DBL™ Pentamidine Isethionate for Injection

1. NAME OF THE MEDICINE

Pentamidine isethionate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of DBL™ Pentamidine Isethionate for Injection contains 300 mg pentamidine isethionate as a freeze dried powder or plug.

Each 4 mg of pentamidine isethionate is equivalent to 2.3 mg pentamidine base.

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Powder for injection.

DBL™ Pentamidine Isethionate for Injection is a white or almost white, odourless or almost odourless hygroscopic powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pentamidine isethionate is indicated for intravenous administration in the treatment of the following conditions:

1. As an alternative first line treatment for *Pneumocystis carinii* infection in AIDS patients;
2. As second line treatment for *Pneumocystis carinii* infection in non-AIDS patients;
3. As second line treatment of Leishmaniasis (visceral and cutaneous), except *Leishmania aethiopica* where it may be used as first line therapy;
4. As second line treatment for Trypanosomiasis (except for the *Trypanosomiasis rhodesiense* strain due to lack of efficacy).

4.2 Dose and method of administration

Dosage

The following dosage regimens are recommended.

P. carinii pneumonia

4 mg/kg bodyweight Pentamidine Isethionate once daily for 14 days, preferably by slow intravenous infusion.

Leishmaniasis

On the basis of current knowledge the following dosage are suggested however the optimal treatment regimen has yet to be established.

- Visceral (Kala-azar): 3 to 4 mg/kg bodyweight Pentamidine Isethionate on alternate days (3 times a week) to a maximum of 10 injections.

- Cutaneous: 3 to 4 mg/kg bodyweight Pentamidine Isethionate once or twice weekly, until the condition resolves.

Trypanosomiasis

Haemolymphete stage only.

4 mg/kg bodyweight Pentamidine Isethionate daily or on alternate days to a total of 7 to 10 injections.

Dosage adjustment

Renal impairment

Creatinine clearance <35 mL/min: There is little information on the kinetics or the adverse effects profile of pentamidine in patients with impaired renal function.

Hepatic impairment

No information available.

Method of administration

DBL™ Pentamidine Isethionate for Injection should be given as a slow intravenous infusion with a patient in a supine position in order to reduce the incidence of sudden severe hypotension. Direct bolus intravenous injection or rapid administration must not be used.

Reconstitution

The contents of a 300 mg vial should be dissolved in 3 mL to 5 mL of Water for Injections. The required dose of Pentamidine Isethionate should then be diluted further in 50 to 250 mL of Glucose Intravenous Infusion 5% or Sodium Chloride Intravenous Infusion 0.9%. The reconstituted solutions should be visually examined before use. Any solutions which are hazy, discoloured or contain visible particulate matter should not be used. Diluted solutions containing Pentamidine Isethionate should be infused over a period of at least 60 minutes under close medical supervision, whilst the patient is kept lying down.

Compatibilities

Reconstituted solutions at concentrations of 100 mg/mL and 60 mg/mL are chemically stable for 48 hours when stored at 2 to 8°C and room temperature under fluorescent light. DBL™ Pentamidine Isethionate for Injection when reconstituted with Water for Injections and diluted

to 1.0 mg/mL and 2.5 mg/mL in Sodium Chloride Intravenous Infusion 0.9% and Glucose Intravenous Infusion 5% retained its potency for at least 48 hours when stored under fluorescent light at 21 ± 2°C. However, to avoid microbial contamination, the prepared solution should be used within 24 hours.

4.3 Contraindications

Patients with a known hypersensitivity to pentamidine.

Pentamidine should not be administered to patients who are pregnant or breastfeeding unless considered essential by the physician.

4.4 Special warnings and precautions for use

Serious warnings and precautions

Severe, sometimes fatal, hypotension, hypoglycaemia, acute pancreatitis, renal impairment and cardiac arrhythmias have been reported. Other life-threatening reactions requiring immediate corrective measures and withdrawal of treatment have included leucopenia (less than 1,000 per cubic millimetre), thrombocytopenia (less than 20,000 per cubic millimetre), acute renal failure, hypocalcaemia, and ventricular tachycardia. A possible case of Stevens-Johnson syndrome has been reported.

Fatalities have been documented following pentamidine administration. The ratio of therapeutic to toxic dose of pentamidine is very low and adverse effects, some of which may be life-threatening, occur frequently during its use. DBL™ Pentamidine Isethionate for Injection should be used only in a hospital setting with facilities to monitor blood glucose, blood count, renal function and hepatic function. Electrocardiograms should be carried out at regular intervals (see Section 4.4 Special warnings and precautions for use: Monitoring and laboratory tests). Extravasation reactions may result in ulceration, tissue necrosis and long-term sequelae (see Section 4.8 Adverse effects (undesirable effects)).

Pentamidine isethionate should be used with caution in patients with the following:

1. Malnutrition
2. Hyperglycaemia or hypoglycaemia
3. Hepatic dysfunction
4. Renal dysfunction
5. Hypertension or hypotension
6. Anaemia, leucopenia or thrombocytopenia

General

DBL™ Pentamidine Isethionate for Injection should only be administered under close medical supervision, and the patient should be very carefully monitored for the development of serious adverse reactions (see Section 4.8 Adverse effects (undesirable effects)).

The administration of DBL™ Pentamidine Isethionate for Injection should be limited to patients in whom *Pneumocystis jirovecii* infection has been confirmed.

Some patients may become nauseated or develop fever after taking each dose of DBL™ Pentamidine Isethionate for Injection. In such cases, the prophylactic use of an antiemetic and/or paracetamol may be considered.

Cardiovascular

Patients may develop sudden, severe hypotension after receiving a single intramuscular or intravenous dose of pentamidine isethionate. Therefore, patients receiving DBL™ Pentamidine Isethionate for Injection should be in a supine position and the blood pressure monitored closely during administration of the drug and several times thereafter until the blood pressure is stable. Equipment for emergency resuscitation should be readily available. DBL™ Pentamidine Isethionate for Injection should be infused over a period of at least 60 minutes to minimise the risk of hypotension.

Severe hypotension with accompanying bradycardia has been observed in a patient after the sixth dose of pentamidine isethionate. This hypotension did not respond to intravenous colloids, graded compression stockings or corticosteroids but resolved within four days of stopping treatment.

Ventricular tachycardia and ECG abnormalities (including QT interval prolongation and torsade de pointes) may develop in patients receiving pentamidine isethionate. ECG's may be required at regular intervals if signs of cardiotoxicity develop.

Endocrine and metabolism

Pentamidine isethionate can produce hypoglycaemia, which may be severe, life-threatening and/or prolonged. It generally occurs after 5 to 7 days of therapy but can even occur up to several days after the drug is discontinued. The duration appears quite variable, persisting for one day to several weeks. Pentamidine isethionate-induced hypoglycaemia has been associated with pancreatic islet cell necrosis and inappropriately high plasma insulin concentrations. Hyperglycaemia and diabetes mellitus, with or without preceding hypoglycaemia, have also occurred, sometimes several months after termination of therapy with pentamidine isethionate.

Hypoglycaemia induced by pentamidine isethionate may be controlled by intravenous administration of dextrose or (oral) diazoxide, but it is not known if such therapy can prevent the subsequent development of diabetes mellitus.

Gastrointestinal

Cases of nausea and vomiting have been observed with pentamidine isethionate treatment.

Haematologic

Leucopenia and thrombocytopenia, which can be severe (e.g., leucocyte count less than 1,000 per cubic millimetre, platelet count less than 20,000 per cubic millimetre), occur occasionally in patients receiving pentamidine isethionate. Cases of anaemia have been observed. In a few cases, pentamidine isethionate therapy has been associated with neutropenia.

Hepatic/Biliary/Pancreatic

Abnormal liver function tests may occur. Liver function should be routinely monitored in patients receiving DBL™ Pentamidine Isethionate for Injection (see Section 4.4 Special warnings and precautions for use: Monitoring and laboratory tests). Cases of acute pancreatitis have been observed with pentamidine isethionate treatment.

Immune

Hypersensitivity reactions at the injection site, such as skin rash and erythema, may occur (see Section 4.4 Special warnings and precautions for use: Skin and Section 4.8 Adverse effects (undesirable effects)).

Skin

Intramuscular injections are often associated with pain, tenderness, erythema, and induration at the site of injection. Sterile abscesses have been observed. Therefore, intramuscular administration should be reserved for patients with adequate muscle mass and limited to the rare situations where intravenous infusion is not feasible.

Vascular

Phlebitis can occur after intravenous injection.

Monitoring and laboratory tests

In order to monitor for possible toxicity, the following tests should be performed before, during and after treatment.

1. Blood urea nitrogen and serum creatinine daily during therapy.
2. Complete blood and platelet counts daily during therapy.
3. Fasting blood glucose measurements should be taken before, daily during therapy, and at regular intervals after completion of therapy. Hyperglycaemia and diabetes mellitus, with or without preceding hypoglycaemia, have occurred up to several months after cessation of therapy.
4. Liver function tests (LFTs) including serum bilirubin, alkaline phosphatase, aspartate aminotransferase (AST/SGOT), and alanine aminotransferase (ALT/SGPT). If baseline measurements are normal and remain so during therapy, test weekly thereafter. When there is baseline elevation in LFTs or LFTs increase during therapy, continue monitoring weekly unless the patient is on other hepatotoxic agents, when monitoring every 3 to 5 days is appropriate.
5. Serum calcium, test weekly.
6. Urine analysis and serum electrolytes daily during therapy.
7. Electrocardiograms at regular intervals.

Use in renal impairment

Severe renal impairment resulting in death may also occur in the presence of various clinical complications (e.g., bacterial sepsis), concurrent administration of other nephrotoxic antibiotic agents or previous evidence of renal disease.

Use in the elderly

There is no information on the safe use of pentamidine in the elderly.

Paediatric use

The safety and efficacy of DBL™ Pentamidine Isethionate for Injection has not been established in the paediatric population, and pharmacokinetic data are extremely limited.

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

Since nephrotoxic effects may be additive, the concurrent or sequential use of pentamidine isethionate with drugs having a nephrotoxic potential (e.g., aminoglycosides, amphotericin B, cisplatin, methoxyflurane or vancomycin) should be undertaken with caution. DBL™ Pentamidine Isethionate for Injection should be administered with caution to patients who are receiving drugs with hepatotoxic potential or medication that can impair the haematopoietic system.

4.6 Fertility, pregnancy and lactation

Effects on fertility

No data available.

Use in pregnancy – Category B3

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

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

Pentamidine has been found to cross the placenta in rats given high doses late in pregnancy. Studies in rabbits have also shown pentamidine to be mildly embryotoxic, with an increase in post-implantation losses and delayed foetal ossification at doses of 1, 3 and 8 mg/kg of bodyweight.

It is not known whether pentamidine isethionate crosses the placenta or causes foetal harm when administered to pregnant women; therefore, pentamidine is contraindicated during pregnancy and should only be used when considered essential.

Use in lactation

Since it is not known whether pentamidine isethionate is distributed into milk, the medicine is contraindicated during lactation and should only be administered to nursing mothers when considered essential.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (undesirable effects)

Fatalities due to severe hypotension, hypoglycaemia, acute pancreatitis, renal impairment and cardiac arrhythmias have been reported in patients treated with pentamidine isethionate.

Life-threatening reactions

Blood and lymphatic system disorders
Leucopenia (less than 1,000 cells per cubic millimetre), thrombocytopenia (less than 20,000 cells per cubic millimetre)

Immune system disorders
Herxheimer reaction

Metabolism and nutrition disorders
Severe hypoglycaemia, hypocalcaemia

Psychiatric disorders
Toxic delirium

Nervous system disorders
Syncope

Cardiac disorders
Cardiac arrhythmias and cardiac arrest (including QT interval prolongation and torsade de pointes), ventricular tachycardia

Vascular disorders
Severe hypotension

Gastrointestinal disorders
Acute pancreatitis

Skin and subcutaneous tissue disorders
Stevens-Johnson syndrome (single possible case)

Renal and urinary disorders
Acute renal failure

The above-mentioned adverse effects can be severe, sometimes fatal, and require immediate corrective measures and withdrawal of treatment.

Other reactions

Other adverse reactions reported are listed in this section per MedDRA system organ class.

Blood and lymphatic system disorders
Anaemia, thrombocytopenia, leucopenia

Metabolism and nutrition disorders
Hypocalcaemia, hypoglycaemia, hyperglycaemia, hyperkalaemia, hyponatraemia, diabetes mellitus

Psychiatric disorders
Hallucinations

Nervous system disorders
Taste disturbances, dizziness, syncope

Cardiac disorders
Tachycardia, bradycardia

Vascular disorders
Hypotension, facial flushing, venous thrombosis

Respiratory, thoracic and mediastinal disorders
Breathlessness

Gastrointestinal disorders
Nausea, vomiting

Hepatobiliary disorders
Abnormal liver function (hepatic dysfunction)

Skin and subcutaneous tissue disorders
Abscess and/or necrosis, rash, itching, alopecia, erythema multiforme

Renal and urinary disorders
Azotaemia, albuminuria, glycosuria, increased creatinine levels

General disorders and administration site conditions
Local reactions at the injection site including abscess, pain, thrombophlebitis

Investigations
Depressed serum folate

4.9 Overdose

There is no information available concerning the treatment of overdosage. There is no specific antidote. In general, overdosage would be expected to produce effects that are an extension of common adverse effects or of the serious metabolic sequelae observed.

Treatment should be symptomatic and supportive. Neither peritoneal dialysis nor haemodialysis appear to remove the drug rapidly enough to cause a precipitous decline in the plasma concentration of pentamidine isethionate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Pentamidine isethionate exhibits antiprotozoal activity against *Pneumocystis carinii*, *Leishmania* and some species of *Trypanosoma*.

The exact mechanism of antiprotozoal action of pentamidine has not been fully elucidated. Several mechanisms of action may be involved, and the role of the mechanism(s) may vary among the different types of protozoa (e.g., trypanosome, sporozoans). Most information on the antiprotozoal activity of pentamidine has been derived from studies involving trypanosomes. *In vitro* studies indicate that the drug interferes with nuclear metabolism.

Microbiology

Pentamidine isethionate exhibits antiprotozoal activity against *Pneumocystis carinii*, *Leishmania* and some species of *Trypanosoma*.

Clinical trials

No data available.

5.2 Pharmacokinetic properties

Limited information is available concerning the pharmacokinetics of pentamidine isethionate.

Absorption

Following a single 4 mg/kg IV dose of pentamidine isethionate (given as a 2-hour infusion), peak plasma pentamidine concentrations averaged 612 nanogram/mL after completion of the IV infusion.

Distribution

Distribution of pentamidine into human body tissues and fluids has not been well characterised, but the drug appears to be rapidly and extensively distributed and/or bound to tissues. Pentamidine has a distribution half-life of 5 to 15 minutes after intravenous administration. Following parenteral administration, highest concentrations have been found in the liver,

followed by the kidneys, adrenals, spleen, lungs and pancreas. Pentamidine penetrates the CNS only very poorly after prolonged therapy.

In vitro, pentamidine is reportedly 69% bound to serum proteins.

It is not known whether pentamidine isethionate crosses the placenta or is distributed into breast milk.

Excretion

Little is known about the elimination in humans. Plasma concentrations of pentamidine have been found to decline in a biphasic manner following a single IV infusion in patients with normal renal function. The mean elimination half-life was found to be 18 minutes in the initial phase and 6.4 hours in the terminal phase. Pentamidine appears to be eliminated very slowly from tissues in which the drug principally accumulates (e.g., liver, lungs). The half-life of pentamidine may be prolonged in patients with impaired renal function, however no correlation between renal function and plasma clearance of pentamidine has been found. It is not known if the drug is excreted in faeces.

Only a small amount (approximately 6%) of the administered dose is excreted unchanged in the urine over a 15-day period.

Following a single 4 mg/kg IV dose of pentamidine isethionate in patients with AIDS or pneumocystis pneumonia who had normal renal function, about 2.5 to 5% of the dose was excreted in urine as unchanged drug over 24 hours, mainly within the first 8 hours after administration. Similar amounts (about 1 to 4% of the dose) were also excreted in urine as unchanged drug in 24 hours in patients with mild to moderate renal impairment.

Limited data suggest that pentamidine is not appreciably removed by haemodialysis or peritoneal dialysis.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

After reconstitution with Water for Injections, DBL™ Pentamidine Isethionate for Injection should not be mixed with any injection solution other than Glucose Intravenous Infusion 5% or Sodium Chloride Intravenous Infusion 0.9%.

6.3 Shelf life

Please refer to carton for expiry date.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

DBL™ Pentamidine Isethionate for Injection is available in 1 vial.

Strength	**Pack Size**
300 mg/vial	1's

7. MANUFACTURER

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

PEN-SIN-0622/0
Date of last revision: June 2022