NOVARTIS

DESFERAL® 500 VIALS

(desferrioxamine mesylate)

Powder for solution for injection

Professional Information

Document status: Final

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SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

DESFERAL® 500 VIALS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Vials containing 500 mg dry active substance, desferrioxamine mesylate.

3. PHARMACEUTICAL FORM

White to cream coloured, odourless lyophilised powder in vials of 500 mg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications.

1. *Therapeutic:*

i. Iron overload:

DESFERAL is of value in increasing urinary excretion of iron in conditions associated with excessive iron storage in the tissues such as haemochromatosis in patients in whom concomitant disorders (e.g. severe anaemia, cardiac disease, hypoproteinaemia) preclude phlebotomy; haemosiderosis, and in iron overload following repeated transfusions e.g. thalassaemia.

Note: Iron excretion must be determined before and after vitamin C administration (see section 4.5).

ii. Acute iron poisoning:

iii. 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.

2. Diagnostic:

For the diagnosis of iron-storage disease or aluminium overload.

DESFERAL test:

This test is based on the principle that in normal subjects, DESFERAL is incapable of raising iron and aluminium excretion above a certain limit.

i. DESFERAL test in patients with normal kidney function:

500 mg DESFERAL should be injected intramuscularly. The urine should then be collected for a period of six hours and its iron content determined. An excretion of 1 to 1,5 mg of iron (18 to 27µmol) during this six-hour period is suggestive of an iron overload; values of more than 1,5 mg (27 µmol) may be regarded as pathological. This test yields reliable results only in cases where renal function is normal.

ii. *DESFERAL infusion test for aluminium overload in end-stage renal failure patients:*

A DESFERAL infusion test is recommended in patients with serum aluminium levels exceeding 60 ng/ml associated with serum ferritin levels above 100 ng/ml. Just before starting a haemodialysis session, a blood sample is taken to determine the serum aluminium level.

During the last 60 minutes of the haemodialysis session, a 5 mg/kg dose (see section 6.6).

At the start of the next haemodialysis session (i.e. 44 hours after the aforementioned DESFERAL infusion), the second blood sample is taken to determine the serum aluminium level once more. The DESFERAL test is considered positive if the increase in serum aluminium above the baseline level exceeds 150 ng/ml. A negative test, however, does not absolutely exclude the diagnosis of aluminium overload.

4.2 Posology and method of administration

i. 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 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.

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 >1000 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.

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 overload. 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 (micrograms/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 2000 ng/ml require about 25 mg/kg/day. Patients with 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 **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 1000 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.

Prolonged regular chelation with DESFERAL has been shown to improve life expectancy in patients with thalassaemia major.

Slow subcutaneous administration:

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).**

Geriatric patients (aged 65 years and above)

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 medicine therapy (see sections 4.4 and 4.8).

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. for 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 medicine 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 section 4.4).

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 4.4).

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 oxidises 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 4.4). 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.

ii. 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, hypovolaemia, 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 µg/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 µg/dL range in asymptomatic patients, as well as in those with self-limited, non-bloody emesis or diarrhoea 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 (for both children and adults) 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 µg/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-rose coloured urine with DESFERAL therapy, the urine colour should return to normal before halting DESFERAL (absence of vin-rose 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 ferrioxamine is excreted from the body. If oliguria or anuria develops, peritoneal dialysis, haemodialysis, or haemofiltration may become necessary.

iii. TREATMENT FOR CHRONIC ALUMINIUM OVERLOAD IN PATIENTS WITH END-STAGE RENAL FAILURE

The iron and aluminium complexes are dialysable. 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. This is particularly the case if bone biopsy findings present evidence of aluminium.

DESFERAL should be administered in a once-weekly 5 mg/kg dose (see section 6.6). For patients with post-desferrioxamine 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- desferrioxamine 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.

4.3 Contraindications

Known hypersensitivity to the active substance, except where successful desensitisation makes treatment possible. Three adult cases and one paediatric case of successful desensitisation has been described in the literature.

Pregnancy and lactation, as teratogenicity has been shown in animals.

4.4 Special warnings and precautions for use

Rapid intravenous infusion

Rapid intravenous infusion may lead to hypotension and shock e.g. flushing, circulatory collapse and urticaria.

Visual and hearing impairment

High doses of DESFERAL, especially in patients with low ferritin plasma levels, may lead to disturbances of vision and hearing. Patients with renal failure who are on maintenance dialysis and have low ferritin levels may be particularly prone to adverse reactions, visual 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.

Special 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 may be reduced in thalassemia patients if the ratio of the mean daily dose (mg/kg) of DESFERAL divided 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 severe renal failure. The iron and aluminium complexes of desferrioxamine are dialysable; their elimination will be increased by dialysis in patients with renal failure.

Isolated cases of acute renal failure have been reported (see section 4.8). Monitoring patients for changes in renal function (e.g. increased serum creatinine) should be considered.

Paediatrics: growth retardation

Patients with low serum ferritin levels on high doses of DESFERAL, or young patients (< 3 years at commencement of treatment) have been associated with growth retardation (see section 4.2). Growth retardation if associated with excessive doses of DESFERAL must be distinguished from growth retardation from iron overload. Growth retardation resulting from DESFERAL use

is rare if the dose is kept below 40 mg/kg. If growth retardation has been associated 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.

Paediatric patients receiving DESFERAL should be monitored for body weight and longitudinal growth every 3 months.

Acute respiratory distress

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 thalassaemic 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 and/or iron 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 other factors (such as dialysis, diabetes mellitus, disturbance of acid base balance, haematological malignancies, immunosuppressive medicines, or a compromised immune system) may play a role in the development of this infection.

Urine discolouration

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

Precautions related to use and handling

DESFERAL should not be given in doses higher than recommended. The medicine 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 Instructions for use). Where intramuscular use is the only option it may be necessary to use higher concentrations to facilitate the injection.

At the recommended concentration of 95 mg/mL, the reconstituted solution is clear and colourless to slightly yellowish. Only clear solutions should be used. Opaque or cloudy 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.

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 500 mg daily). Cardiac dysfunction 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 (See *Dosage and directions for use* **and** *Interactions*).
- Monitoring of cardiac function is advisable during such combined therapy.

Patients treated for chronic aluminum overload

In patients with aluminium-related encephalopathy, high doses of DESFERAL may exacerbate neurological dysfunction (seizures), probably owing to an acute increase in circulating aluminium (see section 4.8). DESFERAL may precipitate the onset of dialysis dementia. Pretreatment with clonazepam has been reported to prevent this neurological deterioration. Also, treatment of aluminium overload may result in hypocalcaemia and aggravation of hyperparathyroidism.

4.5 Interaction with other medicines and other forms of interaction

Concurrent treatment with DESFERAL and prochlorperazine, a phenothiazine derivative, may lead to temporary impairment of consciousness.

In patients with severe chronic iron-storage disease undergoing combined treatment with DESFERAL and high doses of vitamin C (more than 500 mg daily), impairment of cardiac function has been encountered (see section 4.4); this proved reversible when the vitamin C was withdrawn.

Gallium-67-imaging results may be distorted because of the rapid urinary excretion of DESFERAL bound gallium-67. Discontinuation of DESFERAL 48 hours prior to scintigraphy is advisable.

In patients with iron storage disease concomitant oral treatment with vitamin C (150 to 200 mg per day in adults, 50 mg/day in children under 10 years of age, 100 mg per day in older children) may enhance excretion of the iron complex in response to DESFERAL.

Pharmaceutical incompatibilities:

- heparin injectable solution should not be mixed through the same intravenous line.
- physiological saline (0,9 %) should not be used as a solvent for the dry substance,

but it can be employed after reconstitution with water for further dilution.

4.6 Pregnancy and lactation

Pregnancy

There is a limited amount of data on the use of DESFERAL in pregnant patients. Studies in animals (rabbits) have shown reproductive toxicity/teratogenicity. The risk to the fetus/mother is unknown. Safety in human pregnancy has not been established (see section 4.3).

Breastfeeding

DESFERAL passes into the breast milk and its use is best avoided in lactating women.

Because many medicines are excreted in human milk, and because of the potential for serious adverse reactions in breast-fed newborns/infants, a decision should be made whether to abstain from breastfeeding or to abstain from using the medicine, taking into account the importance of the medicine to the mother.

4.7 Effects on ability to drive and use machines

Patients experiencing dizziness or other central nervous disturbances, or impairment of vision or hearing, should refrain from driving a vehicle or operating machinery (see section 4.8).

4.8 Undesirable effects

Adverse reactions from (Table 1) are listed by MedDRA system organ classes. Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent first. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse reaction is based on the following convention (CIOMS III): 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; “not

known" (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 a manifestations of the underlying disease (iron and/or aluminium overload).

Table 1- Adverse reactions reported from clinical studies, post-marketing experience and laboratory findings

Infections and infestations	
Rare:	Mucormycosis
Very rare:	Gastroenteritis Yersinia
Blood and lymphatic system disorders	
Very rare:	Blood disorder (incl. thrombocytopenia, leukopenia)
Immune system disorders	
Very rare:	Anaphylactic shock, anaphylactic reaction, angioedema
Nervous system disorders	
Common:	Headache

Very rare:	Neurological disturbances including dizziness, encephalopathy*, neuropathy peripheral, paraesthesia
Not known:	Seizure (see Special remarks below)
Eye disorders	
Rare: optic neuritis,	Loss of vision, retinal degeneration, cataracts, visual acuity reduced, vision, blurred vision, night blindness, visual field defects, chromatopsia, corneal opacities,
Ear and labyrinth disorders	
Uncommon:	Deafness, tinnitus
Vascular disorders	
Rare:	Hypotension, tachycardia and shock**

Respiratory, thoracic and mediastinal disorders

Uncommon:	Asthma
Very rare:	Acute respiratory distress syndrome, lung infiltration

Gastrointestinal disorders

Common:	Nausea
Uncommon:	Vomiting, abdominal pain
Very rare:	Diarrhoea

Skin and subcutaneous tissue disorders

Common:	Urticaria
Very rare:	Rash

Musculoskeletal and connective tissue disorders

Very common:	Arthralgia, myalgia
Common:	Growth retardation, bone disorder (metaphyseal dysplasia***)
Not known:	Muscle spasms

Renal and urinary disorders

Not known:	Acute kidney injury, renal tubular disorder

General disorders and administration site conditions	
Very common:	Injection site reaction, injection site pain, injection site swelling, injection site extravasation, injection site erythema, injection site pruritus, injection site scab (see Special remarks below)
Common:	Pyrexia
Uncommon:	Injection site vesicles, injection site oedema
Investigations	
Not known:	Blood creatinine increased

** precipitation or exacerbation of aluminum-related dialysis encephalopathy*

*** if precautions for administration are not adhered to (see sections 4.2 and 4.4)*

****in higher doses and young children (see section 4.4 and 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 the serum ferritin should be below 0,025) (see section 4.4).

The various eye disorders are rare, except if high doses are given (see section 4.4).

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/crust are very common, while vesicles, local oedema 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).

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

Seizures have mainly been reported in dialysed patients with aluminum overload (see section 4.4).

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

Patients treated for chronic aluminum overload:

DESFERAL chelation therapy for aluminium overload may result in hypocalcaemia and aggravation of hyperparathyroidism (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after administration of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked

to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/

4.9 Overdose

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 4.8) 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 thalassaemic patients (see section 4.4).

Treatment:

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

DESFERAL is dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 27 Chelating agents (versenates) as heavy metal antidotes

Desferrioxamine mesylate is a chelating agent which forms complexes predominantly with trivalent iron and aluminium ions. The complexes are excreted mainly via the kidneys.

Desferrioxamine mesylate increases the excretion of iron and aluminium and thus reduces iron and aluminium overload, by rapid excretion of the ferrioxamine and aluminoxamine complexes mainly in the urine, but also in the faeces.

It is capable of taking up iron from ferritin, and haemosiderin and only to a small extent from transferrin, thereby forming the iron complex ferrioxamine. Desferrioxamine mesylate, however, does not remove iron from haemoglobin or from other haem-containing substances in the body such as myoglobin and iron-containing enzymes (cytochrome, catalase, and peroxidases).

Desferrioxamine mesylate also mobilises and chelates tissue-bound aluminium, forming aluminoxamine complexes. Chelation occurs on a 1:1 molar basis, therefore 1 g DESFERAL binds 85 mg ferric ion or 41 mg Al3.

5.2 Pharmacokinetic properties

Absorption:

Desferrioxamlne mesylate is rapidly absorbed by the intramuscular and subcutaneous route, but only poorly absorbed from the gastrointestinal tract in the presence of an intact mucosa. During peritoneal dialysis desferrioxamine mesylate is absorbed from the dialysis fluid.

Distribution:

Its serum protein-binding rate is less than 10 %. In healthy subjects and in patients with transfusion induced iron overload, plasma concentrations of between 80 and 130 µmol/liter were recorded 3 minutes after an intravenous injection of desferrioxamine (10 mg/kg), these concentrations falling to one-half within 5 to 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 to formation of the iron complex ferrioxamine (which already commences within a few minutes and the extent of which depends on the individuals iron status) and to metabolic transformation.

During continuous subcutaneous infusion of desferrioxamine (100 mg/kg in 24 ml sterile water at a rate of 1 ml per hour), the plasma concentrations of desferrioxamine and ferrioxamine in healthy subjects and in patients have been shown to rise, depending on the subjects individual iron status (serum ferritin concentrations) to a plateau after 6 or, more frequently, after 12 hours. The 48 hour urinary excretion is higher in patients than in healthy subjects. In patients with iron overload, the increase in iron excretion occurring in response to desferrioxamine can be expected to be roughly just as high in the faeces as in the urine.

Biotransformation:

Four metabolites of desferrioxamine were isolated and identified from urine of patients with iron overload.

Elimination:

Desferrioxamine is primarily eliminated by the kidneys.

Characteristics in patients:

In patients with haemochromatosis peak plasma levels of 7,0 micromol/L (3,9 micrograms/ml were measured for desferrioxamine, and 15,7 micromol/L (9,6 micrograms/ml) for ferrioxamine, 1 hour after an intramuscular injection of 10 mg/kg desferrioxamine. These patients eliminated desferrioxamine and ferrioxamine with half-lives of 5,6 and 4,6 hours, respectively.

In patients dialysed for renal failure who received 40 mg/kg desferrioxamine infused i.v. within 1 hour, the plasma concentration at the end of the infusion was 152 micromol/L (85,2 micrograms/mL) when the infusion was given between dialysis sessions. Plasma concentrations of desferrioxamine were between 13 % and 27 % lower when the infusion was administered during dialysis.

Concentrations of ferrioxamine were in all cases approximately 7,0 micromol/L (4,3 micrograms/ml); and for aluminoxamine 2 to 3 micromol/L (1,2 to 1,8 micrograms/mL). After the infusion was discontinued, the plasma concentration of desferrioxamine decreased rapidly. A smaller fraction of the dose was eliminated with a longer half-life of 14 hours. The plasma concentration of aluminoxamine continued to increase for up to 48 hours after the infusion and reached values of approximately 7 micromol/L (4 micrograms/mL). Following dialysis the plasma concentration of aluminoxamine dropped to 2,2 micromol/L (1,3 micrograms/mL).

Clinical studies:

Desferrioxamine was used as a comparator in a randomized, one-year clinical trial investigating the use of another iron chelator (deferasirox) in patients with beta-thalassemia and transfusional

hemosiderosis. A total of 290 patients were treated with subcutaneous Desferrioxamine at starting doses of 20 to 60 mg/kg for 5 days per week. The study showed a dose-dependent effect of Desferrioxamine on serum ferritin levels, liver iron concentration and iron excretion rate.

6. PHARMACEUTICAL PARTICULAR

6.1 List of excipients

None present.

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Once prepared, solutions of DESFERAL should be stored at room temperature (23 °C or below) for not longer than 24 hours.

6.5 Nature and contents of container

Each vial contains a white to practically white lyophilizate supplied in a clear glass vial in a pack size of 10 (500 mg).

6.6 Special precautions for disposal and other handling

When administered parenterally, the medicine should be used as a 95 mg/mL solution in water for injection except for i.m. injection where a higher concentration may be necessary.

Preparation of powder for solution for injection is given in Tables 2 and 3 for subcutaneous, intravenous and intramuscular administrations, respectively. After the appropriate amount of water for injection is injected into the vial containing DESFERAL powder, the vial is shaken well. Only clear and colourless to slightly yellowish solutions should be used (see section 4.4).

Table 2: 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 Medicine Content after Reconstitution	Final Concentration per mL after Reconstitution
500 mg	5 mL	500 mg/5,3 mL	95 mg/mL
2 grams	20 mL	2 grams/21,1 mL	95 mg/mL

Table 3: 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
500 mg	2 mL	500 mg/2,35 mL	213 mg/mL
2 grams	8 mL	2 grams/9,4 mL	213 mg/mL

The 95 mg/mL DESFERAL solution after reconstitution can be further diluted with routinely employed infusion solutions (NaCl 0,9 %, glucose 5 %, Ringers 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 %).

The DESFERAL solution should not be stored for longer than 24 hours at room temperature (23 °C or below).

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.

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).

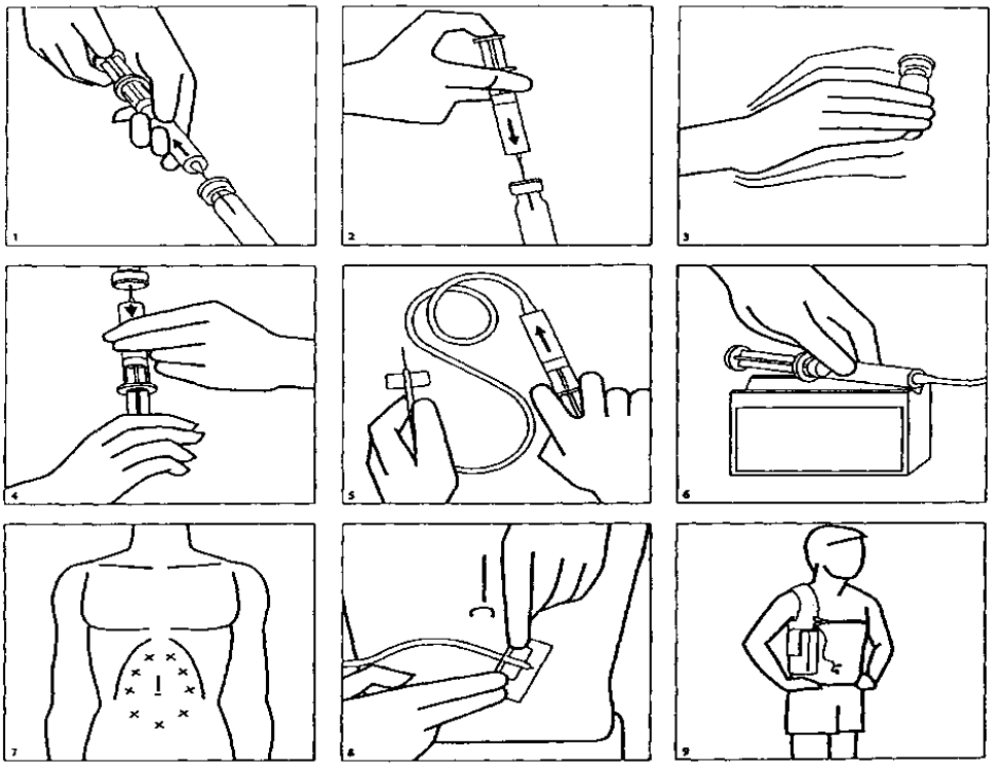
Dissolved DESFERAL can also be added to the dialysis fluid and given intraperitoneally to patients on CAPD or CCPD.

The use of DESFERAL in chronic iron overload by means of a portable infusion pump is as follows:

1. Draw the water for injection into a syringe.
2. After cleaning the rubber stopper of the DESFERAL vial with alcohol, inject the contents 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 syringe, 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 waggled. If it does not 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.



7. HOLDER OF CERTIFICATE OF REGISTRATION

NOVARTIS SOUTH AFRICA (PTY) LTD

Magwa Crescent West Waterfall City,

Jukskei View Johannesburg

2090

8. REFERENCE NUMBER

H2791 (Act 101/1965)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Not applicable.

10. DATE OF REVISION OF THE TEXT

10 August 2022

2009-PSB/GLC-0224-s, 2011-PSB/GLC-0374-s, CDS v2.0 and CDS v3.0