DBL™ Desferrioxamine Mesylate for Injection BP

1. NAME OF THE MEDICINE

Desferrioxamine mesilate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of DBL Desferrioxamine Mesylate for Injection BP contains 500 mg or 2 g of desferrioxamine mesilate.

For the full list of excipients, see section 6.1 **List of Excipients**.

3. PHARMACEUTICAL FORM

Powder for injection.

DBL Desferrioxamine Mesylate for Injection BP is a sterile white to cream coloured powder or lyophilised plug for reconstitution. When reconstituted with Water for Injections a clear solution with a pH of 4.0 - 6.0 is produced.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Chronic iron overload

Desferrioxamine mesilate is used to promote iron excretion in patients with iron overload as a result of multiple blood transfusions frequently used in the treatment of some chronic anaemias and thalassaemia. Long-term therapy with desferrioxamine mesilate slows accumulation of hepatic iron and retards or eliminates progression of hepatic fibrosis.

Patients under the age of 3 years with small degree of iron overload have relatively poor iron mobilisation with desferrioxamine mesilate. The drug is not normally given to such patients unless significant iron mobilisation of 1 mg or more of iron per day can be demonstrated.

Desferrioxamine mesilate is not indicated for the treatment of primary haemochromatosis as phlebotomy is the method of choice for removing excess iron in this disorder.

Acute iron poisoning

Desferrioxamine mesilate is an adjunct to, and not a substitute for, standard measures used in treating acute iron poisoning, which may include induction of emesis, gastric lavage, suction and maintenance of a clear airway, control of shock with intravenous fluids, blood, oxygen and vasopressor and correction of acidosis.

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.

The presence of iron overload, preferably quantified, should be established before initiating therapy with desferrioxamine mesilate.

Chronic iron overload

In young patients with chronic iron overload the main aim of chelation therapy is to attain an iron balance and to prevent haemosiderosis. In older patients with chronic iron overload, the main aim of chelation therapy is a negative iron balance in order to slowly reduce the increased iron stores and to prevent the toxic effects of iron.

Dosage

The dosage schedule for children should be individually titrated according to the extent of iron overload. In children, the earliest age at which therapy with desferrioxamine mesilate should be undertaken is 2 to 3 years. The minimum effective dose is not known, so an initial trial of chelation therapy should be performed. To assess the response to chelation therapy, 24 hour urinary iron excretion should be monitored daily initially and the response to increasing doses of desferrioxamine mesilate established, starting with 0.5 g daily and increasing the dose until urine iron excretion reaches a plateau.

The lowest effective dose resulting in a negative iron balance should be used. In most patients daily doses of 20 to 40 mg/kg body weight are adequate. Higher doses should be administered only if the benefit for the patient outweighs the risk of unwanted effects associated with repeated high daily doses. Maximum doses of 80 mg/kg/day should not be exceeded. If ferritin values fall below 1,000 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.

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

Growth retardation may result from iron overload or excessive desferrioxamine mesilate 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 **Special warnings and precautions for use**).

Monitoring therapy

Once the maintenance dosage has been established, urinary iron excretion rates should be assessed at intervals of a few weeks. The expected rate of excretion of iron is 10 to 20 mg/day. The patient's total iron stores can be estimated by accurate recording of the amount of iron received through transfusions, supplemented by serum ferritin determination. Iron balance can be calculated based on the amount of iron excreted in the urine; negative iron balance is considered to be achieved when the total amount of iron excreted in the urine, plus

a further 50% (approximate mean iron excretion in the stools), exceeds the total iron received from blood transfusions. Chelation therapy is considered satisfactory when serum ferritin levels are close to normal values (<300 microgram/L).

Infusion

Intravenous infusions are usually more effective than subcutaneous infusions, but slow subcutaneous administration by means of a portable, lightweight infusion pump over a period of 8 to 12 hours is regarded as effective and convenient for ambulant patients. In some patients it is possible to achieve a further increase in iron excretion by infusing the same daily dose over a 24 hour period. Desferrioxamine mesilate is not formulated to support subcutaneous bolus injection.

Patients and nurses should be warned against accelerating the intravenous infusions, as an intravenous bolus of desferrioxamine mesilate may lead to flushing, hypotension and circulatory collapse (see section 4.4 **Special warnings and precautions for use**).

Heavily iron loaded patients should receive infusions five to seven times a week as protection against iron toxicity. However, if the iron load is low, infusions may be given three to five times a week.

Intramuscular

Desferrioxamine mesilate may be injected intramuscularly, though this method is less effective than subcutaneous infusion. 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 (i.e., reconstitute each 500 mg vial of DBL Desferrioxamine Mesylate for Injection BP with not less than 1.5 mL of Water for Injections).

Note. Ascorbic acid (approximately 200 mg daily) may be given as an adjuvant after about six months of regular chelation therapy with desferrioxamine mesilate. Ascorbic acid in doses of 150 to 250 mg daily enhances urinary iron excretion, but very high doses have been suspected of giving rise to cardiac complications or ocular toxicity (see section 4.5 **Interactions with other medicines and other forms of interactions**).

Acute iron poisoning

Desferrioxamine mesilate is an adjunct to standard measures generally used in treating acute iron poisoning. These may include gastric lavage, induction of emesis, control of shock and correction of acidosis.

Iron levels

Plasma or serum iron should be measured three to four hours post-ingestion in the case of any iron preparation. Levels taken after four hours may underestimate toxicity because the subject iron may have either been distributed into tissues or be bound to ferritin. In the case of slow release or enteric coated tablets, levels should be repeated at six to eight hours as absorption may be erratic.

As a lesser priority iron binding capacity may usually be measured. Blood for plasma/serum iron measurement should be taken before chelation therapy is commenced. The following quantities are recommended: plasma/serum iron >0.5 mL of blood in serum or heparinised tube (plasma from heparinised blood allows more rapid analysis); total iron binding >2 mL of blood in serum or heparinised tube.

Iron level treatment

<62 micromol/L for general support only; 62 to 90 micromol/L for brief chelation therapy; 90 to 180 micromol/L for vigorous support and chelation; >189 micromol/L for vigorous support and chelation therapy, and possible exchange transfusion or haemodialysis.

Indications for chelation therapy

Desferrioxamine mesilate should be used if serum iron >62 micromol/L or the patient has severe symptoms and serum iron is not yet available.

The end point of desferrioxamine therapy is indicated by the disappearance of reddish-brown coloured urine. In patients in whom reddish-brown coloured urine does not develop, the end point for chelation therapy occurs when serum iron concentration falls to less than 54 micromol/L (300 microgram/100 mL).

To eliminate iron that has already been absorbed, desferrioxamine mesilate should be given either intramuscularly or, preferably, intravenously. The dosage and route of administration should be adapted to the severity of the poisoning, preferably by reference to the serum iron concentrations and total iron binding capacity, which should be monitored regularly. Facilities for monitoring serum iron should be available round the clock. In addition, the total amount of iron ingested and remaining in the gastrointestinal tract should be taken into account.

If the patient is normotensive, desferrioxamine mesilate may be given in a single intramuscular dose: 2 g for an adult and 1 g 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 mesilate 37.1 g over 52 hours has been tolerated without apparent unwanted effects.

Therapy should be continued until the serum iron concentrations are less than the total iron binding capacity. 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 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.

Desferrioxamine test

This test is based on the principle that in normal subjects desferrioxamine mesilate is incapable of raising iron excretion above a certain limit.

Normal renal function

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

Renal failure

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.

Dosage adjustment

Treatment in patients with terminal renal failure

The iron complex is dialysable. In patients with renal failure, its elimination can be increased by dialysis. Administration of desferrioxamine mesilate may precipitate aluminium toxicity in patients on dialysis.

In patients on maintenance haemodialysis or haemofiltration, desferrioxamine mesilate doses between 1 and 4 g per week have proven effective.

Method of administration

Preparation and administration of solution

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 intramuscular 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.

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.

4.3 Contraindications

DBL Desferrioxamine Mesylate for Injection BP is contraindicated in patients with a known hypersensitivity to desferrioxamine (except where desensitisation proves possible) and in patients with an absence of excess iron stores.

4.4 Special warnings and precautions for use

Flushing of the skin, urticaria, hypotension and shock have been reported when desferrioxamine mesilate was administered by rapid intravenous injection. THEREFORE, DBL DESFERRIOXAMINE MESYLATE FOR INJECTION BP SHOULD BE GIVEN INTRAMUSCULARLY OR BY SLOW SUBCUTANEOUS OR SLOW INTRAVENOUS INFUSION. The maximum rate for intravenous infusion should not exceed 15 mg/kg/hour.

Injection-site reactions have been reported following subcutaneous, intravenous and intramuscular administration of desferrioxamine.

Acute fatal pulmonary injury has been reported in patients receiving high dose continuous intravenous infusions of desferrioxamine. The cases were clinically manifested as acute adult respiratory distress syndrome (ARDS), with respiratory failure, hypoxia, pulmonary oedema, low pulmonary compliance, and pulmonary capillary wedge pressures below 18 mm Hg. The respiratory distress developed 32 to 72 hours after commencing the infusion. Therefore, caution should be taken in patients receiving high dose continuous intravenous infusions of desferrioxamine.

Acute respiratory distress syndrome has been described following treatment with excessively high intravenous doses of desferrioxamine in patients with acute iron intoxication, and also in thalassaemic patients. The recommended daily doses should therefore not be exceeded.

It has been reported that iron overload disorder may cause the patient to have an increased susceptibility to infectious diseases. In some cases the use of desferrioxamine has promoted the development of infections, notably with micro-organisms that are iron-dependent such as *Yersinia enterocolitica, Yersinia pseudotuberculosis, Pneumocystis carinii* and *Staphylococcus aureus.* If a patient, while undergoing treatment with desferrioxamine mesilate develops pyrexia accompanied by acute enteritis/enterocolitis, diffuse abdominal pain or pharyngitis, the treatment should be discontinued, appropriate bacteriological tests performed, and suitable antibiotic therapy instituted immediately. Desferrioxamine mesilate treatment may be recommenced once the infection resolves.

Rare reports of severe fungal infections (e.g., cases of mucormycosis or infection with *Pneumocystis carinii* or *Rhizopus)* have been documented in patients undergoing haemodialysis while receiving desferrioxamine mesilate, some with fatal outcome. Although a causal relationship with the medicine has not been firmly established, the known suppressant effect of desferrioxamine mesilate on lymphocytes may have been a contributing factor. If any characteristic signs or symptoms occur desferrioxamine mesilate treatment should be discontinued, mycological tests carried out and appropriate treatment immediately instituted. Mucormycosis has been reported to occur in dialysis patients not receiving desferrioxamine mesilate, thus no causal link with the use of the medicinal product has been established.

Visual and auditory disturbances have been reported when desferrioxamine mesilate has been administered over prolonged periods of time, particularly when the doses used were higher than those recommended or in patients with low 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 desferrioxamine. The visual disturbances observed have been blurring of vision, cataracts after prolonged desferrioxamine therapy for chronic iron storage disease, decreased visual acuity including visual loss, impaired peripheral, colour and night vision and retinal pigmentary abnormalities. The auditory abnormalities reported have been tinnitus and hearing loss including high frequency sensorineural hearing loss, and occasionally deafness. In most cases, both ocular and auditory disturbances were reversible upon immediate cessation of treatment.

Ophthalmological and audiological tests should therefore be carried out before starting treatment with desferrioxamine mesilate, as well as at intervals of about three months during the treatment. By keeping the ratio of the mean daily dose (mg/kg of desferrioxamine) divided by the serum ferritin (micrograms/L) below 0.025, the risk of audiometric abnormalities may be reduced in thalassaemia patients. 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). If disturbances of vision and/or hearing occur, the treatment with desferrioxamine mesilate should be discontinued, in order to improve the chances that the disturbances of vision and/or hearing will prove completely reversible. If treatment with desferrioxamine mesilate is later resumed with a reduced dosage, it should be done under close ophthalmological and/or audiological control and with due regard to the risk-benefit ratio.

Since desferrioxamine therapy may cause neurological effects such as dizziness, in addition to visual impairment, patients should take caution if driving a motor vehicle after treatment with desferrioxamine.

Used alone desferrioxamine mesilate 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.

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. When given

intramuscularly, each gram of desferrioxamine mesilate should be made up in a volume of not less than 3 mL (see section 4.2 **Dose and method of administration**).

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 ferrioxamine complex may be associated with a reddish-brown discolouration of the urine.

The use of inappropriately high doses of desferrioxamine mesilate in patients with low ferritin levels or young children (<3 years at commencement of treatment) has also been associated with growth retardation.

Growth retardation, if associated with excessive doses of 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.

Use in renal impairment

Caution is recommended in patients with severe renal failure as approximately 50% or more of the ferrioxamine formed is excreted via the kidneys. The iron complex is dialysable and its elimination can be increased by dialysis in patients with renal failure.

In patients undergoing haemodialysis who are not overloaded with iron, plasma concentrations of aluminium may rise in response to administration of desferrioxamine mesilate.

Use in the elderly

Clinical studies of desferrioxamine mesilate did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently compared to younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Pediatric use

Growth should be monitored regularly in children receiving long term treatment with desferrioxamine mesilate, since impairment of growth has been documented in such children.

Three monthly checks on body weight and height are recommended in children.

Effects on laboratory tests

Blood creatinine increased.

4.5 Interactions with other medicines and other forms of interactions

Concurrent administration of desferrioxamine mesilate with a single dose of prochlorperazine, a phenothiazine derivative, has lead to a loss of consciousness for 48 to 72 hours, possibly because this combination of medicines removes essential iron from the nervous system. Therefore desferrioxamine mesilate and phenothiazine derivatives should not be used concomitantly.

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

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

Vitamin C (ascorbic acid) given orally in doses of 150 to 250 mg per day improves the chelating action of desferrioxamine and increases the amount of iron excreted. However, concurrent use may cause enhancement of tissue iron toxicity, especially in the heart causing cardiac decompensation. Therefore, this regimen should be used with caution in older patients and patients with cardiac problems. The need for ascorbic acid supplementation should be completely documented by measurements of iron excretion before and after supplements, and the oral dose of ascorbic acid should be given an hour or two after the desferrioxamine infusion has been initiated when adequate concentrations of desferrioxamine have been achieved. Ascorbic acid should not be administered until treatment with desferrioxamine mesilate has been in progress for more than a week. Monitoring of cardiac function is indicated during such combined therapy. Bilateral cataracts have also been documented in a patient on long term combined therapy with ascorbic acid and desferrioxamine.

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

Effects on fertility

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

Use in pregnancy (Category B3[†])

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.

† *Category B3: Drugs which have been taken by only a limited number of pregnant women and women of child bearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.*

Use in lactation

It is not known whether desferrioxamine mesilate is excreted in human breast milk. Because many medicines are excreted in human milk and because of the potential for serious adverse drug effects due to desferrioxamine mesilate occurring in breastfed infants, a decision should be made either to discontinue breastfeeding or the drug, taking into account the importance of the medicine to the mother.

4.7 Effects on ability to drive and use machines

Desferrioxamine mesilate has a major influence on the ability to drive and use machines in patients experiencing central nervous system effects such as dizziness or impaired vision/hearing. Patients should be warned against driving or operating machinery.

4.8 Adverse effects (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 <1/1,000); very rare (<1/10,000) including isolated reports, not known (cannot be estimated from the available data).

The following adverse effects have been observed:

Many of these reactions may occur as manifestations of iron overload.

Vascular disorders

Hypotension, shock.

Cardiac disorders

Tachycardia, arrhythmia.

Respiratory, thoracic and mediastinal disorders

A pulmonary syndrome of a moderate to life-threatening nature has been reported. The patients had tachypnoea, hypoxaemia, a diffuse interstitial pattern on the chest x-ray and restrictive pulmonary dysfunction. In addition cases of acute adult respiratory distress syndrome (ARDS), with respiratory failure, hypoxia, pulmonary oedema, low pulmonary

compliance, and pulmonary arterial wedge pressures below 18 mm Hg have been reported (see section 4.4 **Special warnings and precautions for use**).

Uncommon: Asthma.

Very rare: Adult respiratory distress syndrome (with dyspnoea, cyanosis and lung infiltration); following excessively high intravenous doses of desferrioxamine mesilate.

Immune system disorders

Hypersensitivity reactions occasionally occur. Rash, pyrexia and oedema, anaphylactic shock have been encountered.

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

Nervous system disorders

Headache, neurological disturbances (dizziness, convulsions) and reversible aphasia, peripheral sensory neuropathy and paraesthesia (see section 4.4 **Special warnings and precautions for use**).

Isolated cases: Precipitation of toxic encephalopathy.

Eye disorders

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

Rare: Vision blurred, visual acuity reduced, blindness, impairment of colour vision, night blindness, visual field defect, retinopathy (pigmentary degeneration of the retina), optic neuritis, cataract, corneal opacity, chromatopsia.

Ear and labyrinth disorders

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

Uncommon: Tinnitus; hearing loss (including high frequency sensorineural hearing loss), deafness neurosensory.

Musculoskeletal and connective tissue

Bone dysplasia, characterised by circumferential metaphyseal osseous defects, sharp zones of provisional calcification and widened growth plates, and flattening of the thoracic and lumbar vertebral bodies has been reported in children receiving desferrioxamine for thalassaemia. Growth impairment especially in children.

Very common: Arthralgia/myalgia.

Common: Growth retardation and bone changes (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.

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

Metabolism and nutrition disorders

Hypocalcaemia (transient), hyperparathyroidism, iron deficiency.

Blood and lymphatic system disorders

Thrombocytopenia, leukopenia, eosinophilia, aplastic anaemia and one case of fatal pancytopenia attributed to the use of desferrioxamine has been reported. Inhibition of DNA synthesis in T and B lymphocytes.

Gastrointestinal disorders

Nausea, vomiting, abdominal pain, faeces discoloured, diarrhoea.

Hepatobiliary disorders

Hepatic impairment.

Renal and urinary disorders

Renal failure, aggravation of pyelonephritis, renal tubular disorder.

Dysuria, urine colour change to orange-rose or 'vin rose colour'.

Infections and Infestations

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

General disorders and administration site conditions

Rapid intravenous injection may be followed by localised irritation and pain, swelling and induration, pruritus, erythema and urticaria. Occasionally accompanied by pyrexia, chills and malaise (see section 4.4 **Special warnings and precautions for use**).

Subcutaneous administration of desferrioxamine may cause local irritation of the skin at infusion sites especially when administered in concentrations greater than 10% or doses higher than those recommended. The addition of 1 to 2 mg hydrocortisone to the desferrioxamine solution and/or dilution with additional Water for Injections may alleviate this problem.

Uncommon: Blisters and local oedema at the injection site.

Other

In some patients treated for aluminium intoxication, generalised tonic-clonic seizures, hallucination and delusion, toxic encephalopathy and hyperparathyroid bone disease have been reported on isolated occasions.

Reporting suspected adverse effects

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

4.9 Overdose

Signs and symptoms

Tachycardia, hypotension and gastrointestinal symptoms have occasionally been reported in patients who received above average doses of desferrioxamine mesilate. Accidental administration of desferrioxamine mesilate by the intravenous route may be associated with acute but transient blindness, aphasia, agitation, headache, nausea, bradycardia, acute kidney injury and hypotension.

Acute respiratory distress syndrome has been described following treatment with excessively high intravenous doses of desferrioxamine in patients with acute iron intoxication, and also in thalassaemic patients.

Treatment

There is no specific antidote for desferrioxamine mesilate overdose. Signs and symptoms of overdosage may be eliminated by reducing the dosage. Desferrioxamine is dialysable. Appropriate supportive therapy should be instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Desferrioxamine mesilate is a chelating agent that forms a stable complex by binding the three hydroxamic groups of the molecule to ferric ions and to a lesser degree with aluminium, copper, zinc and calcium ions. Desferrioxamine mesilate readily chelates iron from ferritin and haemosiderin but not readily from transferrin (siderophillin). However, iron recently cleared from plasma is not accessible, and iron deposits in the lungs are not removed.

Ferrioxamine, the resulting octahedral iron complex, is formed in many tissues, but mainly in plasma. This complex is stable, water soluble, and readily excreted by the kidneys. Theoretically, 1 g of desferrioxamine mesilate is capable of sequestering 85 mg of iron (in the ferric form) ie on a 1:1 molar basis, however, the rare complex formation appears to be pH dependent and is most rapid at acid pH. Desferrioxamine mesilate does not remove iron from

haemoglobin or other haemin-containing substances in the body, such as myoglobin and iron-containing enzymes (ie cytochrome, catalases and perioxidases).

Treatment with desferrioxamine mesilate can facilitate excretion of 10 to 50 mg of iron per day from patients with iron overload. A transfusion of 500 mL whole blood provides 250 mg of iron to the body. There is a nonlinear relationship between dose of desferrioxamine mesilate and iron excreted, with reducing efficiency at higher doses.

Desferrioxamine mesilate causes the release of histamines resulting in acute hypotensive episodes following rapid intravenous administration.

Clinical trials

No data available.

5.2 Pharmacokinetic properties

Absorption

Desferrioxamine mesilate is poorly absorbed from the gastrointestinal tract after oral administration; therefore parenteral administration is required. It is rapidly absorbed by the intramuscular and subcutaneous routes.

Distribution

Less than 10% is bound to serum proteins.

Following a single intravenous injection of desferrioxamine (10 mg/kg) in healthy subjects and in patients with transfusion induced iron overload, plasma concentrations of between 80 and 130 micromol/L were recorded after 3 minutes. These concentrations declined rapidly with a half-life of 5 to 10 minutes, and thereafter declined more slowly. The short half-life is due not only to distribution, metabolic transformation and excretion of the active substance, but also to formation of the iron complex ferrioxamine (which commences within a few minutes and proceeds to an extent which depends on the individual's iron status).

Following continuous subcutaneous or intravenous infusion of desferrioxamine (100 mg/kg in 24 mL sterile water at a rate of 1 mL/hr), the plasma concentration of desferrioxamine and ferrioxamine in healthy subjects rose to a plateau after 12 hours, ie to a maximum level of 20 micromol/L for desferrioxamine and 2.75 micromol/L for ferrioxamine. The corresponding values in patients were 8.3 micromol/L for desferrioxamine and 12.9 micromol/L for ferrioxamine.

Metabolism

In healthy subjects, elimination following intramuscular injection was biphasic, with first phase half-life of 1 hour for desferrioxamine and second phase half-life was 6.1 hours. Patients with haemochromatosis showed a single phase of decline with a half life of 5.6 hours.

Excretion

Desferrioxamine is readily metabolised and/or excreted uncombined with iron by the kidneys, hence the need to maintain a constant blood level for optimal iron excretion. Within 12 hours after the intravenous administration of desferrioxamine to 20 volunteers, about 33.1% of the dose was excreted in the urine (the bulk of it in the first 3 hours) in the form of desferrioxamine and ferrioxamine, and the remainder in the form of metabolites. The corresponding figure in a patient with haemochromatosis was 60.5% of the dose. In patients with haemochromatosis, the increase in iron excretion occurring in response to desferrioxamine was approximately as high in the faeces as in the urine.

5.3 Preclinical safety data

Genotoxicity

No evidence of mutagenic potential has been observed *in vitro*.

Carcinogenicity

Long term carcinogenicity studies in animals have not been performed with desferrioxamine mesilate.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Cloudiness or precipitation may result when desferrioxamine mesilate solutions are mixed with injectable solutions containing heparin.

0.9% Sodium Chloride Intravenous Infusion should not be used as a solvent to reconstitute DBL™ Desferrioxamine Mesylate for Injection BP since it produces a hypertonic solution. However, 0.9% Sodium Chloride Intravenous Infusion may be employed, after reconstitution with Water for Injections, for further dilution.

6.3 Shelf life

Refer to outer carton for expiration date.

6.4 Special precautions for storage

Store below 25°C. Protect from light.

To reduce the risk of microbiological contamination, use as soon as practicable after reconstitution. If storage is necessary, hold at 2-8°C for not more than 24 hours.

6.5 Nature and contents of container

The powder for injections are supplied in glass vials with a bromobutyl rubber closure and aluminium seal with plastic flip-off top. DBL Desferrioxamine Mesylate for Injection BP is available as follows:

Strength	Pack
500 mg	10 x 500 mg vials
2 g	1 x 2 g vial

Not all presentations may be available locally.

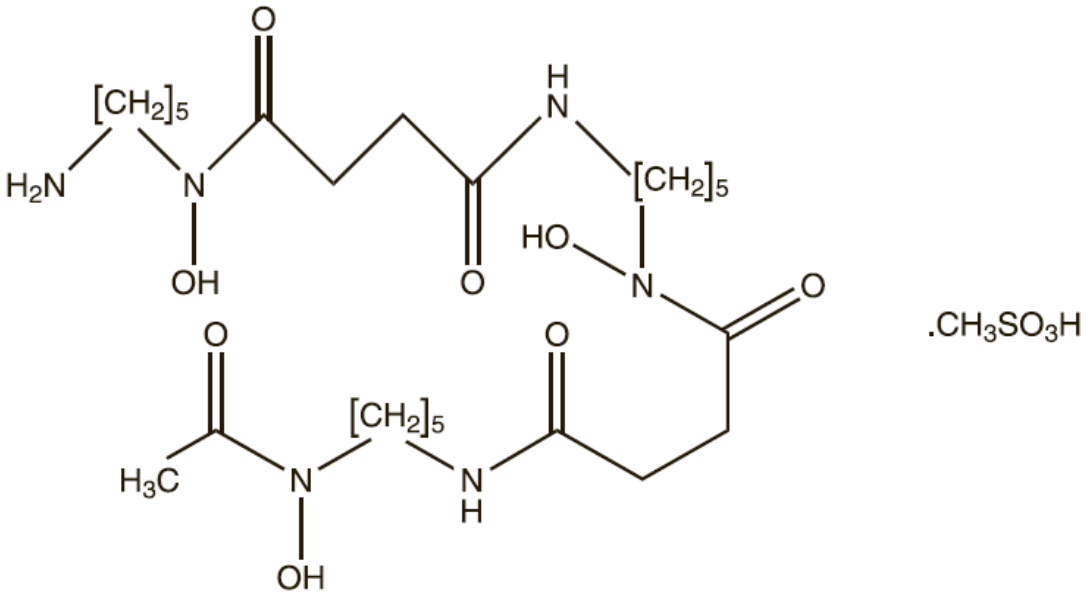
6.6 Special precautions for disposal

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

6.7 Physicochemical properties

Desferrioxamine mesilate is a white to cream powder.

Chemical structure



Chemical name: 30-amino-3,14,25-trihydroxy-3,9,14,20,25-penta-azatriacontane-2,10,13,21,24-pentaone methanesulphonate.

Molecular weight: 656.8.

CAS number

138-14-7

7. MANUFACTURER

Hospira Australia Pty Ltd
1 – 5, 7 – 23 and 25 – 39 Lexia Place
Mulgrave, Victoria, 3170
Australia

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