# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Desferal 500mg Vials Powder for Solution for Injection or Powder for Concentrate for Solution for Infusion

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 500mg deferoxamine mesilate.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Powder for solution for injection or powder for concentrate for solution for infusion.
White to practically white lyophilised powder.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

**Iron overload**

***Monotherapy iron chelation treatment of chronic iron overload***

- primary and secondary haemochromatosis including thalassaemia
- transfusional haemosiderosis; in patients in whom concomitant disorders (eg severe anaemia, hypoproteinaemia, renal failure) preclude phlebotomy.

Treatment of acute iron poisoning

For the diagnosis of iron storage disease and certain anaemias.

**Aluminium overload -** in patients under maintenance dialysis for end stage renal failure with aluminium-related bone disease and/or anaemia, dialysis encephalopathy; and for diagnosis of aluminium overload.

### 4.2 Posology and method of administration

**Treatment for chronic iron overload**

The main aim of chelation therapy in iron overload in young patients is to achieve an iron balance and to prevent haemosiderosis, while in the older patient a negative iron balance is desirable in order to reduce slowly the increased iron stores and to prevent the toxic effects of iron.

***Adults and children:*** Desferal therapy should be commenced after the first 10-20 blood transfusions, or when serum ferritin levels reach 1,000 ng/mL. Growth retardation may result from iron overload or excessive Desferal doses. If chelation is begun before 3 years of age, growth must be monitored carefully and the mean daily dose should not exceed 40mg/kg.

The dosage and mode of administration may be individually adapted according to the degree of iron overload. The lowest effective dosage should be used. To assess the response to chelation therapy, 24 hour urinary ironexcretion may initially be monitored daily and the response to increasing doses of Desferal established. Once the appropriate dosage has been established, urinary iron excretion may be assessed at intervals of a few weeks.

Alternatively, the mean daily dose may be adjusted according to the ferritin value to keep the therapeutic index less than 0.025 (i.e. mean daily dose (mg/kg) of Desferal divided by the serum ferritin level (μg/L) below 0.025. The average daily dose of Desferal is usually between 20-60mg/kg. The therapeutic index is a valuable tool in protecting the patient from excess chelation, but it is not a substitute for careful clinical monitoring.

In general patients with a serum ferritin level of < 2,000ng/mL require about 25mg/kg/day and those with a 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 inadvisable 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 values 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 given are the average daily dose. Since most patients take the drug 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 thalassaemia.

**Slow subcutaneous infusion**

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

**Geriatric patients (aged 65 years and above)**

Use in the elderly: No special dosage regime is necessary but concurrent renal insufficiency should be taken into account.
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 sections 4.4 Special Warnings and precautions for use and 4.8 Undesirable effects).

**Hepatic impairment**

No studies have been performed in patients with hepatic impairment.

**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 to avoid the sudden infusion of residual Desferal which may be present in the dead space of the line, as this may lead to acute collapse (see section 4.4 Special warnings and precautions for use).

**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 circulatory collapse (see section 4.4 Special Warnings and precautions for use).

**Intramuscular administration:**

Since the 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 selected will depend on the patient's iron excretion rate.

**Concomitant use of vitamin C:**

Patients with iron overload usually become vitamin C deficient, 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 4.5 Interactions with other medicaments and other forms of interaction). Vitamin C increases 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 excretion of the iron complex.

**Acute iron poisoning:**

Desferal may be administered parenterally. Desferal is an adjunct to standard measures generally used in treating acute iron poisoning. It is important to initiate treatment as soon as possible.

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 to develop symptomatic iron poisoning).

Any symptomatic patient with a serum iron level greater than 300-350µg/dL regardless of the 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 300-500 µg/dL range in asymptomatic patients, as well as in those with self-limited, non-bloody emesis or diarrhoea without other symptoms.

**Dosage:**

The continuous intravenous administration of Desferal is the preferred route and the recommended rate for infusion is 15mg/kg/hour and should be reduced as soon as the situation permits, usually after 4-6 hours so that the total intravenous dose does not exceed a recommended 80mg/kg in any 24-hour period.

The following suggested criteria are believed to represent appropriate requirements for the 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 (when iron levels fall below 100µg/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 the measured serum iron concentration 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 coloured urine with Desferal therapy, it seems reasonable that urine colour should return to normal before halting Desferal (absence of vin-rosé urine is not sufficient by itself to indicate discontinuation of Desferal).The effectiveness of treatment is dependent on an adequate urine output in order that the iron complex (ferrioxamine) is excreted from the body. Therefore, if oliguria or anuria develop, peritoneal dialysis, haemodialysis or haemofiltration may become necessary to remove ferrioxamine.

It should be noted that the serum iron level may rise sharply when the iron is released from the tissues. Theoretically 100mg Desferal can chelate 8.5mg of ferric iron.

**Diagnosis of iron storage disease and certain anaemias:**

The Desferal test for iron overload is based on the principle that normal subjects do not excrete more than a fraction of a milligram of iron in their urine daily and a standard intramuscular injection of 500mg of Desferal does not increase this above 1mg. In iron storage diseases, however, the increase may be well over 1.5mg. The test yields reliable results only when renal function is normal.

Procedure:

1. The haemoglobin, serum iron and total iron binding capacity are estimated.
2. 500mg of Desferal are given intramuscularly and 400ml of water are drunk.
3. All urine is collected over the next six hours.
4. The urinary iron is estimated in the six hour urine specimen.

An excretion of 1-1.5mg (18-27μmol) of iron during this 6-hour period is suggestive of an iron-storage disease; values of more than 1.5mg (27μmol) can be regarded as pathological.

**Treatment for aluminium overload in patients with terminal renal failure:**

The iron and aluminium complexes of Desferal are dialysable. In patients with renal failure, their elimination will be increased by dialysis.

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 60ng/mL and are associated with a positive Desferal infusion test, particularly if bone biopsy findings present evidence of aluminium-related bone disease.

**Patients on maintenance haemodialysis or haemofiltration:**

5 mg/kg once a week. Patients with post-deferoxamine test serum aluminium levels up to 300ng/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-deferoxamine test serum aluminium value above 300 ng/mL Desferal should be administered by slow i.v. infusion 5 hours prior to the dialysis session.

Four weeks after completion of a three month course of Desferal treatment, a Desferal infusion test should be performed, followed by a second test 1 month later. Serum aluminium increases above baseline of less than 50 ng/ml measured in 2 successive infusion tests indicate that further Desferal treatment is not necessary.

**Patients on Continuous Ambulatory Peritoneal Dialysis [CAPD] or Continuous Cyclic Peritoneal Dialysis [CCPD]:**

5mg/kg once a week prior to the final exchange of the day. It is recommended that the intraperitoneal route be used in these patients. However, Desferal can also be given i.m., by slow infusion i.v. or s.c.

Desferal should be employed in dialysis patients only when symptoms demand treatment and when patients can be monitored regularly for toxicity.

**Diagnosis of aluminium overload:**

A Desferal infusion test is recommended in patients with serum aluminium levels exceeding 60ng/mL associated with serum ferritin levels above 100 ng/mL.
Just before starting a haemodialysis session, a blood sample is taken to determine the baseline serum aluminium level. During the last 60 minutes of the haemodialysis session, a 5mg/kg dose is given as a slow intravenous infusion.

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 an increase in serum aluminium above the baseline level exceeds 150ng/mL. A negative test, however, does not absolutely exclude the diagnosis of aluminium overload. Theoretically 100mg Desferal can bind 4.1mg $Al^{+++}$.

## 4.3 Contraindications

Known hypersensitivity to deferoxamine mesilate unless the patient can be desensitised.

## 4.4 Special warnings and precautions for use

*Renal Impairment*

Desferal should be used with caution in patients with renal dysfunction since the metal complexes are excreted mainly via the kidneys. In these patients, dialysis will increase the elimination of chelated iron and aluminium. Monitoring patients for changes in renal function (e.g. increased serum creatinine) should be considered.
Used alone Desferal may exacerbate neurological dysfunction in patients with aluminium-related encephalopathy. This deterioration (manifest as seizures) is probably related to an acute increase in brain aluminium secondary to elevated circulating levels**.** Desferal may precipitate the onset of dialysis dementia.

Pre-treatment with clonazepam has been shown to afford protection against such dysfunction. Also, treatment of aluminium overload may result in decreased serum calcium and aggravation of hyperthyroidism.

Treatment with Desferal by the intravenous route should only be administered in the form of slow infusions. Rapid intravenous infusion may lead to hypotension and shock (e.g. flushing, tachycardia, collapse and urticaria). If an intramuscular injection is accidentally given intravenously, this may lead to circulatory collapse.

Desferal should not be administered subcutaneously in concentrations and/or doses higher than those recommended [95 mg/ml], otherwise local irritations at the site of administration may occur more frequently. Where intramuscular use is the only option, it may be necessary to use higher concentrations to facilitate the injection.
For subcutaneous infusion, the needle should not be inserted too close to the dermis.

Patients suffering from iron overload are particularly susceptible to infection. There have been reports of Desferal promoting some infections such as Yersinia enterocolitica and Y.pseudotuberculosis. If patients develop fever with pharyngitis, diffuse abdominal pain or enteritis/enterocolitis, Desferal therapy should be stopped, and appropriate treatment with antibiotics should be instituted. Desferal therapy may be resumed once the infection has cleared.

In patients receiving Desferal for aluminium and/or iron overload, very rare cases of zygomycosis, a severe fungal infection have been reported. If any of the characteristic signs or symptoms occur, desferral should be discontinued, mycological tests carried out and appropriate treatment instituted immediately. Zygomycosis may also occur in patients who are not receiving Desferal, indicating that other factor determinants such as dialysis, diabetes mellitus, disturbance of acid-base balance, haematological malignancies, immunosuppressive drugs, or a compromised immune system may play a role in the development of this infection.

Disturbances of vision and hearing have been reported during prolonged Desferal therapy. In particular this has occurred in patients on higher than recommended therapy or in patients with low serum ferritin levels.

Patients with renal failure who are receiving maintenance dialysis and have low ferritin levels may be particularly prone to adverse reactions, visual symptoms having been reported after single doses of Desferal. Therefore, ophthalmological and audiological tests should be carried out both prior to the institution of long-term therapy with Desferal and at 3-monthly intervals during treatment particularly if ferritin levels are low. By keeping the ratio of the mean daily dose (mg/kg) of Desferal divided by the serum ferritin µg/L) below 0.025 the risk of audiometric abnormalities may be reduced in thalassaemia patients.

If disturbances of vision or hearing do occur, treatment with Desferal should be stopped. Such disturbances may be reversible. If Desferal therapy is reinstituted later at a lower dosage, close monitoring of ophthalmological/ auditory function should be carried out with due regard to the risk-benefit ratio.

The use of inappropriately high doses of Desferal in patients with low ferritin levels or young children (<3 years at commencement of treatment) has also been associated with growth retardation. Growth retardation if associated with excessive doses of Desferal must be distinguished from growth retardation from iron overload.

Growth retardation 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 the reduction of the dose may result in a return in growth velocity, however predicted adult height is not attained. Three monthly checks on body weight and height are recommended in children.

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.

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

There is evidence that aluminium intoxication causes reduced erythropoiesis. In dialysed patients with aluminium and/or iron overload treated with desferrioxamine and erythropoietin some dosage adjustment of the latter may be necessary. Regular monitoring of iron stores should be carried out.

**Precautions related to 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 6.6).

Where intramuscular use is the only option it may be necessary to use higher concentrations to facilitate the injection (see section 6.6).

At the recommended concentration of 95 mg/mL, the reconstituted solution is clear, and colorless 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.

## 4.5 Interaction with other medicinal products and other forms of interaction

Oral administration of vitamin C up to a maximum of 200mg daily, given in fractional doses, may serve to enhance excretion of the iron complex in response to Desferal. In general, 50mg suffices for children under 10 years of age and 100mg for older children. Larger doses of vitamin C fail to produce an additional effect.

Vitamin C should not be administered within the first month of starting regular Desferal therapy. In patients with severe chronic iron-storage disease undergoing combined treatment with Desferal and high doses of vitamin C (more than 500mg daily) impairment of cardiac function has been encountered; this proved reversible when the vitamin C was withdrawn.

The following precautions should be taken when Desferal and Vitamin C are to be used concomitantly:

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

Desferal should not be used in combination with prochlorperazine (a phenothiazine derivative) since prolonged unconsciousness may result.

Gallium-67-imaging results may be distorted because of the rapid urinary excretion of Desferal-bound radiolabel. Discontinuation of Desferal 48 hours prior to scintigraphy is advised.

## 4.6 Fertility, pregnancy and lactation

*Pregnancy*
There is a limited amount of data on the use of desferrioxamine in pregnant patients. Studies in animals (rabbits) have shown reproductive toxicity/teratogenicity (see section 5.3 ). The risk to the foetus/mother is unknown.

Desferal should be used during pregnancy only if the expected benefits to the mother outweigh the potential risk to the foetus.

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

## 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 machines.

## 4.8 Undesirable effects

***(The following frequency estimates are used: Very common (1/10); common (1/100 to <1/10); uncommon (1/1,000 to <1/100); rare (1/10,000 to <1/1,000); very rare (<1/10,000).***

Some signs and symptoms reported as adverse effects may also be manifestations of the underlying disease (iron and/or aluminium overload).
The ADRs reported from clinical studies, post-marketing experience and laboratory findings.

**Infections and infestations**
Rare: *Zygomycosis*
Very rare: *Gastroenteritis yersinia*

**Blood and lymphatic system disorders**
Very rare: blood disorders including thrombocytopenia
Unknown: leukopenia

**Immune system disorders**
Very rare: anaphylactic shock, anaphylactic reactions, Angioedema.

**Nervous system disorders**
Very rare: neurological disturbances, including dizziness, neuropathy peripheral, paraesthesia (see section 4.4).
Unknown: convulsion.

**Eye disorders**
Rare: loss of vision, retinal degeneration, optic neuritis, cataracts (visual acuity reduced), vision blurred, night blindness, visual field defect, chromatopsia corneal opacity

**Ear and labyrinth disorders**
Uncommon: deafness neurosensory, 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 generalised.

**Musculoskeletal and connective tissue disorders**
Very common: Arthralgia, myalgia
Common: growth retardation, bone disorder (metaphyseal dysplasia)
Unknown: muscle spasms.

**Renal and urinary disorders**
Unknown: Renal failure, 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
Common: Pyrexia.
Uncommon: Injection site reaction, injection site vesicles, injection site oedema, injection site burning

**Investigations**
Unknown: Blood creatinine increased

**Special remarks**
At the injection site pain, swelling, infiltration, erythema, pruritus and eschar/crust are very common; vesicles, local oedema and burning are uncommon reactions. The local manifestations may be accompanied by systemic reactions like arthralgia/myalgia (very common), headache (common), urticaria (common), nausea (common), pyrexia (common), vomiting (uncommon), or abdominal pain (uncommon) or asthma (uncommon).

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

**Patients treated for chronic aluminum overload**

Desferal chelation therapy aluminum overload may result in hypocalcemia and aggravation of hyperparathyroidism (see section 4.4).

**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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; Email: medsafety@hpra.ie.

## 4.9 Overdose

Desferal is usually administered parenterally and acute poisoning is unlikely to occur, (daily doses of 16g Desferal given by iv infusion have been well tolerated).

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 4.4).

Signs and symptoms: Tachycardia, hypotension and gastrointestinal symptoms have occasionally occurred in patients who received an overdose of Desferal. Accidental administration of desferal by the IV route may be associated with acute but transient loss of vision, aphasia, agitation, headache, nausea, bradycardia, and acute renal failure.

Treatment: There is no specific antidote. Desferal should be discontinued and appropriate symptomatic measures instituted. Desferal is dialysable.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Chelating agent (ATC code: V03ACO1).

Mechanism of action

Desferal is a chelating agent for trivalent iron and aluminium ions. The resulting chelates (feroxamine and aluminoxamine) are stable and non-toxic.

Neither chelate undergoes intestinal absorption, and any formed systemically as a result of parenteral administration is rapidly excreted via the kidneys without deleterious effects. Desferal takes up iron either free or bound to ferritin and haemosiderin. Similarly it mobilises and chelates tissue bound aluminium. It does not remove iron from haemin containing substances including haemoglobin and transferrin. Since both feroxamine and aluminoxamine are completely excreted, Desferal promotes the excretion of iron and aluminium in urine and faeces thus reducing pathological iron or aluminium deposits in the organs and tissues.

## 5.2 Pharmacokinetic properties

**Absorbtion**
Deferoxamine is rapidly absorbed following intramuscular bolus or slow subcutaneous infusion but 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 of Deferoxamine.

During peritoneal dialysis deferoxamine is absorbed if administered in the dialysis fluid.

**Distribution**
In healthy volunteers peak plasma concentrations of deferoxamine (15.5µmol/litre - 8.7µg/ml) and ferrioxamine (3.7µmol/litre - 2.3µg/ml) were observed at 30 minutes and 1 hour respectively, following an injection (10mg/kg) of deferoxamine. After intravenous infusion of 2 g (about 29 mg/kg) deferoxamine to healthy volunteers over two hours, mean steady state concentrations of 30.5µmol/L were reached; distribution of deferoxamine is very rapid with a mean distribution half-life of 0.4hours.
Serum protein binding of deferoxamine is less than 10% in vitro.

**Biotransformation**
Four metabolites of deferoxamine were isolated from urine of patients with iron overload. The following biotransformation reactions were found with deferoxamine: transamination and oxidation yielding an acid metabolite, beta-oxidation also yielding an acid metabolite, decarboxylation and N-hydroxylation yielding neutral metabolites.

**Elimination**
Both deferoxamine and ferrioxamine have a biphasic elimination after intramuscular injection in healthy volunteers; for deferoxamine the apparent distribution half-life is 1 hour and for ferroxamine 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 deferoxamine and 1% as ferrioxamine.

**Characteristics in patients**
In patients with haemochromatosis peak plasma levels of 7.0µmol/litre (3.9µg/ml) were measured for desferrioxamine, and 15.7µmol/litre (9.6µg/ml) for ferrioxamine, 1 hour after intramuscular injection of 10mg/kg deferoxamine. These patients eliminated deferoxamine and ferrioxamine 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 deferoxamine and 12% as ferrioxamine.

In patients with thalassaemia, continuous intravenous infusion of 50 mg/kg/24 h of deferoxamine, resulted in plasma steady state levels of deferoxamine 7.4 µmol/L (4.1µg/ml). Elimination of deferoxamine 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 0.5L/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% and that of deferoxamine in terms of AUC. The apparent monoexponential elimination half-life of the metabolite was 1.3 hours.

**In patients dialysed for renal failure** who received 40mg/kg deferoxamine infused i.v. within 1 hour, the plasma concentration at the end of the infusion was 152 µmol/L (85.2µg/ml) when the infusion was given between dialysis sessions. Plasma concentrations of deferoxamine were between 13% and 27% lower when the infusion was administered during dialysis.

Concentrations of feroxamine were in all cases approx 7.0µmol/litre (4.3µg/ml) with concomitant aluminoxamine levels of 2-3 µmol/L (1.2-1.8 µg/ml). After the infusion was discontinued, the plasma concentration of deferoxamine decreased rapidly with a half-life of 20 minutes. A smaller fraction of the dose was eliminated with a longer half-life of 14 hours.

Plasma concentrations of aluminoxamine continued to increase for up to 48 hours post-infusion and reached values of approx 7µmol/litre (4µg/ml). Following dialysis the plasma concentration of aluminoxamine dropped to 2.2µmol/litre (1.3µg/ml), indicating that the aluminoxamine complex is dialysable.

During peritoneal dialysis deferoxamine is absorbed if administered in the dialysis fluid.

*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.

Desferrioxamine was also used as a comparator in a second open-label, randomized, 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 desferrioxamine at starting doses of 20 to 60 mg/kg at least 5 days per week. At the end of the study, the mean change in liver iron concentration (LIC) was -0.7 mg Fe/g dry weight.

## 5.3 Preclinical safety data

The subcutaneous administration of high doses of deferoxamine to rats, dogs and cats for several weeks caused eye-lens opacity with cataract formation. Deferoxamine did not show evidence of genotoxic/mutagenic effects in in vitro assays (Ames test) and in vivo assay (micronucleas test in rats). Long term carcinogenicity studies have not been performed.
Deferoxamine was not teratogenic in rats and mice. In rabbit fetuses, which were exposed in utero to a maternally toxic doses, some malformations of the axial skeleton were found. Though the results of this study are considered of a preliminary character, deferoxamine-induced teratogenicity in rabbits cannot be excluded under the experimental conditions employed.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Not applicable.

## 6.2 Incompatibilities

Heparin injectable solution.

Physiological saline (0.9%) should not be used as a solvent for the dry substance but, after reconstituion of the Desferal solution with water for injection, it can be used for further dilution.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

## 6.3 Shelf life

36 months.

Reconstituted solution: Single use only.
Chemical and physical in-use stability of the reconstituted solution has been demonstrated for 24 hours at 2-8°C
From a microbiological point of view, the product should be used immediately after reconstitution (commencement of treatment within 3 hours) and discard any remaining solution after use.
If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2-8°C when reconstitution has taken place in controlled and validated aseptic conditions.

## 6.4 Special precautions for storage

Do not store above 25°C.

For storage condition of the reconstituted solution see section 6.3.

## 6.5 Nature and contents of container

Type 1 Ph. Eur. clear, colourless, 7.5mg glass vials, with bromobutyl rubber closure and an AL/pp flip- off cap. Packs of 10 vials of Desferal 500mg.

## 6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Before parenteral administration (subcutaneous and intravenous), the preparation must be diluted with 5mL of water for injections Ph. Eur. to form a 95 mg/mL solution. The 95 mg/mL Desferal solution can be further diluted with routinely employed infusion solutions (NaCl 0.9%, glucose 5%, Ringer's solution Ringer's-lactate solution and peritoneal dialysis solutions such as Dianeal 137 Glucose 2.27%, DIANEAL PD4 Glucose 2.27% and CAPD/DPCA 2 Glucose 1.5%).

When administered intramuscularly, where a higher concentration may be necessary, the preparation must be diluted with 2ml of water for injections Ph. Eur. to form a 213 mg/mL solution.

Preparation of powder for solution for injection is given in Tables 6-1 and 6−2 for subcutaneous, intraveneous 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 colorless to slightly yellowish solutions should be used.

**Table 6-1: 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 |
| 500 mg | 5 mL | 500 mg/5.3 mL | 95 mg/mL |

**Table 6-2: Preparation for intramuscular 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 |
| 500 mg | 2 mL | 500 mg/2.35 mL | 213 mg/mL |

## 7 MARKETING AUTHORISATION HOLDER

Novartis Ireland Limited
Vista Building
Elm Park
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## 8 MARKETING AUTHORISATION NUMBER

PA0896/008/001

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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