NEW ZEALAND DATA SHEET

1.PRODUCT NAME

PENTACARINAT® 300mg Injection, powder

2.QUALITATIVE AND QUANTITATIVE COMPOSITION

Pentamidine Isetionate B.P. 300mg

3.PHARMACEUTICAL FORM

Powder for reconstitution.

Sterile white powder for use after reconstitution

4.CLINICAL PARTICULARS

4.1 Therapeutic indications

Pentamidine isethionate is indicated in the treatment of the following conditions:

1. Pneumonia due to *Pneumocystis jiroveci (carinii)* occurring in debilitated or immunocompromised patients, e.g. in AIDS. Pentamidine isethionate is particularly valuable for patients with a history of allergy to sulphonamides, or who have severe reactions, or a lack of response to treatment with co-trimoxazole in *P. jiroveci (carinii)* pneumonia.

2. Leishmaniasis (visceral and cutaneous) including cases resistant to pentavalent antimony compounds.

3. Early phase African sleeping sickness caused by *Trypanosoma gambiense*.

For aerosol administration via a nebuliser, pentamidine isethionate is indicated for the prevention of *Pneumocystis jiroveci (carinii)* pneumonia in patients infected by the Human Immunodeficiency Virus (HIV).

4.2 Dose and method of administration

Aerosol Administration

Solutions for inhalation should be prepared before administration as described in section 6.6 below and then used immediately.

Children

There is insufficient data available to recommend aerosolised pentamidine isethionate for children

Parenteral Administration

For instructions on reconstitution of the medicine before administration, see section 6.6. In order to reduce the incidence of sudden, severe hypotension, Pentacarinat should be administered parenterally only by deep intramuscular injection or by slow intravenous infusion with the patient lying down. Bolus intravenous injections should be avoided if possible and never be given rapidly.

The following dosage regimens relate to both intramuscular and intravenous administration and are recommended for adults, children and infants:

Pneumocystis Jiroveci (Carinii) Pneumonia

4 mg/kg bodyweight pentamidine isethionate once daily for at least 14 days, preferably by slow intravenous infusion, as intramuscular administration is not recommended for the treatment of *Pneumocytosis jiroveci (carinii)* pneumonia.

Leishmaniasis

Visceral (Kala-azar): 3 to 4 mg/kg bodyweight pentamidine isethionate on alternate days to a maximum of 10 injections, preferably by intramuscular injection.

A repeat course may be necessary.

Cutaneous: 3 to 4 mg/kg bodyweight once or twice weekly by intramuscular injection until the condition resolves.

Trypanosomiasis

4 mg/kg bodyweight pentamidine isethionate once daily or on alternate days, for a total of 7 to 10 injections. The intramuscular or intravenous infusion route may be used.

Elderly

No specific dosage recommendations.

Renal Failure (creatinine clearance <10 mL/min)

***Pneumocystis Jiroveci (Carinii)* Pneumonia:**

In life-threatening cases, 4 mg/kg bodyweight once daily for 7 to 10 days, then 4 mg/kg bodyweight on alternate days, to complete the course of at least 14 doses.

For less severe cases, 4 mg/kg bodyweight on alternate days to complete the course of at least 14 doses.

No dosage reductions are necessary in leishmaniasis and trypanosomiasis.

Hepatic Failure

No specific dosage recommendations

4.3 Contraindications

There are no absolute contraindications to the use of pentamidine isethionate. However, the drug should not be administered to patients with a known hypersensitivity to pentamidine.

4.4 Special warnings and precautions for use

Pentamidine isethionate should be used with particular caution in patients with hepatic and/or renal dysfunction, hypertension or hypotension, hyperglycaemia or hypoglycaemia, leucopenia, thrombocytopenia or anaemia (section 4.8).

Parenteral use

Fatalities due to severe hypotension, hypoglycaemia, acute pancreatitis and cardiac arrhythmias have been reported in patients treated with pentamidine isethionate, by both the IM and IV routes. Baseline blood pressure should be established and patients should receive the drug lying down. Blood pressure should be closely monitored during administration and at regular intervals until treatment is concluded.

Pentamidine isethionate may prolong the QT interval. Cardiac arrhythmias indicative of QT prolongation, such as Torsades de Pointes, have been reported in isolated cases with administration of pentamidine isethionate. Therefore, pentamidine isethionate should be used with care in patients with conditions known to increase the proarrhythmic risk, including patients with long QT syndrome, cardiac diseases (e.g. coronary heart disease, heart failure), a history of ventricular arrhythmias, uncorrected hypokalaemia and/or hypomagnesaemia, brachycardia (<50 bpm), or during concomitant administration of pentamidine isethionate with QT prolonging agents (see Interactions section). Particular caution is necessary if the QTc exceeds 500 msec whilst receiving pentamidine isethionate therapy, continuous cardiac monitoring should be considered in this case. Should the QTc interval exceed 550 msec then an alternative regimen should be considered.

Laboratory monitoring

The following tests should be carried out before, during and after therapy by the parenteral route:

1. Blood urea nitrogen and serum creatinine daily during therapy.

2. Complete blood and platelet counts daily during therapy.

3. Fasting blood glucose measurements daily during therapy, and at regular intervals after the completion of therapy.
   Hyperglycaemia and diabetes mellitus, with or without preceding hypoglycaemia have occurred up to several months after the cessation of therapy.

4. Liver function tests (LFTs) including bilirubin, alkaline phosphatase, aspartate aminotransferase (AST/SGOT), and alanine aminotransferase (ALT/SGPT). If the baseline measurements are normal and remain so during therapy, test weekly. When there is baseline elevation in LFTs and/or LFTs increase during therapy, continue monitoring weekly unless the patient is on other hepatotoxic agents at which point monitoring every 3-5 days is appropriate.

5. Serum calcium test weekly. Serum magnesium, test twice weekly.

6. Urine analysis and serum electrolytes daily during therapy.

7. Electrocardiograms at regular intervals.

Aerosol use:

Patients receiving pentamidine by inhalation should be closely monitored for the development of severe adverse reactions (see *Parenteral use*).

Bronchospasm has been reported to occur following the use of the nebuliser (see section 4.8). This has been particularly noted in patients who have a history of smoking or asthma. This can be controlled by prior use of bronchodilators.

The benefits of aerosolised pentamidine therapy in patients at high risk of a pneumothorax should be weighed against the clinical consequences of such a manifestation.

4.5 Interaction with other medicines and other forms of interaction

Caution is advised when pentamidine isethionate is concomitantly used with drugs that are known to prolong the QT interval such as phenothiazines, tricyclic antidepressants, IV erythromycin and quinolone antibiotics (see section 4.4).

Foscarnet: risk of hypocalcaemia.

4.6 Fertility, pregnancy and lactation

There are no data on the effects of pentamidine on fertility in animals or humans.

Category B3. There is no evidence of the safety of pentamidine isethionate in human pregnancy. A miscarriage within the first trimester of pregnancy has been reported following aerosolised prophylactic administration. Pentamidine isethionate should not be administered to pregnant patients unless it is considered essential.

The use of pentamidine isethionate is to be avoided in breast-feeding mothers unless it is considered essential by the physician.

4.7 Effects on ability to drive and use machines

Pentamidine has no known effect on the ability to drive and use machinery. Dizziness has been reported which should be considered when driving or using machinery.

4.8 Undesirable effects

The following CIOMS frequency rating is used, when applicable:

Very common ≥ 10%; Common ≥ 1 and < 10%; Uncommon ≥ 0.1 and < 1%: Rare ≥ 0.01 and < 0.1%; Very rare < 0.01%;

Inhalation Route:

A miscarriage has been reported following prophylactic aerosolised administration.

Immune system disorders:
Hypersensitivity reactions, including anaphylactic reactions and anaphylactic shock and angioedema have been reported.

Metabolism and nutrition disorders:
Hypoglycaemia has been reported.

Nervous system disorders:
Light-headedness has been reported.

Cardiac disorders:
Bradycardia has been reported.

Vascular disorders:
Hypotension has been reported.

Respiratory, thoracic and mediastinal disorders:
Common: local reactions ranging in severity from cough, shortness of breath, wheezing, bronchospasms, particularly in patients with a history of smoking or asthma, which can usually be controlled by prior use of bronchodilators
Rare: eosinophilic pneumonia
Pneumothorax in patients presenting a history of *Pneumocystis jirovecii (carinii)* pneumonia have been reported. Although the aetiology of the pneumothorax was not linked primarily to the aerosolised administration of pentamidine in the majority of cases, a causal relationship to pentamidine cannot be ruled out.

Gastrointestinal disorders:
Common: taste disturbance, nausea
Acute pancreatitis has been reported.

Skin and subcutaneous tissue disorders:
Rash has been reported.

Renal and urinary disorders:
Renal insufficiency has been reported.

General disorders and administration site conditions:
Fever, decrease in appetite, fatigue have been reported.

Parenteral (IM And IV Routes)

Severe reactions, sometimes fatal, due to hypotension, hypoglycaemia, acute pancreatitis, and cardiac arrhythmias have been reported. Other life-threatening reactions requiring immediate corrective measures and withdrawal of pentamidine isethionate can include leucopenia (<1000 per cubic millimetre), thrombocytopenia (<20,000 per cubic millimetre), acute renal failure (serum creatinine >6 mg/dL), hypocalcaemia, and ventricular tachycardia.

Raised serum creatinine phosphokinase (CPK) and lactic dehydrogenase levels have also been observed.

Blood and lymphatic system disorders:
Common: leucopenia, thrombocytopenia and anaemia

Immune system disorders:
Hypersensitivity reactions, including anaphylactic reactions and anaphylactic shock and angioedema have been reported.

Metabolism and nutrition disorders:
Very common: azotemia (elevated serum creatinine levels 2.4 to 6 mg/dL)
Common: hypoglycaemia, hyperglycaemia, diabetes mellitus with or without preceding hypoglycaemia have occurred up to several months after cessation of therapy, hyperkalaemia, hypocalcaemia, hypomagnesaemia

Nervous system disorders:
Common: syncope and dizziness
Extremity paraesthesia as well as facial and perioral hypoesthesia have been reported with IV administration of pentamidine, both in children and adults. The cases occurred during or shortly after the IV infusions and resolved after completion or interruption of the infusion.

Cardiac disorders:
Rare: QT interval prolongation, cardiac arrhythmia
Torsades de Pointes, bradycardia have been reported.

Vascular disorders:
Common: hypotension, flushing

Gastrointestinal disorders:
Common: nausea and vomiting, taste disturbances
Rare: pancreatitis

Hepatobiliary disorders:
Common: abnormal liver function tests

Skin and subcutaneous tissue disorders:
Common: rash
A possible case of Stevens-Johnson syndrome has been reported.

Renal and urinary disorders:
Very common: acute renal failure, macroscopic haematuria

General disorders and administration site conditions:

Very common: local reactions ranging in severity from discomfort and pain to induration, abscess formation and muscle necrosis

Rhabdomyolysis has been reported following intramuscular administration of pentamidine isethionate.

4.9 Overdose

Treatment is symptomatic. Cardiac rhythm disorders, including Torsades de Pointes, have been reported following overdose of pentamidine isethionate.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5.PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiprotozoal

Pentamidine isethionate is an aromatic diamidine. It acts by interfering with DNA and folate transformation, and by inhibiting RNA phospholipid and protein synthesis.

5.2 Pharmacokinetic properties

Plasma levels fall rapidly during the first two hours following an intravenous infusion of pentamidine isethionate to one-twentieth of peak levels, followed by a much slower decline. Elimination half-life was estimated to be about 6 hours in patients with normal renal function and extended to about 9 hours in patients with impaired renal function. After deep intramuscular administration, peak concentrations are lower but decline in a similar fashion, with an elimination half-life of about 9 hours.

Pentamidine appears to be widely distributed in the body and probably accumulates in tissue, particularly the liver and kidneys. Only a small amount is excreted unchanged in the urine.

When pentamidine isethionate is administered via a nebuliser, peak plasma concentrations are found to be approximately 10% of that observed with equivalent intramuscular doses and less than 5% of that observed following intravenous administration.

However, aerosol administration results in a 10-fold increase in pentamidine concentration in bronchial alveolar lavage (BAL) fluid supernatant, and an 80-fold increase in BAL sediment concentrations, when compared with equivalent intravenous doses.

Limited data suggest that the half-life of pentamidine in BAL fluid is greater than 10 to 14 days. Peak plasma concentrations after inhalation therapy were found to be approximately 10% of those observed with equivalent intramuscular doses and less than 5% of those observed following intravenous administration. This suggests that systemic effects by the inhalation route are less likely. Long-term pulmonary parenchymal effects of aerosolised pentamidine are not known. Lung volume and alveolar capillary diffusion, however, have not been shown to be affected by high doses of pentamidine administered by inhalation to Acquired Immune Deficiency Syndrome (AIDS) patients.

6.PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

After reconstitution with Water for Injections B.P., Pentacarinat should not be mixed with any injection solutions other than Glucose Intravenous Infusion 5% B.P. and 0.9% (Normal) Sodium Chloride Injection B.P.

6.3 Shelf life

Shelf life of powder as packaged for sale:

5 years

Store the dilute reconstituted drug solution between 2-8°C. Discard all unused portions within 24 hours of preparation.

Concentrated solutions for administration by inhalation or intramuscular routes should be used immediately.

6.4 Special precautions for storage

For storage conditions after reconstitution see section 6.3.

Store the dry product below 30°C.

6.5 Nature and contents of container and special equipment for use and administration

This product is supplied in 5 single dose vials. Each vial contains 300mg of pentamidine isethionate B.P. for injections and for aerosol administration via a nebuliser.

6.6 Special precautions for disposal and other handling

If the preparation of the solution is to be undertaken in the home setting it should be reconstituted in a clean area that is not used for food preparation and care should be taken to minimise exposure to the inhalation of atmospheric pentamidine.

All bystanders including medical personnel are advised to minimise exposure to atmospheric pentamidine from nebulisers.

After reconstitution with Water for Injections B.P., Pentacarinat should not be mixed with any injection solutions other than Glucose Intravenous Infusion 5% B.P. and 0.9% (Normal) Sodium Chloride Injection B.P.

Dosage equivalence: 4 mg of pentamidine isethionate contains 2.3 mg pentamidine base. 1 mg of pentamidine base is equivalent to 1.74 mg pentamidine isethionate.

Displacement value: 300 mg of pentamidine isethionate displaces approximately 0.15 mL of water.

Aerosol administration

Adults

Prophylactic Use (Secondary Prevention) for Pneumocystis Jiroveci (Carinii) Pneumonia – 300 mg once a month

The contents of one vial of 300 mg pentamidine isethionate are dissolved in 4 to 6 mL of Water for Injections B.P. The freshly prepared solution is then placed in the appropriate nebuliser.

The freshly prepared solution should be administered by inhalation using a suitable nebuliser such as a 'Respirgard II', modified 'Acorn System 22' or an equivalent device. The device should be fitted with either a portable compressor or piped oxygen at a flow rate of 6 to10 litres per minute.

The optimal particle size for alveolar deposition is between 1 and 2 microns.

A suitable, well-fitted one-way system should be employed such that the nebuliser stores the aerosolised drug during exhalations and disperses exhaled pentamidine into a reservoir. A filter should be fitted to the exhaust line to reduce atmospheric pollution. It is advisable to use a suitable exhaust tube, which vents directly through a window to the external atmosphere. Care should be taken to ensure that passers-by will not be exposed to the exhaust.

Parenteral Administration

Pentacarinat must be reconstituted only with Water for Injections B.P. The reconstituted solution may be further diluted for intravenous infusion using either Glucose Intravenous Infusion 5% B.P. or 0.9% Sodium Chloride Injection B.P. It must not be mixed or diluted with any other injection solution.

For deep intramuscular administration the contents of one 300 mg pentamidine isethionate vial should be dissolved in 3 mL of Water for Injections B.P. The dose calculated for the individual patient should then be administered by deep intramuscular injection, preferably into the buttock.

For slow intravenous infusion, the contents of one 300 mg pentamidine isethionate vial should be dissolved in a known volume (3 to 5 mL) of Water for Injections B.P. The dose calculated for an individual patient may then be diluted further in 50 to 250 mL of Glucose Intravenous Infusion 5% B.P. or in 0.9% Sodium Chloride Injection B.P. The resulting solution should be infused over a period of at least 60 minutes with the patient remaining supine and under close medical supervision.

7.MEDICINE SCHEDULE

Prescription medicine

8.SPONSOR

Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics
PO Box 62027
Sylvia Park Auckland 1644
Freecall: 0800 283 684
Email: medinfo.australia@sanofi.com

9.DATE OF FIRST APPROVAL

13 July 1989

10.DATE OF REVISION OF THE TEXT

20 June 2022

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
8	Change of sponsor