respectively. The affinity of DFO for divalent ions such as Fe^{2+}, Cu^{2+}, Zn^{2+} and Ca^{2+} is substantially lower (complex formation constants 10^{14} or below). Chelation occurs on a 1:1 molar basis, so that 1 g DFO can theoretically bind 85 mg trivalent iron or 41 mg trivalent aluminium.

Pharmacodynamics

Owing to its chelating properties, DFO can take up free iron, wether in the plasma or in cells, thereby forming a ferrioxamine (FO) complex. Urinary iron excretion of FO is predominantly a reflection of iron derived from plasma turnover whereas faecal iron reflects mainly intrahepatic iron chelation. Iron can be chelated from ferritin and haemosiderin, but this is relatively slow at

clinically relevant concentrations of DFO. DFO does not remove iron from transferrin, haemoglobin or from other haemin-containing substances.

Deferoxamine has a dose-dependent effect on serum ferritin, liver iron concentration and iron excretion rate.

DFO can also mobilize and chelate aluminium, forming an aluminoxamine complex.
Since the complexes with iron and aluminium are completely excreted, DFO promotes the excretion of iron and aluminium in the urine and faeces, and thus reduces pathological iron or aluminium deposits in the organs.

Clinical efficacy
See "Pharmacodynamics"

11. Pharmacokinetics

Absorption
DFO is rapidly absorbed following intramuscular bolus injection or slow subcutaneous infusion, in contrast, it 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 µmol/litre (8.7 µg/ml) were measured 30 minutes after an intramuscular injection of 10 mg/kg DFO. One hour after injection the peak plasma concentration of ferrioxamine was 3.7 µmol/litre (2.3 µg/ml). After intravenous infusion of 2 g (about 29 mg/kg) of DFO to healthy volunteers for 2 hours, mean steady-state concentrations of 30.5 µmol/litre were reached. Distribution of DFO is very rapid with a mean half-life of 0.4 hours. Less than 10 % of DFO is bound to serum proteins *in vitro*.
DFO crosses the placenta, but it is not known whether it also passes into breast milk.

Metabolism

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

Elimination

Both DFO and the ferrioxamine complex are eliminated biphasically after intramuscular injection in healthy volunteers. DFO and the ferrioxamine complex have an apparent distribution half-life of 1 hour and 2.4 hours, respectively. The apparent terminal half-life is 6 hours for both. Within 6 hours of injection, 22% of the dose appears in the urine as DFO and 1% as the ferrioxamine complex.

Pharmacokinetics in special patient populations

In **patients with haemochromatosis**, peak plasma levels measured one hour after intramuscular injection of 10mg/kg DFO were 7.0 µmol/litre (3.9 µg/ml) for DFO, and 15.7 µmol/litre (9.6 µg/ml) for FO,. 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 thalassaemia**, steady-state plasma concentrations of 7.4 µmol/litre (4.1 µg/ml) were measured following intravenous infusion of 50 mg DFO per kg per 24 hours. 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 hours. Total plasma clearance was 0.5 litres/hour/kg and the volume of distribution at steady state was approx. 1.35 litres/kg. In terms of AUC, levels of the main iron-binding metabolite were approx. 54% of those of DFO in terms of AUC. The apparent monoexponential elimination half-life of the metabolite was 1.3 hours.

In **renally impaired dialysis patients** who received 40 mg/kg DFO infused i.v. within one hour, the plasma concentration at the end of the infusion was 152 µmol/litre (85.2 µg/ml) when the infusion was given between two dialysis sessions. Plasma concentrations of DFO were between 13% and 27% lower

when the infusion was administered during dialysis. In all patients, plasma concentrations of ferrioxamine were about 7.0 µmol/litre (4.3 µg/ml), and those of aluminoxamine were about 2-3 µmol/litre (1.2-1.8 µg/ml). After the infusion was discontinued, the plasma concentration of DFO decreased rapidly with a half-life of 20 minutes. A small fraction of the dose was eliminated with a longer half-life of 14 hours. Plasma concentrations of aluminoxamine continued to increase for up to 48 hours after infusion and reached values of about 7 µmol/litre (4 µg/ml). Following dialysis the plasma concentration of aluminoxamine dropped to 2.2 µmol/litre (1.3 µg/ml).

12. Preclinical data

Subcutaneous administration of high doses of DFO to rats, dogs and cats for several weeks caused lens opacity with cataract formation.

There was no evidence that DFO had any genotoxic or mutagenic effects *in vitro* (Ames test) or *in vivo* (micronucleus test in rats). Long-term carcinogenicity studies have not been performed.

DFO was not teratogenic in rats or mice. In rabbit fetuses exposed *in utero* to maternally toxic doses, some malformations of the axial skeleton were found.

13. Other information

List of excipients:

Solvent: Water for injection

Incompatibilities
Heparin solution for injection.
Physiological saline (0.9%) should not be used as a solvent for the dry substance. It may, however, be used for further dilution after reconstitution of the Desferal solution with water for injection.

Effect on diagnostic tests
DFO interferes with the colorimetric determination of iron in blood and other body fluids. It may also interfere with the colorimetric determination of various active substances in the urine.

*Shelf life*The expiry date of the product is indicated on the packaging materials

Special precautions for storage
Do not store above 25°C. protect from light
Keep out of the reach of children.

One Desferal vial is for single use only and should be used immediately after reconstitution (commencement of treatment within 3 hours). When reconstitution is carried out under validated aseptic conditions, the reconstituted solution may be stored at room temperature for a maximum of 24 hours before administration.
Use immediately after dilution with routinely employed infusion solutions.

Nature and content of container:
1 vial contains powder for solution for injection (dry active substance for injection)
Each box contains 10 vials
Instructions for use and handling

When administered parenterally (i.v. and s.c.), the drug should preferably be used as a 95 mg/ml solution in water for injection, except for i.m. injection, where a higher concentration may be necessary. 5 ml water for injection is injected into the vial containing 500 mg Desferal powder. If there is no option other than intramuscular injection, a 213 mg/ml solution in water for injection should preferably be used. 2 ml water for injection is injected into the vial containing 500 mg Desferal powder — and the vial is shaken thoroughly (see "Dosage / Administration"). Only clear and colourless to slightly yellowish solutions may be used.

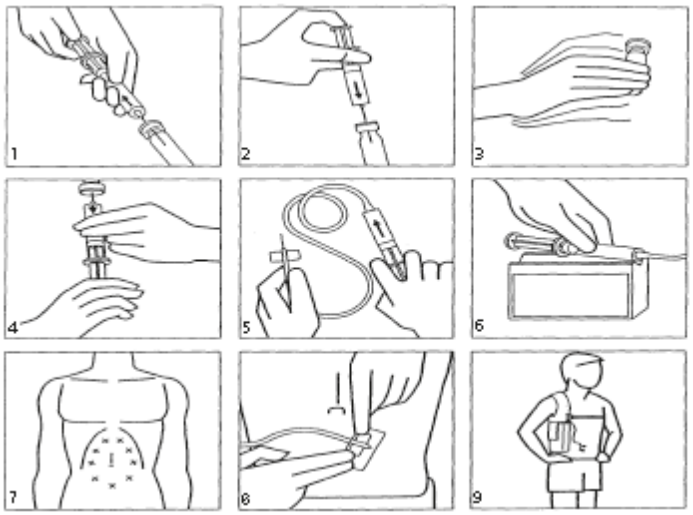
The 95 mg/ml Desferal solution after reconstitution,may be further diluted with standard infusion solutions (0.9% NaCl, 5% glucose, Ringer’s solution, Ringer’s lactate solution, peritoneal dialysis solutions such as Dianeal PD4 [2.27% glucose] and CAPD/DPCA 2 [1.5% glucose]).

For the Desferal infusion test and the treatment of chronic aluminium overload, the 5.3 ml Desferal solution in the 500 mg vial is an adequate dose (5 mg/kg) for a patient with 100 kg body weight (see "Dosage / Administration"). The appropriate amount of Desferal solution for the patient body weignt is withdrawn from the vial and added to 150 ml 0.9% saline solution.
The medicinal product may only be mixed with the solutions specified above.

Administration by means of a portable infusion pump is appropriate for the long-term treatment of patients with iron overload. Instructions for preparation of the solution and for administration are as follows:

1. Draw the water for injection into a syringe.
2. Clean the rubber stopper of the Desferal vial with alcohol, and inject the contents of the syringe (cf. 1) into the vial.
3. Shake the vial vigorously to dissolve the powder.
4. Draw the resulting solution into the syringe.
5. Attach one end of the extension tube to the syringe, connect the other end to the butterfly-type needle, and fill the empty space in the tube with the solution in the syringe.
6. Place the syringe in the infusion pump.
7. To give the infusion, insert the butterfly-type needle under the skin (subcutaneously). The site chosen can be on the abdomen, arm or thigh. Before inserting the needle, the site might first be thoroughly disinfected with alcohol. Insert the needle firmly up to the wings into a fold of skin formed by your free hand. The tip of the needle should move freely when the needle is waggled. If this is not the case, the tip of the needle may be too close to the surface of the skin. Insertion should then be reattempted at a new site after disinfection with alcohol.
8. When the needle is correctly positioned (i.e. moves freely), it should be fixed in place using adhesive tape.

Patients usually carry the pump on their body using a belt or shoulder strap. Many patients find overnight use most convenient.



Do not use after the expiry date (= EXP) printed on the pack.

14. Manufacturer:

Wasserburger Arzneimittelwerk GmbH, Wasserburg, Germany
for Novartis Pharma AG, Basel, Switzerland.

15. Registration Holder:

Novartis Israel Ltd., P.O.B 7126, Tel Aviv.

License number: 107-07-21532

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