NEW ZEALAND DATA SHEET

1. PRODUCT NAME

DBL™ Desferrioxamine Mesylate for Injection BP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DBL Desferrioxamine Mesylate for Injection BP contains 500 mg or 2 gram of desferrioxamine mesilate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

DBL Desferrioxamine Mesylate for Injection BP Powder for injection. It is is a sterile, lyophilised powder for reconstitution.

Desferrioxamine mesilate BP is a white to cream powder. When reconstituted with Water for Injections BP a clear solution with a pH of 3.5 to 5.5 is produced.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Monotherapy iron chelation treatment for chronic iron overload, e.g.

- transfusional haemosiderosis, as seen in thalassaemia major, sideroblastic anaemia, auto-immune haemolytic anaemia, and other chronic anaemias.
- idiopathic (primary) haemochromatosis in patients in whom concomitant disorders (e.g. severe anaemia, cardiac disease, hypoproteinaemia) preclude phlebotomy
- iron overload associated with porphyria cutanea tarda in patients unable to tolerate phlebotomy.
- Treatment for acute iron poisoning.

Treatment for chronic aluminium overload in patients with end-stage renal failure (under maintenance dialysis) with

- aluminium-related bone disease,
- dialysis encephalopathy or
- aluminium-related anaemia.

4.2 Dose and method of administration

Desferrioxamine mesilate may be administered intramuscularly, or via intravenous, or subcutaneous infusion. When administered subcutaneously the needle should not be inserted too close to the dermis.

Only clear pale yellow desferrioxamine mesilate solutions should be used. Opaque, cloudy or discoloured solutions should be discarded.

Heparin is pharmaceutically incompatible with desferrioxamine mesilate solutions (refer Section 6.2 Incompatibilities).

Dosage

Treatment for chronic iron overload

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

Children and Adults

It is recommended that therapy with desferrioxamine mesilate be started after the first 10-20 blood transfusions or when the serum ferritin level has reached 1000 nanogram/mL.

Growth retardation may result from iron overload or excessive desferrioxamine mesilate doses. If chelation is begun before 3 years of age growth must be monitored carefully and the mean daily dose should not exceed 40 mg/kg.

The dosage and the mode of administration may be individually determined and adapted during the course of therapy according to the severity of the patient's iron burden. The lowest effective dosage should be used. To assess the response to chelation therapy, 24-hour urinary iron excretion may initially be monitored daily and the response to increasing doses of desferrioxamine mesilate established. Once the appropriate dosage has been established, urinary iron excretion rates may be assessed at intervals of a few weeks. The therapeutic index is a valuable tool in protecting the patient from excess chelation, but it is not a substitute for careful clinical monitoring.

The average daily dose of desferrioxamine mesilate is usually between 20 and 60 mg/kg. In general patients with a serum ferritin level of less than 2000 nanogram/mL require about 25 mg/kg/day. Patients with a serum ferritin level between 2000 and 3000 nanogram/mL require 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 to regularly exceed an average daily dose of 50 mg/kg/day except when very intensive chelation is needed in patients who have completed growth. If ferritin values fall below 1000 nanogram/mL, the risk of desferrioxamine mesilate toxicity increases; it is important to monitor these patients particularly carefully and perhaps to consider lowering the total weekly dose. The doses given are the average daily dose. Since most patients take the drug on less than 7 days a week, the

actual dose per infusion usually differs from the average daily dose; e.g. if an average daily dose of 40 mg/kg/day is required and the patient wears the pump 5 nights a week, each infusion should contain 56 mg/kg.

Regular chelation with desferrioxamine mesilate has been shown to improve life expectancy in patients with thalassaemia.

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

Intravenous infusion during blood transfusion

The availability of an intravenous line during blood transfusions makes it possible to administer an intravenous infusion with no additional inconvenience to the patient. This is particularly useful for patients who comply poorly with subcutaneous infusions.

The desferrioxamine mesilate 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 DBL Desferrioxamine Mesylate for Injection BP as usual. Because of the limited amount of drug that can be administered by IV infusion during blood transfusion, the clinical benefit of this mode of administration is limited. Patients and nurses should be warned against accelerating the intravenous infusion, as an intravenous bolus of desferrioxamine mesilate may lead to acute collapse, flushing, hypotension and circulatory collapse (see section 4.4 Special warnings and precautions for use).

Continuous intravenous infusion

Implanted intravenous systems can be used when intensive chelation is carried out. Continuous intravenous infusion is indicated in patients who are incapable of continuing subcutaneous infusions and in those who have cardiac problems secondary to iron overload. The dose of desferrioxamine mesilate depends on the extent of the patient's iron overload. The 24-hour urinary iron excretion should be measured regularly where intensive chelation (i.v.) is required, and the dose adjusted accordingly.

Care should be taken when flushing the line to avoid the sudden infusion of residual desferrioxamine mesilate which may be present in the dead space of the line, as this may lead to acute collapse, flushing, hypotension and circulatory collapse (see section 4.4 Special warnings and precautions for use).

Intramuscular administration

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

The maximum locally tolerated dose by intramuscular injection lies in the range 0.5 to 1.5 g. The volume of solution should be not less than 3 mL for each gram of desferrioxamine mesilate (ie reconstitute each 500 mg vial of DBL Desferrioxamine Mesylate for Injection BP with not less than 1.5 mL of Water for Injections).

Whichever route of administration is chosen, the individual maintenance dose to be selected will depend on the patient's iron excretion rate.

If the patient is normotensive, desferrioxamine mesilate may be given in a single intramuscular dose: 2g for an adult and 1g for a child. However, intravenous infusion is preferable since the rate of administration can be controlled and adapted to the patient's condition.

If the patient is hypotensive, the intravenous route is recommended. The maximum rate for intravenous administration is 15 mg/kg/hour and is reduced after four to six hours so that the total intravenous dose in general, does not exceed 80 mg/kg/24 hours. However, in an adult patient with severe iron poisoning, an infusion of desferrioxamine mesylate 37.1g over 52 hours has been tolerated without apparent unwanted effects.

Concomitant use of vitamin C

Patients with iron overload usually become vitamin C deficient, probably because iron oxidises the vitamin. As an adjuvant to chelation therapy, vitamin C in doses up to 200 mg daily may be given in divided doses, starting after an initial month of regular treatment with DBL Desferrioxamine Mesylate for Injection BP (see section 4.4 Special warnings and precautions for use). Vitamin C increases availability of iron for chelation. In general, 50 mg suffices for children under 10 years of age and 100 mg for older children. Larger doses of vitamin C fail to produce any additional increase in excretion of the iron complex.

Treatment for acute iron poisoning

Adults and children:

DBL Desferrioxamine Mesylate for Injection BP is an adjunct to standard measures generally used in treating acute iron poisoning.

DBL Desferrioxamine Mesylate for Injection BP treatment is indicated in any of the following situations:

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

The continuous intravenous administration of DBL Desferrioxamine Mesylate for Injection BP 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-h period. The following suggested criteria are believed to represent appropriate requirements for cessation of DBL Desferrioxamine Mesylate for Injection BP. Chelation therapy should be continued until all of the following criteria are satisfied:

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

- ideally, a corrected serum iron level should be normal or low (when iron level falls below 100 microgram/dL). Given that laboratories cannot measure serum iron concentrations accurately in the presence of desferrioxamine mesilate, it is acceptable to discontinue DBL Desferrioxamine Mesylate for Injection BP when all other criteria are met if the measured serum iron concentration is not elevated,

- repeat abdominal radiograph test should be obtained in patients who initially demonstrated multiple radiopacities to ensure they have disappeared before DBL Desferrioxamine Mesylate for Injection BP is discontinued because they serve as a marker for continued iron absorption,

- if the patient initially developed vin-rosé coloured urine with DBL Desferrioxamine Mesylate for Injection BP therapy, it seems reasonable that urine colour should return to normal before halting DBL Desferrioxamine Mesylate for Injection BP (absence of vin-rosé urine is not sufficient by itself to indicate discontinuation of DBL Desferrioxamine Mesylate for Injection BP).

The effectiveness of treatment is dependent on an adequate output of urine in order to ensure that the iron complex ferrioxamine is excreted from the body. If oliguria or anuria develops, peritoneal dialysis, haemodialysis, or haemofiltration may become necessary to remove ferrioxamine.

It should be noted that the serum iron level may rise sharply when the iron is released from the tissues.

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

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

Patients with evidence of symptoms or organ dysfunction due to aluminium overload should receive desferrioxamine mesilate treatment. Even in asymptomatic patients, desferrioxamine mesilate treatment should be considered if serum aluminium levels are consistently above 60 nanogram/mL and are associated with a positive desferrioxamine mesilate infusion test (see below), particularly if bone biopsy findings present evidence of aluminium-related bone disease.

Adults and children:

DBL Desferrioxamine Mesylate for Injection BP should be administered as a once-weekly 5 mg/kg dose in patients on maintenance haemodialysis or haemofiltration (see section 4.2 Dose and method of administration). For patients with post-desferrioxamine (desferrioxamine) test serum aluminium levels up to 300 nanogram/mL, DBL Desferrioxamine Mesylate for Injection BP 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). For patients with a post-desferrioxamine test serum aluminium value above 300 nanogram/mL, DBL Desferrioxamine Mesylate for Injection BP should be administered by slow i.v. infusion 5 hours prior to the dialysis session. After completing the first 3-month course of DBL Desferrioxamine Mesylate for Injection BP treatment, followed by a 4-week wash-out period, a desferrioxamine mesilate infusion test should be performed. If two successive desferrioxamine mesilate infusion tests performed at 1-month intervals yield serum aluminium levels less than 50 nanogram/mL above baseline, further desferrioxamine mesilate treatment is not recommended.

In patients on continuous ambulatory peritoneal dialysis (CAPD) or continuous cyclic peritoneal dialysis (CCPD) DBL Desferrioxamine Mesylate for Injection BP should be given once weekly at a 5 mg/kg dose prior to the final exchange of the day. It is recommended that the intraperitoneal route be used in these patients. However, DBL Desferrioxamine Mesylate for Injection BP can also be given i.m., by slow infusion i.v. or s.c..

Desferrioxamine mesilate test

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

1. **Desferrioxamine mesilate test for iron overload in patients with normal kidney function**

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

2. **Desferrioxamine mesilate infusion test for aluminium overload in end-stage renal failure patients**

A desferrioxamine mesilate infusion test is recommended in patients with serum aluminium levels exceeding 60 nanogram/mL associated with serum ferritin levels above 100 nanogram/mL.

Just before starting a haemodialysis session, a blood sample is taken to determine the baseline serum aluminium level.

During the last 60 minutes of the haemodialysis session a 5 mg/kg dose (see section 4.2 Dose and method of administration) is given as a slow intravenous infusion.

At the start of the next haemodialysis session (i.e. 44 hours after the aforementioned desferrioxamine mesilate infusion) the second blood sample is taken to determine the serum aluminium level once more.

The desferrioxamine mesilate test is considered positive if an increase in serum aluminium above the baseline level exceeds 150 nanogram/mL. A negative test, however, does not absolutely exclude the diagnosis of aluminium overload.

In patients with terminal renal failure receiving haemodialysis, serum iron values should be determined before and after the administration of desferrioxamine mesilate 500 mg intramuscularly or intravenously. A continuous increase in serum iron during the following hours is suggestive of overload.

Method of administration

Preparation

For parenteral administration, DBL Desferrioxamine Mesylate for Injection BP should be reconstituted with Water for Injections (5 mL for the 500 mg vial and 20 mL for the 2 gram vial) to produce an approximate 10% solution (see below). However for IM administration, each 500 mg vial of DBL Desferrioxamine Mesylate for Injection BP may be reconstituted with not less than 1.5 mL of Water for Injections. The drug should be completely dissolved to produce a clear solution before use. DBL Desferrioxamine Mesylate for Injection BP 500 mg vials reconstituted with 5 mL will yield desferrioxamine mesilate concentrations of 93.5 mg/mL (the displacement volume of DBL Desferrioxamine Mesylate for Injection BP is approximately 7% when reconstituted with 5 mL of Water for Injections BP).

For intravenous infusion, further dilution may be performed with 0.9% Sodium Chloride Intravenous Infusion, 5% Glucose Intravenous Infusion or Ringer's-Lactate Intravenous Infusion at a concentration of 1 to 8 mg/mL, although these should not be used as solvents for the dry substance. For subcutaneous administration, the reconstituted solution may be given undiluted.

Administration of solution

Dissolved desferrioxamine mesilate can also be added to the dialysis fluid and given intraperitoneally to patients on chronic ambulatory peritoneal dialysis or continuous cycling peritoneal dialysis.

Desferrioxamine is sometimes used for home infusions. If home use is to be instituted, it is important that patients and families be fully instructed on the safe and appropriate technique of administration.

The use of DBL Desferrioxamine Mesylate for Injection BP in chronic iron overload by means of a portable infusion pump is described as follows:

1. Draw the water for injection into a syringe.
2. After cleaning the rubber stopper of the DBL Desferrioxamine Mesylate for Injection BP vial with alcohol, inject the content of the syringe into the vial.
3. Shake the vial well to dissolve the drug.
4. Draw the dissolved drug into the syringe.
5. Attach the extension tube to the syringe, connect the extension tube to the butterfly-type needle, and then fill the empty space in the tube with the solution in the syringe.
6. Place the syringe into the infusion pump.

7. For infusion you may insert the butterfly-type needle under the skin of the abdomen, the arm, upper leg, or the thigh. It is important to clean the skin very thoroughly with alcohol before you insert the needle firmly up to the wings into a fold of the skin, formed by your free hand. The tip of the needle should move freely when the needle is waggled. If it doesn't move freely, the tip of the needle may be too close to the skin. Try again at a new site after cleaning it with alcohol.
8. Then fix the needle and tape it down.
9. Patients usually wear the pump on the body using a belt or shoulder holster. Many patients regard overnight use as the most convenient.

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 other drug therapy (see sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects).

Clinical studies of desferrioxamine mesilate did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently to younger subjects.

Use in Hepatic impairment

No studies have been performed in patients with hepatic impairment.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

Desferrioxamine mesilate should not be administered subcutaneously in concentrations and/or doses higher than those recommended as otherwise local irritation at the site of administration may occur more frequently.

Prolonged or high doses of desferrioxamine mesilate, especially in patients with low ferritin plasma levels, may lead to disturbances of vision and hearing (see section 4.8). 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 desferrioxamine mesilate. The risk of side effects is reduced when low-dose therapy is employed. If visual or auditory disturbances occur, the drug should be discontinued immediately. The changes induced by desferrioxamine mesilate are usually reversible if identified early. Treatment with desferrioxamine mesilate may be resumed later at a reduced dose, with close monitoring of audiovisual function be carried out with due regard to the risk-benefit ratio. A detailed ophthalmological assessment is recommended (visual field

measurements, funduscopy, colour vision testing using pseudoisochromatic plates and the Farnsworth D-15 colour test, slit lamp investigation, visual evoked potential studies).

Approximately half of the metal complex is excreted via the kidneys in iron-overloaded patients with normal renal function. Accordingly, in patients with severe renal failure caution is indicated. The iron and aluminium complexes of desferrioxamine are dialysable; in patients with renal failure their elimination will be increased by dialysis. In these patients, dialysis will increase the elimination of chelated iron and aluminium. Monitoring of patients for changes in renal function (e.g. increased serum creatinine) should be considered.

Patients with low serum ferritin levels on high doses of desferrioxamine mesilate, or patients at young age (< 3 years at commencement of treatment) have been associated with growth retardation (see section 4.2 Dose and method of administration and 4.8 Undesirable effects). Growth retardation if associated with excessive doses of desferrioxamine mesilate must be distinguished from growth retardation from iron overload. Growth retardation from desferrioxamine mesilate 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 desferrioxamine mesilate in patients with acute iron intoxication, and also in thalassaemic patients. The recommended daily doses should therefore not be exceeded.

In patients suffering from iron overload it has been reported that desferrioxamine mesilate increases susceptibility to infections, notably with micro-organisms that are iron-dependent such as *Yersinia enterocolitica*, *Yersinia pseudotuberculosis, Pneumocystis carinii and Staphylococcus aureus*. If a patient under treatment with desferrioxamine mesilate develops pyrexia accompanied by acute enteritis/enterocolitis, diffuse abdominal pain or pharyngitis, treatment should be temporarily discontinued, bacteriological tests performed, and suitable antibiotic therapy started at once. After the infection has resolved, treatment with desferrioxamine mesilate can be resumed.

In patients receiving desferrioxamine mesilate for haemodialysis, aluminium and/or iron overload, very rare cases of mucormycosis or infection with *Pneumocystis carinii or Rhizopus*, severe fungal infections, sometimes with fatal outcome, have been reported. If any of the suspected signs or symptoms occur, desferrioxamine mesilate should be discontinued, mycological tests carried out and appropriate treatment instituted immediately. Mucormycosis may also occur in patients who are not receiving desferrioxamine mesilate, indicating that other factor determinants such as dialysis, diabetes mellitus, disturbance of acid-base balance, haematological malignancies, immunosuppressive drugs, or a compromised immune system may play a role in the development of this infection.

Urinary excretion of parenterally administered iron has been reported to exacerbate latent pyelonephritis, this may also occur with desferrioxamine therapy. Desferrioxamine should be used with caution in patients with pyelonephritis.

Desferrioxamine mesilate has some neurotoxic effects which may be due to its ability to chelate copper or zinc. It has a suppressant effect on lymphocytes.

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

Desferrioxamine mesilate should not be given in doses higher than recommended. The drug should not be given at concentrations higher than a 10% solution in water for injection as this increases the risk of local reactions by the subcutaneous route (see section 4.2 Dose and method of administration). Where intramuscular use is the only option it may be necessary to use higher concentrations to facilitate the injection.

At the recommended concentration of 10%, the reconstituted solution appears clear, and colourless to slightly yellowish. Only clear solutions should be used. Opaque or cloudy solutions should be discarded. Due care must be taken with the injection technique.

For subcutaneous infusion, the needle should not be inserted too close to the dermis.

In patients with severe chronic iron overload, impairment of cardiac function has been reported following concomitant treatment with desferrioxamine mesilate and high doses of vitamin C (more than 500 mg daily). The cardiac dysfunction was reversible when vitamin C was discontinued. The following precautions should be taken when desferrioxamine mesilate and vitamin C are to be used concomitantly:

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

Specialist ophthalmological and audiological testing are recommended before the start ofdesferrioxamine mesilate treatment and thereafter at regular intervals (every 3 months) particularly if ferritin levels are low. By keeping the ratio of the mean daily dose (mg/kg) of desferrioxamine mesilate divided by the serum ferritin (microgram/L) below 0.025 the risk of audiometric abnormalities may be reduced in thalassaemia patients.

Paediatric patients receiving desferrioxamine mesilate should be monitored for body weight and longitudinal growth every 3 months (see section 4.2 Dose and method of administration).

In patients with aluminium-related encephalopathy, high doses of desferrioxamine mesilate may exacerbate neurological dysfunction (seizures), probably owing to an acute increase in brain aluminium secondary to elevated circulating levels. Desferrioxamine mesilate may precipitate the onset of dialysis dementia. Pretreatment with clonazepam has been reported to prevent this neurological deterioration. Also, treatment of aluminium overload may result in decreased serum calcium and aggravation of hyperparathyroidism.

Other

The subcutaneous administration of high doses of desferrioxamine to rats, dogs and cats for several weeks caused eye-lens opacity with cataract formation.

4.5 Interaction with other medicines and other forms of interaction

Desferrioxamine mesilate should not be used in combination with prochlorperazine (a phenothiazine derivative) since prolonged unconsciousness may result. Caution is advised when desferrioxamine mesilate is used in combination with any phenothiazine.

The neuro-ophthalmic toxicity of desferrioxamine mesilate may also be potentiated by concurrent use of phenothiazines or methyl dopa.

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 desferrioxamine mesilate; 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 desferrioxamine mesilate regularly, and should not be administered within the first month of desferrioxamine mesilate therapy. In patients with severe chronic iron-storage disease undergoing combined treatment with desferrioxamine mesilate and high doses of vitamin C (more than 500 mg daily), impairment of cardiac function has been encountered (see section 4.4); this proved reversible when the vitamin C was withdrawn. Vitamin C supplements should not therefore be given to patients with cardiac failure.

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

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

4.6 Fertility, pregnancy and lactation

Fertility

Desferrioxamine mesilate is teratogenic in animal experiments (see **Pregnancy**).

Pregnancy

Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

In teratogenicity studies, desferrioxamine mesilate in daily doses up to 4.5 times the maximum human daily dose appeared to cause delayed ossification in mice and skeletal anomalies in rabbits. No adverse effects were observed in similar studies in rats. There are no adequate or well controlled studies in pregnant women. For this reason, desferrioxamine mesilate should not be administered to pregnant women (especially during the first three months of pregnancy) or to women who may become pregnant unless the potential benefits outweigh the potential risks to the fetus.

Lactation

It is not known whether desferrioxamine passes into the breast milk.

Desferrioxamine 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.

4.7 Effects on ability to drive and use machinery

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

4.8 Undesirable effects

Frequency estimate: very common > 10%, common > 1% to < 10%; uncommon > 0.1% to < 1%; rare > 0.01% to < 0.1%; very rare < 0.01% including isolated reports, not known (cannot be estimated from the available data).

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

Infections and infestations

Rare: Mucormycosis (some fatal).

Very rare: Gastroenteritis yersinia infections.

Infections caused by *Pneumocystis carinii*, *Staphylococcus aureus*, *Rhizopus* may develop in patients receiving desferrioxamine (see section 4.4 Special warnings and precautions for use).

Blood and lymphatic system disorder

Very rare: Blood dyscrasias (e.g. thrombocytopenia), aplastic anaemia.

Not known: Leukopenia, eosinophilia and inhibition of DNA synthesis in T and B lymphocytes.

One case of fatal pancytopenia attributed to the use of desferrioxamine has been reported.

Immune system disorders

Hypersensitivity reactions occasionally occur. Rash and pyrexia have been encountered.

Rare: Anaphylactic/anaphylactoid reactions with or without shock, angioedema, including laryngeal oedema.

Metabolism and nutrition disorders

Hypocalcaemia (transient), hyperparathyroidism, iron deficiency.

Nervous system disorders

Unknown: Reversible aphasia.

Common: Headache.

Rare: Nervous system disorder, dizziness, seizures (mainly reported in dialysed patients with aluminium overload), exacerbation of neurological impairment in aluminium-related encephalopathy.

Isolated cases: Peripheral sensory, motor or mixed neuropathy, paraesthesia, precipitation of toxic encephalopathy (see section 4.4).

Eye disorders

Visual impairment including acute visual neurotoxicity, lenticular opacities and irreversible blindness.

Rare: vision blurred, visual acuity reduced, blindness, impairment of colour vision (dyschromatopsia), night blindness (nyctalopia), visual field defect, retinopathy (pigmentary degeneration of the retina), optic neuritis, cataract (lens opacities) chromatopsia, corneal opacity, except if high doses are given (see section 4.4).

Ear and labyrinth disorders

Auditory disturbances included acute auditory neurotoxicity and irreversible loss of hearing.

Uncommon: Deafness neurosensory, high-frequency sensorin.eural hearing loss, tinnitus are uncommon if doses are kept within guidelines and if doses are reduced when ferritin levels fall (ratio of the mean daily dose of desferrioxamine mesilate divided by the serum ferritin should be below 0.025).

Vascular disorders

Hypotension or shock may occur if the recommended precautions for the administration of desferrioxamine mesilate are not followed (see section 4.2 and section 4.4).

Cardiac disorders

Tachycardia, arrhythmia.

Respiratory, thoracic and mediastinal disorders

Uncommon: Asthma

Very rare: Acute respiratory distress syndrome (ARDS) with dyspnoea, cyanosis and lung infiltration following excessively high intravenous doses of desferrioxamine mesilate (see section 4.4).

Unknown: ARDS with respiratory failure, hypoxia, pulmonary oedema, low pulmonary compliance, and pulmonary arterial wedge pressures below 18 mmHg. A pulmonary syndrome of a moderate to life-threatening nature with tachypnoea, hypoxaemia, a diffuse interstitial pattern on the chest x-ray and restrictive pulmonary dysfunction.

Gastrointestinal disorders

Rare: Diarrhoea, nausea, vomiting, abdominal pain.

Unknown: Faeces discoloured.

Hepatobiliary disorders

Rare: Hepatic impairment.

Skin and subcutaneous tissue disorders

Rare: Pruritus, urticaria, generalised rash.

Musculoskeletal and connective tissue

Very common: Arthralgia/myalgia.

Common: Growth retardation and bone changes (e.g. metaphyseal dysplasia) are common in chelated patients given doses of above 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.

Rare: Muscle spasms and bone pain have also been reported in isolated cases.

Renal and urinary disorders

Very rare: Renal impairment (see section 4.4).

Not known: Acute renal failure, renal tubular disorder, dysuria, aggravation of pyelonephritis. Urine colour change to orange-rose or 'vin rose colour'.

General disorders and administration site conditions

Very common: Infiltration and eschar/scab.

Common: Pain, swelling, induration, erythema, burning, pruritus, urticaria, rash at the injection/infusion site. Occasionally accompanied by pyrexia, chills and malaise.

Uncommon: Blisters and local oedema at the injection site.

Investigations:

Not known: Blood creatinine increased.

Some of the adverse events mentioned above must be considered as signs and symptoms of the underlying disease. Excretion of iron complex during treatment with desferrioxamine mesilate causes reddish-brown discolouration of the urine.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

Signs and symptoms

Inadvertent administration of an overdose or inadvertent intravenous bolus administration/rapid intravenous infusion may be associated with hypotension, tachycardia and gastrointestinal disturbances; acute but transient blindness, aphasia, agitation, headache, nausea, bradycardia, as well as acute renal failure have been reported.

Acute respiratory distress syndrome has been described following treatment with excessively high IV doses of deferoxamine in patients with acute iron intoxication, and also in thalassemic patients.

Treatment

There is no specific antidote. DBL Desferrioxamine Mesylate for Injection BP should be discontinued and appropriate symptomatic measures undertaken. Appropriate supportive therapy should be instituted.

Desferrioxamine mesilate is dialysable.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Desferrioxamine forms complexes predominantly with ferric iron and with trivalent aluminium ions: the complex formation constants are 10^{31} and 10^{25}, respectively. The affinity of desferrioxamine for divalent ions such as Fe^{2+}, Cu^{2+}, Zn^{2+}, Ca^{2+} is substantially lower (complex formation constants 10^{14} or below). Chelation occurs at a 1:1 molar basis, so that 1 g desferrioxamine can theoretically bind 85 mg ferric iron or 41 mg Al^{3+}.

Owing to its chelating properties, desferrioxamine is capable of taking up free iron, either in plasma or in cells thereby forming the complex ferrioxamine. Urinary iron excretion of ferrioxamine is predominantly a reflection of iron derived from plasma turnover whereas faecal iron reflects mainly intrahepatic iron chelation. Iron may be chelated from ferritin and haemosiderin but is relatively slow at clinically relevant concentrations of desferrioxamine. Desferrioxamine, however, does not remove iron from transferrin or from haemoglobin or from other haemin-containing substances.

Desferrioxamine can also mobilise and chelate aluminium, forming an aluminoxamine complex.

Since both complexes, ferrioxamine and aluminoxamine, are completely excreted, desferrioxamine promotes the excretion of iron and aluminium in the urine and faeces and thus reduces pathological iron or aluminium deposits in the organs.

5.2 Pharmacokinetic properties

Absorption

Desferrioxamine 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. The absolute bioavailability is less than 2% after oral administration of 1 g desferrioxamine.

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

Distribution

In healthy volunteers peak plasma concentrations of 15.5 micromol/L (8.7 microgram/mL) were measured 30 minutes after an intramuscular injection of 10 mg/kg desferrioxamine. One hour after injection the peak concentration of ferrioxamine was 3.7 micromol/L (2.3 microgram/mL). After intravenous infusion of 2 g (about 29 mg/kg) of desferrioxamine to healthy volunteers over 2 hours mean steady state concentrations of desferrioxamine of 30.5 micromol/L were reached; distribution of desferrioxamine is very rapid with a mean distribution half-life of 0.4 hours.

Less than 10% of desferrioxamine is bound to serum proteins *in vitro*.

Biotransformation

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

Elimination

Both desferrioxamine and ferrioxamine have a biphasic elimination after intramuscular injection in healthy volunteers; for desferrioxamine 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 desferrioxamine and 1% as ferrioxamine.

Characteristics in patients

In **patients with haemochromatosis** peak plasma levels of 7.0 micromol/L (3.9 microgram/mL) were measured for desferrioxamine, and 15.7 micromol/L (9.6 microgram/mL) for ferrioxamine, 1 hour after an intramuscular injection of 10 mg/kg desferrioxamine. These patients eliminated desferrioxamine and ferrioxamine with half-lives of 5.6 and 4.6 hours, respectively. Six hours after the injection 17 % of the dose was excreted in the urine as desferrioxamine and 12 % as ferrioxamine.

In **patients with thalassaemia** continuous intravenous infusion of 50 mg/kg/24 h of desferrioxamine resulted in plasma steady state levels of desferrioxamine of 7.4 micromol/L (4.1 microgram/mL). Elimination of desferrioxamine 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 desferrioxamine in terms of AUC. The apparent monoexponential elimination half-life of the metabolite was 1.3 hours.

In **patients dialysed for renal failure** who received 40 mg/kg desferrioxamine infused i.v. within 1 hour, the plasma concentration at the end of the infusion was 152 micromol/L (85.2 microgram/mL) when the infusion was given between dialysis sessions. Plasma concentrations of desferrioxamine were between 13 % and 27 % lower when the infusion was administered during dialysis. Concentrations of ferrioxamine were in all cases approx. 7.0 micromol/L (4.3 microgram/mL); and for aluminoxamine 2-3 micromol/L (1.2-1.8 microgram/mL). After the infusion was discontinued, the plasma concentration of desferrioxamine 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. The plasma concentrations of aluminoxamine continued to increase for up to 48 hours after the infusion and reached values of approx. 7 micromol/L (4 microgram/mL). Following dialysis the plasma concentration of aluminoxamine dropped to 2.2 micromol/L (1.3 microgram/mL), indicating that the aluminoxamine complex is dialysable.

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

5.3 Preclinical safety data

Genotoxicity

In rabbits desferrioxamine 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 desferrioxamine mesilate appears to be free of teratogenic activity.

Evidence of mutagenicity has been observed in mouse lymphoma cells.

Carcinogenicity

Long-term carcinogenicity studies have not been performed.

Reproductive and developmental toxicity

Desferrioxamine was not teratogenic in rats and mice. In rabbit foetuses, which were exposed in utero to maternally toxic doses, some malformations of the axial skeleton were found. Though the results of this study are considered of a preliminary character, desferrioxamine-induced teratogenicity in rabbits cannot be excluded under the experimental conditions employed.

6. PHARMACEUTICAL PARTICUALRS

6.1 List of excipients

None

6.2 Incompatibilities

- Heparin injectable solution.

- Physiological saline (0.9%) should not be used as a solvent for the dry substance; but, after reconstitution of the DBL Desferrioxamine Mesylate for Injection BP solution with water for injection, it can be employed for further dilution.

6.3 Shelf life

24 months from date of manufacture stored at or below 25°C.

24 hours reconstituted stored at 2° to 8°C (Refrigerate, do not freeze).

6.4 Special precautions for storage

Store below 25°C. Protect from light.

6.5 Nature and contents of container

DBL Desferrioxamine Mesylate for Injection BP 500 mg is available in packs of 10 vials.

DBL Desferrioxamine Mesylate for Injection BP 2 g is available in packs of 1 vial.

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand
Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

DBL Desferrioxamine Mesylate for Injection BP 500 mg 17 April 1997

DBL Desferrioxamine Mesylate for Injection BP 2 g 23 August 2001

10. DATE OF REVISION OF THE TEXT

20 October 2023

Summary table of changes

Section changed	Summary of new information
Throughout	Minor editorial corrections and use of MedDRA terminology
4.2	Clarification regarding use in elderly
4.4	Warnings regarding severe fungal infections clarified
4.8	Adverse effects terminology and listings amended to reflect Australian Product Information.