Safeguarding public health

Public Assessment Report

Decentralised Procedure

Deferoxamine 500 mg Powder for Solution for Injection or Infusion

Deferoxamine 2 g Powder for Solution for Injection or Infusion

UK/H/3325/001-2/DC

UK licence no: PL 24598/0020-21

Noridem Enterprises Limited

LAY SUMMARY

On 14 March 2012, the Medicine and Healthcare products Regulatory Agency (MHRA) granted Noridem Enterprises Ltd., Marketing Authorisations (licences) for the medicinal products Deferoxamine 500 mg and 2 g Powder for Solution for Injection or Infusion (PL 24598/0020-21). These licences were granted via the decentralised procedure (UK/H/3325/001-2/DC), with the UK as the Reference Member State (RMS) and Cyprus, Germany, Greece and Italy as the Concerned Member State (CMS). These are prescription-only medicines (POM).

Deferoxamine Powder for Solution for Injection or Infusion is used to excess iron or aluminium from the blood. Deferoxamine Powder for Solution for Injection or Infusion contains the active ingredient deferoxamine mesilate and belongs to a group of substances called “chelating agents” which bind to the iron and aluminium in the blood to form a complex which is excreted from the body.

Excess iron or aluminium in the body maybe a result of iron poisoning, due to certain illness such as thalassaemia (ahereditary type of anaemia) and haemocromatosis (a disorder of iron metabolism) or as a side effect of blood transfusion or kidney dialysis.

Deferoxamine Powder for Solution for Injection or Infusion can also be used to test whether you have certain anaemias or diseases affecting the amount of iron in the blood.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Deferoxamine 500 mg and 2 g Powder for Solution for Injection or Infusion outweigh the risks; hence Marketing Authorisations have been granted.

TABLE OF CONTENTS

Module 1

Product Name	Deferoxamine 500 mg and 2 g Powder for Solution for Injection or Infusion
Type of Application	Generic, Article 10(1)
Active Substance	Deferoxamine mesilate
Form	Powder for Solution for Injection or Infusion
Strength	500 mg 2 g
Marketing Authorisation Holder	Noridem Enterprises Limited Evagorou and Makariou, Mitsi Building 3, Nicosia CY-1065 Cyprus
Reference Member State (RMS)	UK
Concerned Member State (CMS)	Cyprus, Germany, Greece and Italy
Procedure Number	UK/H/3325/001-2/DC
End of Procedure	8 February 2012

Module 2
SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Deferoxamine 500 mg Powder for Solution for Injection of Infusion (PL 24598/0020) is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Deferoxamine 500 mg Powder for Solution for Injection or Infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains deferoxamine mesilate 500 mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

A sterile, lyophilised powder available in vials containing 500mg of deferoxamine mesilate.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

• Treatment for chronic iron overload, e.g.

- transfusional haemosiderosis in patients receiving regular transfusions (e.g. thalassaemia major).
- primary and secondary haemochromatosis in patients in whom concomitant disorders (e.g. severe anaemia, hypoproteinaemia, renal or cardiac failure) preclude phlebotomy.

• Treatment for acute iron poisoning.

• For the diagnosis of iron storage disease and certain anaemias.

• Aluminium overload in patients on maintenance dialysis for end stage renal failure where preventative measures (e.g. reverse osmosis) have failed and with proven aluminium related bone disease and/or anaemia, dialysis encephalopathy; and for diagnosis of aluminium overload.

4.2 Posology and method of administration

Deferoxamine mesilate may be administered intramuscularly, intravenously, or subcutaneously. When administered subcutaneously the needle should not be inserted too close to the dermis.

The drug should preferably be employed in the form of a 10% solution, by dissolving the contents of a 500 mg vial in 5ml of water for injection.

The 10% Deferoxamine solution can be diluted with routinely employed infusion solutions (Sodium Chloride 0.9% Infusion, Dextrose 5% Infusion, combination of Sodium Chloride 0.9% and Dextrose 5% Infusion solutions, Ringer's Lactate), although these should not be used as solvent for the dry substance.
Dissolved Deferoxamine can also be added to dialysis fluid and given intraperitoneally to patients on continuous ambulatory peritoneal dialysis (CAPD) or continuous cyclic peritoneal dialysis (CCPD).

Treatment of acute iron poisoning

Adults and children:

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

Parenteral Deferoxamine treatment should be considered 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 radio-opacities (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 micro g/dL regardless of the total iron binding capacity (TIBC). It has also been suggested that a conservative approach without Deferoxamine therapy or challenge should be considered when serum iron levels are in the 300 to 500 micro g/dL range in asymptomatic patients, as well as in those with self-limited, non-bloody emesis or diarrhoea without other symptoms.

The dosage and route of administration should be adapted to the severity of the poisoning.

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

However, if the option to infuse intravenously is not available and if the intramuscular route is used the normal dosage is 2 g for an adult and 1g for a child, administered as a single intramuscular dose.

The decision to discontinue Deferoxamine therapy must be a clinical decision; however, the following suggested criteria are believed to represent appropriate requirements for the cessation of Deferoxamine. Chelation therapy should be continued until all of the following criteria are satisfied:

• the patient must be free of signs and symptoms of systemic iron poisoning (e.g. no acidosis, no worsening hepatoxicity).

• ideally, a corrected serum iron level should be normal or low (when iron level falls below 100 micro g/dL). Given that laboratories cannot measure serum iron concentrations accurately in the presence of Deferoxamine, it is acceptable to discontinue Deferoxamine 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 radio-opacities to ensure they have disappeared before Deferoxamine is discontinued because they serve as a marker for continued iron absorption.

• if the patient initially developed vin-rose coloured urine with Deferoxamine therapy, it seems reasonable that urine colour should return to normal before halting Deferoxamine (absence of vin-rose urine is not sufficient by itself to indicate discontinuation of Deferoxamine).

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 or haemodialysis 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 100 mg Deferoxamine can chelate 8.5 mg of ferric iron.

Chronic Iron Overload
The main aim of therapy in *patients with iron overload not complicated by toxic effects* is to achieve an iron balance and prevent haemosiderosis, whilst *in patients with severe iron overload* a negative iron balance is desirable in order to slowly deplete the increased iron stores and to prevent the toxic effects of iron.

Adults and children:
Deferoxamine therapy should be commenced after the first 10- 20 blood transfusions, or when serum ferritin levels reach 1000 ng/mL, indicating saturation of the transferrin. The dose and mode of administration should be individually adapted according to the degree of iron overload.

Growth retardation may result from iron overload or excessive Deferoxamine doses. If chelation is started before 3 years of age growth must be monitored carefully and the mean daily dose should not exceed 40mg/kg. (see section 4.4).
Dose:

The lowest effective dose should be used. The average daily dose will probably lie between 20 and 60 mg/kg/day. Patients with serum ferritin levels of < 2000 ng/mL should require about 25 mg/kg/day, and those with levels between 2000 and 3000 ng/mL about 35 mg/kg/day. Higher doses should only be employed if the benefit for the patient outweighs the risk of unwanted effects.

Patients with higher serum ferritin may require up to 55 mg/kg/day. It is inadvisable regularly to 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 1000 ng/mL, the risk of Deferoxamine toxicity increases; it is important to monitor these patients particularly carefully and perhaps to consider lowering the total weekly dose.

To assess the chelation therapy, 24 hour urinary iron excretion should initially be monitored daily. Starting with a dose of 500 mg daily the dose should be raised until a plateau of iron excretion is reached. Once the appropriate dose has been established, urinary iron excretion rates can 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 Deferoxamine divided by the serum ferritin level (mcg/L) below 0.025).
Mode of administration:
Slow subcutaneous infusion by means of a portable, light-weight, infusion pump over a period of 8-12 hours is effective and particularly convenient for ambulant patients. It may be possible to achieve a further increase in iron excretion by infusing the same daily dose over a 24 hour period. Patients should be treated 5-7 times a week depending on the degree of iron overload.
Deferoxamine is not formulated to be administered as a subcutaneous bolus.

Since the subcutaneous infusions are more effective, intramuscular injections are given only when subcutaneous infusions are not feasible.

Deferoxamine can be administered by intravenous infusion during blood transfusion.

Due to the small quantity of deferoxamine that can be administered by intravenous infusion during blood transfusion, the clinical benefit is limited.

The Deferoxamine 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 to the venous site of injection. The patient's pump should be used to administer Deferoxamine as usual. Patients and nurses should be warned against accelerating the infusion, as an intravenous bolus of Deferoxamine may lead to flushing, hypotension and acute collapse (see section 4.4).

Continuous intravenous infusion is recommended for patients incapable of continuing subcutaneous infusions and in those who have cardiac problems secondary to iron overload. 24 hour urinary iron excretion should be measured regularly where intensive chelation (i.v.) is required, and the dose adjusted accordingly. Implanted intravenous systems can be used when intensive chelation is carried out.

Care should be taken when flushing the line to avoid the sudden infusion of residual Deferoxamine which may be present in the dead space of the line, as this may lead to flushing; hypotension and acute collapse (see section 4.4).

Diagnosis of iron storage disease and certain anaemias

The Deferoxamine 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 that a standard intramuscular injection of 500 mg of Deferoxamine will not increase this above 1 mg (18 μmol). In iron storage diseases, however, the increase may be well over 1.5 mg (27 μmol). It should be borne in mind that the test only yields reliable results when renal function is normal.

Deferoxamine is administered as 500 mg intramuscular injection. Urine is then collected for a period of 6 hours and its iron content determined.

Excretion of 1-1.5 mg (18-27 μmol) of iron during this 6-hour period is suggestive of iron overload; values greater than 1.5 mg (27 μmol) can be regarded as pathological.

Treatment for aluminium overload in patients with end stage renal failure
Patients should receive Deferoxamine if:

• they have symptoms or evidence of organ impairment due to aluminium overload.

• they are asymptomatic but their serum aluminium levels are consistently above 60 ng/mL and associated with a positive Deferoxamine test (see below), particularly if a bone biopsy provides evidence of aluminium related bone disease.

The iron and aluminium complexes of Deferoxamine are dialysable. In patients with renal failure their elimination will be increased by dialysis.
Adults and children:
Patients on maintenance haemodialysis or haemofiltration: 5 mg/kg once a week. Patients with post-deferoxamine test serum aluminium levels up to 300 ng/mL: Deferoxamine should be given as a slow i.v. infusion during the last 60 minutes of a dialysis session (to reduce loss of free drug in the dialysate).

Patients with a post- deferoxamine test serum aluminium value above 300 ng/ml: Deferoxamine should be administered by slow i.v. infusion 5 hours prior to the dialysis session.

Four weeks after the completion of a three month course of Deferoxamine treatment a Deferoxamine infusion test should be performed, followed by a second test 1 month later. Serum aluminium increases of less than 50ng/mL above baseline measured in 2 successive infusion tests indicate that further Deferoxamine treatment is not necessary.
Patients on CAPD or CCPD: 5 mg/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, Deferoxamine can also be given i.m., by slow infusion i.v. or s.c.

Diagnosis of aluminium overload in patients with end stage renal failure
A Deferoxamine infusion test is recommended in patients with serum aluminium levels > 60ng/mL associated with serum ferritin levels >100 ng/mL.

Just before starting the haemodialysis session, a blood sample is taken to determine the baseline level 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 Deferoxamine infusion) the second blood sample is taken to determine the serum aluminium level once more.

An increase in serum aluminium above baseline of more than 150 ng/mL is suggestive of aluminium overload. It should be noted that a negative test does not completely exclude the possibility of aluminium overload.

Theoretically 100 mg Deferoxamine can bind 4.1 mg Al^{3+}.

Use in the elderly

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 treatment with other medicines.

4.3 Contraindications
Hypersensitivity to deferoxamine mesilate unless the patients can be desensitised.

4.4 Special warnings and precautions for use
Deferoxamine should be used with caution in patients with renal impairment since the metal complexes are excreted via the kidneys. In these patients, dialysis will increase the elimination of chelated iron and aluminium.

Used alone Deferoxamine may exacerbate neurological impairment 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. Pre-treatment with clonazepam has been shown to afford protection against such impairment. Also, treatment of aluminium overload may result in decreased serum calcium and aggravation of hyperparathyroidism.

Treatment with Deferoxamine 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).

Deferoxamine should not be administered s.c. in concentrations and/or doses higher than those recommended as local irritation at the site of administration may occur more frequently.

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

In patients receiving Deferoxamine for aluminium and/or iron overload there have been rare reports of mucormycosis (a severe fungal infection), some with fatal outcome. If any characteristic signs or symptoms occur Deferoxamine treatment should be discontinued, mycological tests carried out and appropriate treatment immediately instituted. Mucormycosis has been reported to occur in dialysis patients not receiving Deferoxamine, thus no causal link with the use of the drug has been established.

Disturbances of vision and hearing have been reported during prolonged Deferoxamine 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 Deferoxamine. Therefore, ophthalmological and audiological tests should be carried out both prior to the institution of long-term therapy with Deferoxamine and at 3-monthly intervals during treatment. By keeping the ratio of the mean daily dose (mg/kg of Deferoxamine) divided by the serum ferritin (micro g/L) below 0.025 the risk of audiometric abnormalities may be reduced in thalassaemia patients. A detailed ophthalmological assessment is recommended (visual field measurements, fundoscopy, and colour vision testing using pseudoisochromatic plates and the Farnsworth D-15 colour test, slit lamp investigation, visual evoked potential studies).

If disturbances of vision or hearing do occur, treatment with Deferoxamine should be stopped. Such disturbances are usually reversible. If Deferoxamine therapy is re-instituted 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 Deferoxamine in patients with low ferritin levels or young children (< 3 years at commencement of treatment) has also been associated with growth retardation; dose reduction has been found to restore the growth rate to pretreatment levels in some cases. Three monthly checks on body weight and height are recommended in children.

Growth retardation if associated with excessive doses of Deferoxamine must be distinguished from growth retardation from iron overload. Growth retardation from Deferoxamine 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, predicted adult height is not attained.

Acute respiratory distress syndrome has been described following treatment with excessively high i.v. doses of Deferoxamine in patients with acute iron intoxication, and also in thalassaemic patients (see section 4.8). The recommended daily doses should therefore not be exceeded.

It should be noted that deferoxamine will affect aluminium levels and may necessitate some dosage adjustment of erythropoietin if co-prescribed.

In patients with severe chronic iron overload, impairment of cardiac function has been reported following concomitant treatment with Deferoxamine and high doses of vitamin C (more than 500 mg daily in adults). The cardiac dysfunction was reversible when vitamin C was discontinued. The

following precautions should be taken when vitamin C and Deferoxamine are to be used concomitantly:

- Vitamin C supplements should not be given to patients with cardiac failure.
- Start supplemental vitamin C only after an initial month of regular treatment with Deferoxamine.
- Give vitamin C only if the patient is receiving Deferoxamine regularly, ideally soon after setting up the infusion pump.
- Do not exceed a daily vitamin C dose of 200 mg in adults, given in divided doses.

Clinical monitoring of cardiac function is advisable during such combined therapy.

4.5 Interaction with other medicinal products and other forms of interaction

Oral administration of Vitamin C (up to a maximum of 200 mg daily, given in divided doses) may serve to enhance excretion of the iron complex in response to Deferoxamine; larger doses of vitamin C fail to produce an additional effect. Monitoring of cardiac function is indicated during such combined therapy. Vitamin C should be given only if the patient is receiving Deferoxamine regularly and should not be administered within the first month of Deferoxamine therapy. In patients with severe chronic iron-storage disease undergoing combined treatment with Deferoxamine and high doses of Vitamin C (more than 500 mg daily) impairment of cardiac function has been encountered; this proved reversible when the Vitamin C was withdrawn. Vitamin C supplements should not, therefore, be given to patients with cardiac failure.

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

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

4.6 Fertility, Pregnancy and lactation

Pregnancy

Deferoxamine mesilate has caused teratogenic effects in animals when given during pregnancy. (see also section 5.3.)

Lactation

It is not known whether deferoxamine mesilate is excreted into the breast milk.

Deferoxamine mesilate should not be given to pregnant or lactating women, unless, in the judgement of the physician, the expected benefits to the mother outweigh the potential risk to the child. This particularly applies to the first trimester.

Fertility

There are no data from the use of deferoxamine mesilate on fertility

4.7 Effects on ability to drive and use machines

Patients experiencing CNS effects such as dizziness or impaired vision or hearing should be warned against driving or operating machinery.

4.8 Undesirable effects

Frequency estimate: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to ≤ 1/100), rare (≥ 1/10,000 to ≤ 1,000), very rare (≤ 1/10,000) including isolated reports.
Some signs and symptoms reported as adverse effects may also be manifestations of the underlying disease (iron and/or aluminium overload)

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).

Immune system disorders

Very rare: anaphylactic shock, anaphylactic reactions, angioneurotic oedema.

Eye disorders
Rare: loss of vision, scotoma, retinal degeneration, optic neuritis, cataracts (visual acuity decreased), blurred vision, night blindness, visual field defects, chromatopsia (impairment of colour vision), corneal opacities, (see section 4.4). Eye disorders are rare, except if high doses are given.

Ear and labyrinth disorders
Uncommon: deafness neurosensory, tinnitus (see section 4.4). Keeping within dose guidelines helps minimise risk of hearing side effects.

Skin and subcutaneous tissue disorders
Very rare: rash generalised.

Musculoskeletal and connective tissue disorders
Common: growth retardation and bone disorder (e.g. metaphyseal dysplasia) are common in chelated patients given doses of 60 mg/kg, especially those who begin iron chelation in the first three years of life. If doses are kept to 40 mg/kg or below, the risk is considerably reduced (see section 4.4).

Respiratory, thoracic and mediastinal disorders
Very rare: acute respiratory distress lung infiltration (see section 4.4).

Nervous system disorders
Very rare: neurological disturbances, dizziness, precipitation or exacerbation of aluminium-related dialysis encephalopathy, neuropathy peripheral, paraesthesia (see section 4.4).

Gastrointestinal disorders
Very rare: diarrhoea.

Renal and urinary disorders
Very rare: renal impairment (see section 4.4).

Vascular disorders
Rare: hypotension, tachycardia and shock if precautions for administration are not followed (see section 4.2 and section 4.4).

Blood and lymphatic system disorders
Very rare: blood disorders (e.g. thrombocytopenia).

Infections and infestations
Rare: *Mucormycosis* infections have been reported (see section 4.4).
Very rare: *Gastroenteritis yersinia* infections have been reported (see section 4.4).

Patients treated for aluminium overload
In patients treated for aluminium overload, the therapy with Deferoxamine may result in decreased serum calcium and aggravation of hyperparathyroidism (see section 4.4).

4.9 Overdose

Deferoxamine is usually administered parenterally and acute poisoning is unlikely to occur.
Acute respiratory distress syndrome has been reported following treatment with excessively high intravenous doses of Deferoxamine in patients with acute iron poisoning and in patients with thalassemia.

Signs and symptoms
Tachycardia, hypotension and gastro-intestinal symptoms have occasionally occurred in patients who received an overdose of Deferoxamine. Accidental administration of Deferoxamine by the i.v. route may be associated with acute but transient loss of vision, aphasia, agitation, headache, nausea, bradycardia, hypotension and acute renal failure.

Treatment
There is no specific antidote to Deferoxamine but signs and symptoms may be eliminated by reducing the dosage and Deferoxamine is dialysable. Appropriate supportive therapy should be instituted.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Chelating agent (ATC code: V03AC01)

Deferoxamine is a chelating agent for trivalent iron and aluminium ions; the resulting chelates (ferrioxamine 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. Deferoxamine 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 ferrioxamine and aluminoxamine are completely excreted, Deferoxamine 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

Absorption

Deferoxamine is rapidly absorbed after intramuscular bolus injection or slow subcutaneous infusion, but only poorly absorbed from the gastrointestinal tract in the presence of intact mucosa.
During peritoneal dialysis deferoxamine is absorbed if administered in the dialysis fluid.

Distribution

In healthy volunteers peak plasma concentrations of deferoxamine (15.5 micro mol/L (87 micro g/mL)) were measured 30 minutes after an intramuscular injection of 10 mg/kg deferoxamine. One hour after injection the peak concentration of ferrioxamine was 3.7 micro mol/L (2.3 micro g/mL). Less than 10% of deferoxamine is bound to serum proteins *in vitro.*

Biotransformation

Four metabolites of deferoxamine were isolated from urine of patients with iron overload. The following biotransformation reactions were found to occur 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 a biphasic elimination after intramuscular injection in healthy volunteers; for deferoxamine the apparent distribution half-life is 1 hour, and for ferrioxamine 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 7.0 µmol/L (3.9 mcg/mL) were measured for deferoxamine, and 15.7 µmol/L (9.6 mcg/mL) for ferrioxamine, 1 hour after an intramuscular injection of 10 mg/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 dialysed for renal failure who received 40 mg/kg deferoxamine infused i.v. within 1 hour, the plasma concentration at the end of the infusion was 152 µmol/L (85.2 mcg/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 ferrioxamine were in all cases approximately 7.0 µmol/L (4.3 mcg/mL) with concomitant aluminoxamine levels of 2-3 µmol/litre (1.2-1.8 mcg/mL). After the infusion was discontinued, the plasma concentrations 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 approximately 7 µmol/L (4 mcg/mL). Following dialysis the plasma concentration of aluminoxamine fell to 2.2 µmol/L (1.3 mcg/mL), indicating that the aluminoxamine complex is dialysable.

In patients with thalassaemia continuous intravenous infusion of 50mg/kg/24h of deferoxamine resulted in plasma steady state levels of deferoxamine of 7.4 µmol/L. 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 0.5 L/h/kg and the volume of distribution at steady state was estimated at 1.35 L/kg. Exposure to the main iron binding metabolite was around 54%

of that of deferoxamine in terms of AUC. The apparent monoexponential elimination half-life of the metabolite was 1.3 hours.

5.3 Preclinical safety data

In rabbits deferoxamine mesilate caused skeletal malformations. However, these teratogenic effects in the fetuses were observed at doses which were toxic to the mother animal. In mice and rats deferoxamine mesilate appears to be free of teratogenic activity.

Long-term carcinogenicity studies have not been performed.

Evidence of mutagenicity has been observed in mouse lymphoma cells.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

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

6.3 Shelf life

48 months

6.4 Special precautions for storage

Vial: Store below 25°C.

From a microbiological point of view, the product should be used immediately after reconstitution (commencement of treatment within 3 hours). When the reconstitution is carried out under validated aseptic conditions the reconstituted solution may be stored for a maximum of 24 hours at 25°C before administration. If not used immediately, in-use storage times and conditions prior to administration are the responsibility of the user. Unused solution should be discarded.

6.5 Nature and contents of container

Glass (Ph. Eur., type I) vials containing a white to practically white lyophilisate, closed with rubber (Ph. Eur., type I) stoppers.
Pack Size: Bt x 10 vials x 500 mg

6.6 Special precautions for disposal

Single use only, whereby any unused solution should be discarded.

The use of freshly prepared solutions is recommended. These maintain potency for at least 24 hours at 25°C.

The reconstituted solution should be clear. Do not use if particles are present.

Deferoxamine injection should preferably be employed in the form of a 10% aqueous solution, by dissolving the contents of a 500 mg vial in 5ml of Water for injections.

Intramuscular administration: The volume of solvent should be not less than 3 mL for each gram of deferoxamine mesilate (i.e. reconstitute each 500 mg vial of Deferoxamine injection with not less than 1.5 mL of Water for injections).

Intravenous administration: Administration by the intravenous route should be in the form of slow infusion. The 10% deferoxamine mesilate solution can be diluted with routinely employed infusion solutions (Sodium Chloride 0.9% Infusion, Dextrose 5% Infusion, combination of Sodium Chloride 0.9% and Dextrose 5% infusion solutions, Ringer's Lactate), although these should not be used as solvent for the dry substance. The rate of infusion should not exceed 15 mg/kg/hr for the first 1 g of deferoxamine mesilate. Subsequent IV dosing must be at a slower rate, not exceeding 125 mg/hr.

Subcutaneous Administration: Deferoxamine injection should be administered over 8-24 hours, utilizing a small portable pump capable of providing continuous mini-infusion.

Intraperitoneal administration: The 10% deferoxamine mesilate solution can also be added to dialysis fluid and given intraperitoneally to patients on continuous ambulatory peritoneal dialysis (CAPD) or continuous cyclic peritoneal dialysis (CCPD).

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 24598/0020

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14/03/2012

10 DATE OF REVISION OF THE TEXT

14/03/2012

The UK Summary of Product Characteristics (SmPC) for Deferoxamine 2 g Powder for Solution for Injection of Infusion (PL 24598/0021) is as follows:

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Deferoxamine 2 g Powder for Solution for Injection or Infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains deferoxamine mesilate 2 g.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

A sterile, lyophilised powder available in vials containing 2g of deferoxamine mesilate.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

• Treatment for chronic iron overload, e.g.

- transfusional haemosiderosis in patients receiving regular transfusions (e.g. thalassaemia major).
- primary and secondary haemochromatosis in patients in whom concomitant disorders (e.g. severe anaemia, hypoproteinaemia, renal or cardiac failure) preclude phlebotomy.

• Treatment for acute iron poisoning.

• For the diagnosis of iron storage disease and certain anaemias.

• Aluminium overload in patients on maintenance dialysis for end stage renal failure where preventative measures (e.g. reverse osmosis) have failed and with proven aluminium related bone disease and/or anaemia, dialysis encephalopathy; and for diagnosis of aluminium overload.

4.2 Posology and method of administration

Deferoxamine mesilate may be administered intramuscularly, intravenously, or subcutaneously. When administered subcutaneously the needle should not be inserted too close to the dermis.

The drug should preferably be employed in the form of a 10% solution, by dissolving the contents of a 2 g vial in 20 ml of water for injection.

The 10% Deferoxamine solution can be diluted with routinely employed infusion solutions (Sodium Chloride 0.9% Infusion, Dextrose 5% Infusion, combination of Sodium Chloride 0.9% and Dextrose 5% Infusion solutions, Ringer's Lactate), although these should not be used as solvent for the dry substance.
Dissolved Deferoxamine can also be added to dialysis fluid and given intraperitoneally to patients on continuous ambulatory peritoneal dialysis (CAPD) or continuous cyclic peritoneal dialysis (CCPD).

Treatment of acute iron poisoning
Adults and children:

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

Parenteral Deferoxamine treatment should be considered 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 radio-opacities (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 micro g/dL regardless of the total iron binding capacity (TIBC). It has also been suggested that a conservative approach without Deferoxamine therapy or challenge should be considered when serum iron levels are in the 300 to 500 micro g/dL range in asymptomatic patients, as well as in those with self-limited, non-bloody emesis or diarrhoea without other symptoms.

The dosage and route of administration should be adapted to the severity of the poisoning.

Dosage:

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

However, if the option to infuse intravenously is not available and if the intramuscular route is used the normal dosage is 2 g for an adult and 1g for a child, administered as a single intramuscular dose.

The decision to discontinue Deferoxamine therapy must be a clinical decision; however, the following suggested criteria are believed to represent appropriate requirements for the cessation of Deferoxamine. Chelation therapy should be continued until all of the following criteria are satisfied:

- the patient must be free of signs and symptoms of systemic iron poisoning (e.g. no acidosis, no worsening hepatoxicity).

- ideally, a corrected serum iron level should be normal or low (when iron level falls below 100 micro g/dL). Given that laboratories cannot measure serum iron concentrations accurately in the presence of Deferoxamine, it is acceptable to discontinue Deferoxamine 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 radio-opacities to ensure they have disappeared before Deferoxamine is discontinued because they serve as a marker for continued iron absorption.

- if the patient initially developed vin-rose coloured urine with Deferoxamine therapy, it seems reasonable that urine colour should return to normal before halting Deferoxamine (absence of vin-rose urine is not sufficient by itself to indicate discontinuation of Deferoxamine).

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 or haemodialysis 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 100 mg Deferoxamine can chelate 8.5 mg of ferric iron.

Chronic Iron Overload

The main aim of therapy in *patients with iron overload not complicated by toxic effects* is to achieve an iron balance and prevent haemosiderosis, whilst *in patients with severe iron overload* a negative iron balance is desirable in order to slowly deplete the increased iron stores and to prevent the toxic effects of iron.

Adults and children:
Deferoxamine therapy should be commenced after the first 10- 20 blood transfusions, or when serum ferritin levels reach 1000 ng/mL, indicating saturation of the transferrin. The dose and mode of administration should be individually adapted according to the degree of iron overload.

Growth retardation may result from iron overload or excessive Deferoxamine doses. If chelation is started before 3 years of age growth must be monitored carefully and the mean daily dose should not exceed 40mg/kg. (see section 4.4).
Dose:

The lowest effective dose should be used. The average daily dose will probably lie between 20 and 60 mg/kg/day. Patients with serum ferritin levels of < 2000 ng/mL should require about 25 mg/kg/day, and those with levels between 2000 and 3000 ng/mL about 35 mg/kg/day. Higher doses should only be employed if the benefit for the patient outweighs the risk of unwanted effects.

Patients with higher serum ferritin may require up to 55 mg/kg/day. It is inadvisable regularly to 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 1000 ng/mL, the risk of Deferoxamine toxicity increases; it is important to monitor these patients particularly carefully and perhaps to consider lowering the total weekly dose.

To assess the chelation therapy, 24 hour urinary iron excretion should initially be monitored daily. Starting with a dose of 500 mg daily the dose should be raised until a plateau of iron excretion is reached. Once the appropriate dose has been established, urinary iron excretion rates can 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 Deferoxamine divided by the serum ferritin level (mcg/L) below 0.025).

Mode of administration:
Slow subcutaneous infusion by means of a portable, light-weight, infusion pump over a period of 8-12 hours is effective and particularly convenient for ambulant patients. It may be possible to achieve a further increase in iron excretion by infusing the same daily dose over a 24 hour period. Patients should be treated 5-7 times a week depending on the degree of iron overload.
Deferoxamine is not formulated to be administered as a subcutaneous bolus.

Since the subcutaneous infusions are more effective, intramuscular injections are given only when subcutaneous infusions are not feasible.

Deferoxamine can be administered by intravenous infusion during blood transfusion.

Due to the small quantity of deferoxamine that can be administered by intravenous infusion during blood transfusion, the clinical benefit is limited.

The Deferoxamine 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 to the venous site of injection. The patient's pump should be used to administer Deferoxamine as usual. Patients and nurses should be warned against accelerating the infusion, as an intravenous bolus of Deferoxamine may lead to flushing, hypotension and acute collapse (see section 4.4).

Continuous intravenous infusion is recommended for patients incapable of continuing subcutaneous infusions and in those who have cardiac problems secondary to iron overload. 24 hour urinary iron excretion should be measured regularly where intensive chelation (i.v.) is required, and the dose adjusted accordingly. Implanted intravenous systems can be used when intensive chelation is carried out.

Care should be taken when flushing the line to avoid the sudden infusion of residual Deferoxamine which may be present in the dead space of the line, as this may lead to flushing; hypotension and acute collapse (see section 4.4).

Diagnosis of iron storage disease and certain anaemias
The Deferoxamine 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 that a standard intramuscular injection of 500 mg of Deferoxamine will not increase this above 1 mg (18 μmol). In iron storage diseases, however, the increase may be well over 1.5 mg (27 μmol). It should be borne in mind that the test only yields reliable results when renal function is normal.

Deferoxamine is administered as 500 mg intramuscular injection. Urine is then collected for a period of 6 hours and its iron content determined.

Excretion of 1-1.5 mg (18-27 μmol) of iron during this 6-hour period is suggestive of iron overload; values greater than 1.5 mg (27 μmol) can be regarded as pathological.

Treatment for aluminium overload in patients with end stage renal failure

Patients should receive Deferoxamine if:

- they have symptoms or evidence of organ impairment due to aluminium overload.

- they are asymptomatic but their serum aluminium levels are consistently above 60 ng/mL and associated with a positive Deferoxamine test (see below), particularly if a bone biopsy provides evidence of aluminium related bone disease.

The iron and aluminium complexes of Deferoxamine are dialysable. In patients with renal failure their elimination will be increased by dialysis.
Adults and children:
Patients on maintenance haemodialysis or haemofiltration: 5 mg/kg once a week. Patients with post-deferoxamine test serum aluminium levels up to 300 ng/mL: Deferoxamine should be given as a slow i.v. infusion during the last 60 minutes of a dialysis session (to reduce loss of free drug in the dialysate).

Patients with a post- deferoxamine test serum aluminium value above 300 ng/ml: Deferoxamine should be administered by slow i.v. infusion 5 hours prior to the dialysis session.

Four weeks after the completion of a three month course of Deferoxamine treatment a Deferoxamine infusion test should be performed, followed by a second test 1 month later. Serum aluminium increases of less than 50ng/mL above baseline measured in 2 successive infusion tests indicate that further Deferoxamine treatment is not necessary.
Patients on CAPD or CCPD: 5 mg/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, Deferoxamine can also be given i.m., by slow infusion i.v. or s.c.

Diagnosis of aluminium overload in patients with end stage renal failure
A Deferoxamine infusion test is recommended in patients with serum aluminium levels > 60ng/mL associated with serum ferritin levels >100 ng/mL.

Just before starting the haemodialysis session, a blood sample is taken to determine the baseline level 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 Deferoxamine infusion) the second blood sample is taken to determine the serum aluminium level once more.

An increase in serum aluminium above baseline of more than 150 ng/mL is suggestive of aluminium overload. It should be noted that a negative test does not completely exclude the possibility of aluminium overload.

Theoretically 100 mg Deferoxamine can bind 4.1 mg Al^{3+}.

Use in the elderly
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 treatment with other medicines.

4.3 Contraindications
Hypersensitivity to deferoxamine mesilate unless the patients can be desensitised.

4.4 Special warnings and precautions for use
Deferoxamine should be used with caution in patients with renal impairment since the metal complexes are excreted via the kidneys. In these patients, dialysis will increase the elimination of chelated iron and aluminium.

Used alone Deferoxamine may exacerbate neurological impairment 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. Pre-treatment with clonazepam has been shown to afford protection against such impairment. Also, treatment of aluminium overload may result in decreased serum calcium and aggravation of hyperparathyroidism.

Treatment with Deferoxamine 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).

Deferoxamine should not be administered s.c. in concentrations and/or doses higher than those recommended as local irritation at the site of administration may occur more frequently.

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

In patients receiving Deferoxamine for aluminium and/or iron overload there have been rare reports of mucormycosis (a severe fungal infection), some with fatal outcome. If any characteristic signs or symptoms occur Deferoxamine treatment should be discontinued, mycological tests carried out and appropriate treatment immediately instituted. Mucormycosis has been reported to occur in dialysis patients not receiving Deferoxamine, thus no causal link with the use of the drug has been established.

Disturbances of vision and hearing have been reported during prolonged Deferoxamine 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 Deferoxamine. Therefore, ophthalmological and audiological tests should be carried out both prior to the institution of long-term therapy with Deferoxamine and at 3-monthly intervals during treatment. By keeping the ratio of the mean daily dose (mg/kg of Deferoxamine) divided by the serum ferritin (micro g/L) below 0.025 the risk of audiometric abnormalities may be reduced in thalassaemia patients. A detailed ophthalmological assessment is recommended (visual field measurements, fundoscopy, and colour vision testing using pseudoisochromatic plates and the Farnsworth D-15 colour test, slit lamp investigation, visual evoked potential studies).

If disturbances of vision or hearing do occur, treatment with Deferoxamine should be stopped. Such disturbances are usually reversible. If Deferoxamine therapy is re-instituted 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 Deferoxamine in patients with low ferritin levels or young children (< 3 years at commencement of treatment) has also been associated with growth retardation; dose reduction has been found to restore the growth rate to pretreatment levels in some cases. Three monthly checks on body weight and height are recommended in children.

Growth retardation if associated with excessive doses of Deferoxamine must be distinguished from growth retardation from iron overload. Growth retardation from Deferoxamine 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, predicted adult height is not attained.

Acute respiratory distress syndrome has been described following treatment with excessively high i.v. doses of Deferoxamine in patients with acute iron intoxication, and also in thalassaemic patients (see section 4.8). The recommended daily doses should therefore not be exceeded.

It should be noted that deferoxamine will affect aluminium levels and may necessitate some dosage adjustment of erythropoietin if co-prescribed.

In patients with severe chronic iron overload, impairment of cardiac function has been reported following concomitant treatment with Deferoxamine and high doses of vitamin C (more than 500 mg daily in adults). The cardiac dysfunction was reversible when vitamin C was discontinued. The

following precautions should be taken when vitamin C and Deferoxamine are to be used concomitantly:
- Vitamin C supplements should not be given to patients with cardiac failure.
- Start supplemental vitamin C only after an initial month of regular treatment with Deferoxamine.
- Give vitamin C only if the patient is receiving Deferoxamine regularly, ideally soon after setting up the infusion pump.
- Do not exceed a daily vitamin C dose of 200 mg in adults, given in divided doses.

Clinical monitoring of cardiac function is advisable during such combined therapy.

4.5 Interaction with other medicinal products and other forms of interaction

Oral administration of Vitamin C (up to a maximum of 200 mg daily, given in divided doses) may serve to enhance excretion of the iron complex in response to Deferoxamine; larger doses of vitamin C fail to produce an additional effect. Monitoring of cardiac function is indicated during such combined therapy. Vitamin C should be given only if the patient is receiving Deferoxamine regularly and should not be administered within the first month of Deferoxamine therapy. In patients with severe chronic iron-storage disease undergoing combined treatment with Deferoxamine and high doses of Vitamin C (more than 500 mg daily) impairment of cardiac function has been encountered; this proved reversible when the Vitamin C was withdrawn. Vitamin C supplements should not, therefore, be given to patients with cardiac failure.

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

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

4.6 Fertility, Pregnancy and lactation

Pregnancy

Deferoxamine mesilate has caused teratogenic effects in animals when given during pregnancy. (see also section 5.3.)

Lactation

It is not known whether deferoxamine mesilate is excreted into the breast milk.

Deferoxamine mesilate should not be given to pregnant or lactating women, unless, in the judgement of the physician, the expected benefits to the mother outweigh the potential risk to the child. This particularly applies to the first trimester.

Fertility

There are no data from the use of deferoxamine mesilate on fertility

4.7 Effects on ability to drive and use machines

Patients experiencing CNS effects such as dizziness or impaired vision or hearing should be warned against driving or operating machinery.

4.8 Undesirable effects

Frequency estimate: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to ≤ 1/100), rare (≥ 1/10,000 to ≤ 1,000), very rare (≤ 1/10,000) including isolated reports.
Some signs and symptoms reported as adverse effects may also be manifestations of the underlying disease (iron and/or aluminium overload).

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).

Immune system disorders

Very rare: anaphylactic shock, anaphylactic reactions, angioneurotic oedema.

Eye disorders

Rare: loss of vision, scotoma, retinal degeneration, optic neuritis, cataracts (visual acuity decreased), blurred vision, night blindness, visual field defects, chromatopsia (impairment of colour vision), corneal opacities, (see section 4.4). Eye disorders are rare, except if high doses are given.

Ear and labyrinth disorders
Uncommon: deafness neurosensory, tinnitus (see section 4.4). Keeping within dose guidelines helps minimise risk of hearing side effects.

Skin and subcutaneous tissue disorders
Very rare: rash generalised.

Musculoskeletal and connective tissue disorders
Common: growth retardation and bone disorder (e.g. metaphyseal dysplasia) are common in chelated patients given doses of 60 mg/kg, especially those who begin iron chelation in the first three years of life. If doses are kept to 40 mg/kg or below, the risk is considerably reduced (see section 4.4).

Respiratory, thoracic and mediastinal disorders
Very rare: acute respiratory distress lung infiltration (see section 4.4).

Nervous system disorders
Very rare: neurological disturbances, dizziness, precipitation or exacerbation of aluminium-related dialysis encephalopathy, neuropathy peripheral, paraesthesia (see section 4.4).

Gastrointestinal disorders
Very rare: diarrhoea.

Renal and urinary disorders
Very rare: renal impairment (see section 4.4).

Vascular disorders
Rare: hypotension, tachycardia and shock if precautions for administration are not followed (see section 4.2 and section 4.4).

Blood and lymphatic system disorders
Very rare: blood disorders (e.g. thrombocytopenia).

Infections and infestations
Rare: *Mucormycosis* infections have been reported (see section 4.4).
Very rare: *Gastroenteritis yersinia* infections have been reported (see section 4.4).

Patients treated for aluminium overload
In patients treated for aluminium overload, the therapy with Deferoxamine may result in decreased serum calcium and aggravation of hyperparathyroidism (see section 4.4).

4.9 Overdose

Deferoxamine is usually administered parenterally and acute poisoning is unlikely to occur.
Acute respiratory distress syndrome has been reported following treatment with excessively high intravenous doses of Deferoxamine in patients with acute iron poisoning and in patients with thalassemia.

Signs and symptoms
Tachycardia, hypotension and gastro-intestinal symptoms have occasionally occurred in patients who received an overdose of Deferoxamine. Accidental administration of Deferoxamine by the i.v. route may be associated with acute but transient loss of vision, aphasia, agitation, headache, nausea, bradycardia, hypotension and acute renal failure.

Treatment
There is no specific antidote to Deferoxamine but signs and symptoms may be eliminated by reducing the dosage and Deferoxamine is dialysable. Appropriate supportive therapy should be instituted.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Chelating agent (ATC code: V03AC01)

Deferoxamine is a chelating agent for trivalent iron and aluminium ions; the resulting chelates (ferrioxamine 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. Deferoxamine 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 ferrioxamine and aluminoxamine are completely excreted, Deferoxamine 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

Absorption

Deferoxamine is rapidly absorbed after intramuscular bolus injection or slow subcutaneous infusion, but only poorly absorbed from the gastrointestinal tract in the presence of intact mucosa.
During peritoneal dialysis deferoxamine is absorbed if administered in the dialysis fluid.

Distribution

In healthy volunteers peak plasma concentrations of deferoxamine (15.5 micro mol/L (87 micro g/mL)) were measured 30 minutes after an intramuscular injection of 10 mg/kg deferoxamine. One hour after injection the peak concentration of ferrioxamine was 3.7 micro mol/L (2.3 micro g/mL). Less than 10% of deferoxamine is bound to serum proteins *in vitro.*

Biotransformation

Four metabolites of deferoxamine were isolated from urine of patients with iron overload. The following biotransformation reactions were found to occur 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 a biphasic elimination after intramuscular injection in healthy volunteers; for deferoxamine the apparent distribution half-life is 1 hour, and for ferrioxamine 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 7.0 µmol/L (3.9 mcg/mL) were measured for deferoxamine, and 15.7 µmol/L (9.6 mcg/mL) for ferrioxamine, 1 hour after an intramuscular injection of 10 mg/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 dialysed for renal failure who received 40 mg/kg deferoxamine infused i.v. within 1 hour, the plasma concentration at the end of the infusion was 152 µmol/L (85.2 mcg/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 ferrioxamine were in all cases approximately 7.0 µmol/L (4.3 mcg/mL) with concomitant aluminoxamine levels of 2-3 µmol/litre (1.2-1.8 mcg/mL). After the infusion was discontinued, the plasma concentrations 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 approximately 7 µmol/L (4 mcg/mL). Following dialysis the plasma concentration of aluminoxamine fell to 2.2 µmol/L (1.3 mcg/mL), indicating that the aluminoxamine complex is dialysable.

In patients with thalassaemia continuous intravenous infusion of 50mg/kg/24h of deferoxamine resulted in plasma steady state levels of deferoxamine of 7.4 µmol/L. 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 0.5 L/h/kg and the volume of distribution at steady state was estimated at 1.35 L/kg. Exposure to the main iron binding metabolite was around 54% of that of deferoxamine in terms of AUC. The apparent monoexponential elimination half-life of the metabolite was 1.3 hours.

5.3 Preclinical safety data

In rabbits deferoxamine mesilate caused skeletal malformations. However, these teratogenic effects in the fetuses were observed at doses which were toxic to the mother animal. In mice and rats deferoxamine mesilate appears to be free of teratogenic activity.

Long-term carcinogenicity studies have not been performed.

Evidence of mutagenicity has been observed in mouse lymphoma cells.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

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

6.3 Shelf life

48 months

6.4 Special precautions for storage

Vial: Store below 25°C.

From a microbiological point of view, the product should be used immediately after reconstitution (commencement of treatment within 3 hours). When the reconstitution is carried out under validated aseptic conditions the reconstituted solution may be stored for a maximum of 24 hours at 25°C before administration. If not used immediately, in-use storage times and conditions prior to administration are the responsibility of the user. Unused solution should be discarded.

6.5 Nature and contents of container

Glass (Ph. Eur., type I) vials containing a white to practically white lyophilisate, closed with rubber (Ph. Eur., type I) stoppers.
Pack Size: Bt x 1 vial x 2 g

6.6 Special precautions for disposal

Single use only, whereby any unused solution should be discarded.

The use of freshly prepared solutions is recommended. These maintain potency for at least 24 hours at 25°C.

The reconstituted solution should be clear. Do not use if particles are present.

Deferoxamine injection should preferably be employed in the form of a 10% aqueous solution, by dissolving the contents of a 2g vial in 20 ml of Water for injections.

Intramuscular administration: The volume of solvent should be not less than 3 mL for each gram of deferoxamine mesilate (i.e. reconstitute each 500 mg vial of Deferoxamine injection with not less than 1.5 mL of Water for injections).

Intravenous administration: Administration by the intravenous route should be in the form of slow infusion. The 10% deferoxamine mesilate solution can be diluted with routinely employed infusion solutions (Sodium Chloride 0.9% Infusion, Dextrose 5% Infusion, combination of Sodium Chloride 0.9% and Dextrose 5% infusion solutions, Ringer's Lactate), although these should not be used as solvent for the dry substance. The rate of infusion should not exceed 15 mg/kg/hr for the first 1 g of deferoxamine mesilate. Subsequent IV dosing must be at a slower rate, not exceeding 125 mg/hr.

Subcutaneous Administration: Deferoxamine injection should be administered over 8-24 hours, utilizing a small portable pump capable of providing continuous mini-infusion.

Intraperitoneal administration: The 10% deferoxamine mesilate solution can also be added to dialysis fluid and given intraperitoneally to patients on continuous ambulatory peritoneal dialysis (CAPD) or continuous cyclic peritoneal dialysis (CCPD).

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 24598/0021

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14/03/2012

10 DATE OF REVISION OF THE TEXT

14/03/2012

Module 3
Product Information Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

Deferoxamine 500 mg & 2g Powder for Solution for Injection or Infusion

Deferoxamine mesilate

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or you notice any side effects not listed in this leaflet please tell your doctor or pharmacist.

The name of your medicine is the following:
- Deferoxamine 500 mg Powder for Solution for Injection or Infusion
- Deferoxamine 2 g Powder for Solution for Injection or Infusion

In the rest of this leaflet your medicine is called Deferoxamine injection.

In this leaflet:

1. WHAT DEFEROXAMINE INJECTION IS AND WHAT IT IS USED FOR

Deferoxamine injection is used to remove excess iron or aluminium from your blood.
The active ingredient of Deferoxamine injection is deferoxamine mesilate and it belongs to a group of substances called 'chelating agents'. This means that it binds to the iron and aluminium in the blood, to form a complex which is then excreted from the body.
You may have too much iron or aluminium in your blood as a result of iron poisoning, due to certain illnesses such as thalassaemia (a hereditary type of anaemia) and haemocromatosis (a disorder of iron metabolism), or as a side effect of blood transfusion or kidney dialysis.
Deferoxamine injection can also be used to test whether you have certain anaemias or diseases affecting the amount of iron in your blood.

2. BEFORE YOU TAKE DEFEROXAMINE INJECTION

The doctor or nurse giving you this medicine will ask some questions about you. They need the following information before you have this medicine for the first time.

Do not take Deferoxamine injection
- If you have shown signs of hypersensitivity (severe allergy) to deferoxamine.

Do not take Deferoxamine injection if the above statement is true.

Take special care with Deferoxamine injection

Before treatment with Deferoxamine injection starts, tell your doctor or nurse if:
- You are pregnant, suspect you may be pregnant or planning to become pregnant.
- You are breast-feeding.
- You have any kidney problems.
- You have a heart disorder.
- You have thalassaemia (a type of anaemia).
- You have hyperparathyroidism (a metabolic disease resulting in excess calcium in the blood and problems with the bones).
- Aluminium has affected your nerves. If so, you may be given a dose of clonazepam before you are given Deferoxamine injection.

During treatment with Deferoxamine injection:
- If you are treated with Deferoxamine injection for a long time or you have kidney problems and are on dialysis, deferoxamine may affect your vision or hearing. If this occurs you must tell your doctor immediately. Your doctor may give you regular eye and hearing tests, usually every 3 months.
- You must tell your doctor before having some radiotherapy diagnostic tests (X-rays or scans), as the results of the tests may be false.
- Deferoxamine may affect your child's growth, if it is under 3 years of age. Your child's doctor will regularly check the body weight and height of your child, usually every 3 months.

Taking other medicines
Please tell your doctor or nurse if you are taking or have recently taken any other medicines. Remember also any medicines you may be taking that do not need a prescription.
If you are taking any of the following medicines it is very important to tell your doctor:
- Prochlorperazine, a medicine used to control vertigo (sense of instability and rotation) or nausea and vomiting (feeling or being sick) and some types of mental illness.
- Erythropoietin, a medicine used to increase the number of red blood cells.
- Vitamin C supplements.

Pregnancy and breast-feeding
- If you are pregnant, or think you may be pregnant you must tell your doctor immediately, as deferoxamine may cause problems to your baby, especially during the first three months of pregnancy.
- If you are breastfeeding, you must tell your doctor as deferoxamine may be in the breast milk and may affect your baby.

Your doctor will advise you if you should have this medicine during pregnancy and breast-feeding.

Driving and using machines
Deferoxamine injection can make you feel dizzy or drowsy. It can also affect your vision or hearing. Do not drive, operate machines or do anything else which requires concentration until you know how your medicine affects you.

3. HOW TO TAKE DEFEROXAMINE INJECTION

A doctor or a nurse will usually give you this medicine.
It will be diluted with water for injections and may be further diluted with glucose solution, sodium chloride solution, a mixture of glucose and sodium chloride solution or added to a dialysis fluid before it is given to you.
It will be given as an injection into a muscle (intramuscularly), into a vein over a period of time via a drip (called slow intravenous infusion), under the skin (subcutaneously), or into the abdominal cavity (intraperitoneally).
Your doctor will decide the amount (dose) of your medicine to give you. This will depend on your medical condition, your body weight, your age and how well your kidneys are working.
The usual doses and ways of taking Deferoxamine injection are as follows:

Acute iron poisoning:
Deferoxamine injection is usually given intravenously (injected into a vein). The recommended dose is 15 mg/kg body weight every hour. The dose may be reduced after 4 to 6 hours. The maximum recommended dose is 80 mg/kg body weight every 24 hours.
Deferoxamine injection may also be given to you intramuscularly (injected into a muscle). In this case, the recommended dose is 2 g for adults and 1 g for children, given in a single injection.

Iron overload:
Deferoxamine injection is usually given subcutaneously (a slow injection under the skin) or intramuscularly (injection into a muscle). The way of taking Deferoxamine and the correct dose for you will be determined by your doctor and it will depend on how much extra iron there is in your blood. The usually recommended dose is 20 - 60 mg/kg body weight, given 5 - 7 times a week. For children under 3 years of age, the average daily dose is not more than 40 mg/kg.

Aluminium overload:
Deferoxamine injection is usually given by slow intravenous injection.
The correct dose for you will be determined by your doctor and it will depend on how much extra aluminium you have in your blood.
If you are on dialysis, the usual dose is 5 mg/kg body weight, once a week. It will either be given during the last 60 minutes of your dialysis or 5 hours before your dialysis starts.
If you are on peritoneal dialysis (CAPD or CCPD), the usual dose is 5 mg/kg body weight, once a week.
Deferoxamine injection is either mixed with the fluid in your dialysis bag or given by any of the other ways listed above.

Diagnosis of conditions associated with iron overload:
Deferoxamine injection is usually given intramuscularly (injected into a muscle). The usual dose is 500 mg. After you have received Deferoxamine injection, your doctor or nurse will probably collect urine samples for about 6 hours. They will then do tests on your urine to see how much iron is in it.

Diagnosis of conditions associated with aluminium overload:
The usual dose of Deferoxamine injection is 5 mg/kg body weight. It is usually given by slow intravenous infusion (slow injection into a vein) during the last hour of dialysis.
Your doctor or nurse will probably take a blood sample before you are given Deferoxamine injection and before your dialysis starts. You will probably have another blood test before your next session of haemodialysis. Blood tests will show how much aluminium is in your blood.

Use in older patients:
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 treatment with other medicines.

If you take more Deferoxamine injection than you should
As this medicine will usually be given to you by a doctor or nurse, is unlikely that you will have too much or too little. However, if you have any concerns, tell your doctor or nurse.

If you forget to take Deferoxamine injection
A doctor or a nurse will usually give you this medicine. If you miss one of your appointments, please let your doctor know immediately.

If you stop taking Deferoxamine injection

It is very important to finish the course of treatment your doctor has prescribed, even if you start to feel better. If you do not finish the course of treatment, your condition may get worse again.

If you have any further questions on the use of your medicine, ask your doctor, nurse or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Deferoxamine injection can cause side effects, although not everyone gets them. The expected benefit of your medicine will usually be greater than the risk of you suffering any harmful side effects. Your urine may turn a reddish-brown colour. This is because the extra iron that sticks to deferoxamine and passes into your urine is reddish-brown in colour. This is usually nothing to worry about, but if you have any concerns you should talk to your doctor or nurse.

Important: The following are very serious side effects. If you get any of the below symptoms you must seek medical advice immediately.
- Serious allergic reaction. The first signs of a serious allergic reaction may be sudden itchy rash (hives), swelling of the hands, feet, ankles, face, lips, mouth or throat, sudden difficulty in swallowing or breathing and feeling that you are going to faint (low blood pressure).
- Symptoms of a severe infection, such as fever, sore throat, abdominal pain (pain in the stomach or intestines) and severe diarrhoea.
- Impaired vision/eye disorders
- Loss of hearing and tinnitus (a ringing or booming sensation in ears)
- Serious skin infections

The chance of you having a side effect is described using words and numbers below.
The following are very common side effects. They probably affect more than 1 in 10 people:
- Pain in muscles and/or joints
- Pain, swelling, redness of skin, itch or formation of crust at the site of injection

The following are common side effects. They probably affect more than 1 in 100 people and up to 1 in 10 people:
- Headache
- Fever
- Nausea (feeling sick)
- Itchy rash
- Bone disorders, slowing down of growth (especially in children under 3)

The following are uncommon side effects. They probably affect more than 1 in 1,000 people and up to 1 in 100 people:
- Vesicles (skin blisters containing fluid)
- Vomiting (being sick)
- Local swelling and burning sensation
- Stomach pain
- Asthma (difficulty in breathing and wheezing)
- Problems with the ears, such as tinnitus or loss of hearing.

The following are rare side effects. They probably affect more than 1 in 10,000 people and up to 1 in 1,000 people:
- Eye problems, such as blurred vision, impaired vision or loss of vision, not being able to see colours (colour blindness), not being able to see at night (night blindness), blind spots, changes in the retina (a membrane at the back of the eye sensitive to light), and cloudiness on the front of the eye.
- Low blood pressure (light headedness, dizziness, faintness).
- Tachycardia
- Shock
- Infections caused by fungus.

The following are very rare side effects. They probably affect up to 1 in 10,000 people:
- Allergic reactions.
- Skin rash covering most of the body.
- A serious condition which causes severe breathing problems called Acute Respiratory Distress Syndrome.
- Diarrhoea.
- Problems with the kidneys.
- Blood disorders which can make you look pale or cause tiredness, headaches, nosebleeds, dizziness or being short of breath when exercising. You might also get more frequent viral infections (fever, chills, sore throat or mouth ulcers), or find that you bleed or bruise more easily than normal.
- Stomach and gut infections.
- Other effects such as dizziness, loss of feeling in their hands, feet, arms or legs, numbness or tingling (pins and needles).
- In patients on dialysis: personality changes, headache, confusion, paralysis of part or all of the body, stiff neck, abnormal speech and eye movements.

In patients having too much aluminium in their blood, treatment with deferoxamine may result in decreased serum calcium and aggravation of hyperparathyroidism.
If you experience any of these side effects, tell your doctor as soon as possible.
If you notice any side effects which are not listed in this leaflet, please tell your doctor, nurse or pharmacist.

5. HOW TO STORE DEFEROXAMINE INJECTION

Keep your medicine out of the reach and sight of children.
Do not use your medicine after the expiry date which is stated on the carton and on the label of the glass container (vial) after abbreviation (EXP). The expiry date refers to the last day of that month.
Vial: Store below 25° C.
After dilution: Do not refrigerate or freeze.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 25°C.
Do not use the solution if it is not clear, not free of particles or there has been a colour change.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Deferoxamine injection contains

The active substance is deferoxamine mesilate. There are no other ingredients in your medicine.

What Deferoxamine injection looks like

Deferoxamine injection is a white or off-white powder for solution for injection or infusion. This means that a liquid must be added to make a solution, before it can be given to you as an injection. In some cases, more liquid may be added to make a weaker solution which can be given to you as an infusion (drip).
Normally, your doctor or nurse will prepare your medicine before it is given to you.

Contents of the pack

Each pack contains 10 vials (glass containers) of Deferoxamine injection 500 mg or 1 vial of Deferoxamine injection 2 g. Not all pack sizes may be available.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: Noridem Enterprises Ltd., Evagorou & Makariou, Mitsi Building 3, Office 115, 1065 Nicosia, Cyprus.
Manufacturer: DEMO S.A., 21st km National Road Athens-Lamia, 14568 Krioneri, Athens, Greece.

This medicinal product is authorised in the Member States of the EEA under the following names:

UK: Deferoxamine 500 mg & 2g Powder for Solution for Injection or Infusion
DE:Deferoxamine/Noridem 500 mg & 2 g Pulver zur Herstellung einer Injektions-bzw. Infusionslösung
IT: Deferoxamine/Noridem 500 mg Polvere per soluzione iniettabile / per infusione
CY: Deferoxamine 500mg & 2g Κόνις για ενέσιμο διάλυμα ή διάλυμα για έγχυση
EL: Deferoxamine 500mg & 2g Κόνις για ενέσιμο διάλυμα ή διάλυμα για έγχυση

This leaflet was approved in 02/2012

The following information is intended for medical or healthcare professionals only

Instructions for use and handling:
Single use only, whereby any unused solution should be discarded.

The use of freshly prepared solutions is recommended. These maintain potency for at least 24 hours at 25°C.

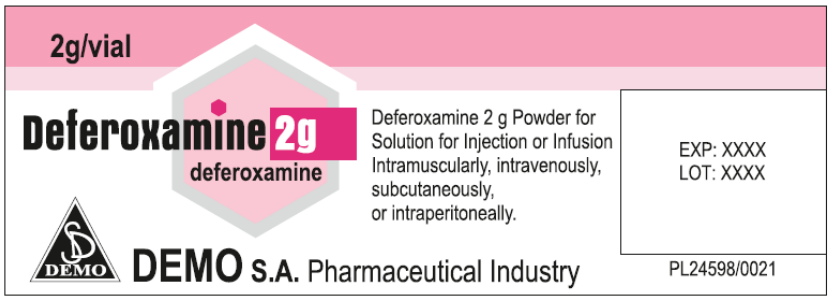
The reconstituted solution should be clear. Do not use if particles are present.

Deferoxamine injection should preferably be employed in the form of a 10% aqueous solution, by dissolving the contents of one 500 mg vial in 5ml of Water for injections or 2g vial in 20 ml of Water for injections.
Intramuscular administration: The volume of solvent should be not less than 3 mL for each gram of deferoxamine mesilate (i.e. reconstitute each 500 mg vial of Deferoxamine injection with not less than 1.5 mL of Water for injections).
Intravenous administration: Administration by the intravenous route should be in the form of slow infusion. The 10% deferoxamine mesilate solution can be diluted with routinely employed infusion solutions (Sodium Chloride 0.9% Infusion, Dextrose 5% Infusion, combination of Sodium Chloride 0.9% and Dextrose 5% infusion solutions, Ringer's Lactate), although these should not be used as solvent for the dry substance. The rate of infusion should not exceed 15 mg/kg/hr for the first 1 g of deferoxamine mesilate. Subsequent IV dosing must be at a slower rate, not exceeding 125 mg/hr.
Subcutaneous Administration: Deferoxamine injection should be administered over 8-24 hours, utilizing a small portable pump capable of providing continuous mini-infusion.
Intraperitoneal administration: The 10% deferoxamine mesilate solution can also be added to dialysis fluid and given intraperitoneally to patients on continuous ambulatory peritoneal dialysis (CAPD) or continuous cyclic peritoneal dialysis (CCPD).

If this leaflet is difficult to see or read please contact the following address for help: Fannin Limited, Fannin House, South County Business Park, Leopardstown, Dublin 18, Ireland Tel +353-1-2907000

Module 4
Labelling


500mg/vial
Deferoxamine
deferoxamine
500mg
Deferoxamine 500 mg
Powder for Solution
for Injection or Infusion.
Intramuscularly, intravenously,
subcutaneously, or intraperitoneally.
DEMO S.A.
Pharmaceutical Industry
PL24598/0020
EXP: XXXX
LOT: XXXX
10 vials x 500mg
Deferoxamine
500mg
Each single dose glass vial contains 500 mg of deferoxamine mesilate.
Powder for Solution for Injection or Infusion
500 mg of Deferoxamine
Intramuscularly, intravenously,
subcutaneously, or intraperitoneally.
Keep out of the reach and sight of children
Store below 25°C.
Medicinal product subject to medical prescription.
Powder for Solution
for Injection
or Infusion
Marketing Authorisation Holder:
Noridem Enterprises Ltd.
Evagorou & Makariou, Mitsi Building 3, Suit.115
1065 Nicosia, Cyprus.
Manufactured by:
DEMO S.A.
Pharmaceutical Industry, Athens, Greece
PL24598/0020
POM
5 205411 002192


2g/vial
Deferoxamine 2g
deferoxamine
Deferoxamine 2 g Powder for Solution for Injection or Infusion
Intramuscularly, intravenously, subcutaneously, or intraperitoneally.
EXP: XXXX
LOT: XXXX
DEMO S.A. Pharmaceutical Industry
PL24598/0021


1 vial x 2g
Each single dose glass vial contains 2 g of deferoxamine mesilate.
Powder for Solution for Injection or Infusion
2 g of Deferoxamine
Intramuscularly, intravenously, subcutaneously, or intraperitoneally.
Keep out of the reach and sight of children
Store below 25°C.
Medicinal product subject to medical prescription.
Deferoxamine 2g
deferoxamine
Powder for Solution for Injection or Infusion
Marketing Authorisation Holder:
Noridem Enterprises Ltd.
Evagorou & Makariou,
Mitsi Building 3, Suit.115
1065 Nicosia, Cyprus.
Manufactured by:
DEMO S.A.
Pharmaceutical Industry
Athens, Greece
PL24598/0021
POM
5 205411 002208
EXP: XXXX
LOT: XXXX

Module 5
Scientific discussion during initial procedure

I INTRODUCTION

On 8 February 2012, Cyprus, Germany, Greece Italy and the UK agreed to grant a Marketing Authorisation (MA) to Noridem Enterprises Ltd, for the medicinal products Deferoxamine 500 mg and 2 g Powder for Solution for Injection or Infusion. The MA was granted via a Decentralised Procedure (DCP), with the UK as Reference Member State (RMS UK/H/3325/001-2/DC). After the national phase, a MA was granted in the UK on 14 March 2012 (PL 24598/0020-21).

These applications were made under Article 10(1) of Directive 2001/83/EC as amended for Deferoxamine 500 mg and 2 g Powder for Solution for Injection or Infusion, containing the known active substance deferoxamine mesilate. The reference medicinal products for these applications are Desferal 500 mg and 2 g Powder for Solution for Injection or Infusion (PL 00008/5073R), granted to Ciba-Geigy on 20 October 1988 after reviewing a product licence of right given in 1973, on the 31 October 1997 the licence underwent a Change of Ownership and is currently granted to Novartis Pharmaceuticals UK Limited (PL 00101/0523).

Deferoxamine mesilate is the mesilate salt of this chelating agent that binds free iron in a stable complex, preventing it from engaging in chemical reactions. Deferoxamine chelates iron from intra-lysosomal ferritin and ferrioxamine, a water-soluble complex excreted by the kidneys and in the feces via the bile. This agent does not readily chelate iron bound to transferrin, hemoglobin, myoglobin or cytochrome. It is used to treat acute and chronic iron and aluminium overload.

No new non-clinical or clinical efficacy studies were conducted for this application, which is acceptable given that the applications were for generic versions of products that have been licensed for over 10 years. A bioequivalence study is not necessary to support these applications for parenteral solutions.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of this product. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the pharmacovigilance system, as described by the Marketing Authorisation Holder (MAH), fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. The Marketing Authorisation Holder has provided adequate justification for not submitting a Risk Management Plan (RMP). As the application is for a generic version of an already authorised reference product, for which safety concerns requiring additional risk minimisation have not been

identified, a risk minimisation system is not considered necessary. The reference product has been in use for many years and the safety profile of the active is well established.

The MAH has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). This was an application for a generic product and there is no reason to conclude that marketing of this product will change the overall use pattern of the existing market.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Deferoxamine 500 mg Powder for Solution for Injection or Infusion Deferoxamine 2 g Powder for Solution for Injection or Infusion
Name(s) of the active substance(s) (INN)	Deferoxamine mesilate
Pharmacotherapeutic classification (ATC code)	Iron chelating agents V03AC01
Pharmaceutical form and strength(s)	Powder for Solution for Injection or Infusion 500 mg and 2 g
Reference numbers for the Decentralised Procedure	UK/H/3325/01-2/DC
Reference Member State	United Kingdom
Member States concerned	Cyprus, Germany, Greece and Italy
Marketing Authorisation Number(s)	PL 24598/0020 PL 24598/0021
Name and address of the authorisation holder	Noridem Enterprises Ltd, Evagorou and Makariou, Mitsi Building 3, Office 115, Nicosia CY-1065, Cyprus.

III SCIENTIFIC OVERVIEW AND DISCUSSION

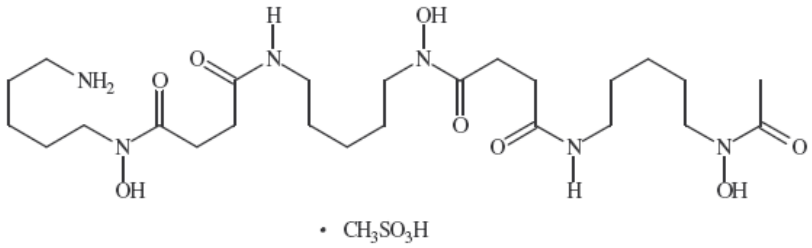
III.1 QUALITY ASPECTS

DRUG SUBSTANCE

INN: Deferoxamine mesilate

Chemical name: Butanediamide, N'-[5-[[4-[[5-(acetylhydroxyamino)pentyl]amino]-1,4-dioxobutyl]hydroxyamino]pentyl]-N-(5-aminopentyl)-N-hydroxy, monomethanesulfonate.

Structure:



Molecular formula: $C_{26}H_{52}N_6O_{11}S$.

Molecular weight: 656.79

General Properties

Description: White to almost-white, hygroscopic powder.

Solubility: It is freely soluble in water, slightly soluble in methanol and very slightly soluble in ethanol.

The active substance, deferoxamine mesilate is the subject of a European Pharmacopeia (Ph. Eur) monograph.

Manufacture

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for all working standards.
Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

DRUG PRODUCT

Description and Composition

The drug product is presented as a single dose, sterile, lyophilised powder available in vials containing either 500mg or 2 g of deferoxamine mesilate.

Other Ingredients

There are no other ingredients in this medicinal product.

The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in, or used in the manufacturing process for the proposed product. Furthermore, no genetically modified organisms are used in the manufacture of the medicinal product.

Pharmaceutical Development

The aim of the pharmaceutical development programme was to produce a robust, reproducible freeze-dried powder that could be considered generic medicinal products of Desferal® 500 mg and 2 g powder for solution for injection or infusion (Novartis Pharmaceuticals UK Limited). Suitable pharmaceutical development data have been provided for these applications.

The physico-chemical properties of the drug products have been compared with the reference products. These data demonstrate that the proposed products can be considered generic medicinal products of Desferal® 500 mg and 2 g powder for solution for injection or infusion (Novartis Pharmaceuticals UK Limited).

Comparative impurity data were provided for the test and reference products. The impurity profiles were found to be similar, with all impurities within the specification limits.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls were considered appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted on pilot-scale batches and are accepted. A commitment has been made to provide the data from the first three commercial batches in-line with the process validation protocol submitted.

Finished Product Specification

Finished product specifications are provided for both release and shelf–life, and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and adequately validated, as appropriate. Batch data are provided and are compliant with the proposed release specifications. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

The finished product is licensed for marketing in neutral glass (type I) vial with a rubber (type I) stopper. The product contained in outer cardboard cartons and packaged with the Patient Information Leaflet (PIL). Deferoxamine 500 mg and 2 g Powder for Solution for Injection or Infusion

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with Directive 2002/72/EC (as amended), concerning products in contact with parenteral products. The glass vials and rubber stoppers comply with Ph Eur requirements.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 48 months has been set, when the vial is unopened, which is satisfactory. Storage instructions are 'Store below 25°C". After opening 'in-use' product stability study was carried out on Deferoxamine 500 mg and 2 g Powder for Solution for Injection of Infusion to establish the time period over which the product could be used after the vial has been opened. From a microbiological point of view, the product should be used immediately after reconstitution (commencement of treatment within 3 hours). When the reconstitution is carried out under validated aseptic conditions the reconstituted solution may be stored for a maximum of 24 hours at 25°C before administration. If not used immediately, in-use storage times and conditions prior to administration are the responsibility of the user. Unused solution should be discarded.

Bioequivalence Study
The product is an aqueous parenteral solution at the time of administration and contains the same concentration of the active substance as the reference product, Desferal 500 mg and 2 g Powder for Solution for Injection or Infusion; bioequivalence studies from a quality perspective can be waived.

Quality Overall Summary
A satisfactory quality overall summary is provided and has been prepared by an appropriately qualified expert. The *curriculum vita* of the expert has been provided.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC, PIL and labelling are pharmaceutically acceptable. Colour mock-ups of the labelling and PIL have been provided. The labelling is satisfactory.

The applicant has submitted results of PIL user testing. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that is contains.

MAA Form
The MAA form is pharmaceutically satisfactory.

Conclusion
There are no objections to the approval of Deferoxamine 500 mg and 2 g Powder for Solution for Injection of Infusion from a pharmaceutical point of view.

III.2 NON-CLINICAL ASPECTS

The pharmacodynamic, pharmacokinetic and toxicological properties of deferoxamine mesilate are well-known. Therefore, no further studies are required and the applicant has provided none.

Since Deferoxamine 500 mg and 2 g Powder for Solution for Injection or Infusion is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

The non-clinical overview was written by a suitably qualified person and is satisfactory. The *curriculum vita* of the expert has been provided.

The SmPC is satisfactory from a non-clinical viewpoint and is consistent with that for the reference product.

There are no objections to approval of Deferoxamine 500 mg and 2 g Powder for Solution for Injection or Infusion from a non-clinical point of view.

III.3 CLINICAL ASPECTS

Pharmacokinetics

No new data have been submitted and none are required for an application of this type.

Deferoxamine 500 mg and 2 g Powder for Solution for Injection or Infusion are generic versions of Desferal 500 mg and 2 g Powder for Solution for Injection or Infusion. The use of the reference product is well-established in the UK. Both the reference products and the test products contain the same quantitative and qualitative composition of the active ingredient, deferoxamine mesilate.

According to CPMP guidelines, the applicant is not required to submit a bioequivalence study if the product is to be administered as an aqueous intravenous solution containing the same active substance, in the same concentration as the currently authorised product (CPMP/EWP/1401/98, subpoint 5.1.6, Parenteral solutions).

Pharmacodynamics

No new data have been submitted and none are required for applications of this type.

Clinical efficacy

No new data have been submitted and none are required for applications of this type.

Clinical safety

No new safety data have been submitted or are required for these generic applications. As deferoxamine mesilate is a well-known product with an acceptable adverse event profile, this is satisfactory.

Expert Report

A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified physician. The *curriculum vita* of the expert has been provided.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels

The SmPCs and PILs are medically acceptable, and consistent with those for the reference products. The labelling is medically acceptable and in-line with current requirements.

MAA form

The MAA form is medically satisfactory.

Conclusion

There are no objections to approval of Deferoxamine 500 mg and 2 g Powder for Solution for Injection or Infusion from a clinical point of view.

IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY

The important quality characteristics of Deferoxamine 500 mg and 2 g Powder for Solution for injection of Infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY

The applicant's products Deferoxamine 500 mg and 2 g Powder for Solution for Injection or Infusion has been demonstrated to be generic versions of the reference products Desferal 500 mg and 2 g Powder of Solution for Injection or Infusion (Novartis Pharmaceuticals UK Limited).

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE

The SmPCs and PILs are acceptable, and consistent with those for the reference product. The labelling is acceptable and in-line with current requirements.

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

BENEFIT/RISK ASSESSMENT

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant's products Deferoxamine 500 mg and 2 g Powder for Solution for Injection or Infusion and the reference products Desferal 500 mg and 2 g Powder for Solution for Injection or Infusion (Novartis Pharmaceuticals Limited UK), are interchangeable. Extensive clinical experience with deferoxamine mesilate is considered to have demonstrated the therapeutic value of the active substance. The benefit/risk is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome