

Data Sheet

PENTACARINAT[®]

Name of Medicine

Pentamidine isethionate B.P. injection, 300mg

Presentation

A sterile white powder supplied in single dose vials. Each vial contains 300mg of pentamidine isethionate B.P. for injections and for aerosol administration via a nebuliser.

Uses

Actions

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

Pharmacokinetics

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.

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. For aerosol administration via a nebuliser is indicated for the prevention and treatment of *Pneumocystis jiroveci (carinii)* pneumonia in patients infected by the Human Immunodeficiency Virus (HIV).
3. Leishmaniasis (visceral and cutaneous) including cases resistant to pentavalent antimony compounds.
4. Early phase African sleeping sickness caused by *Trypanosoma gambiense*.

Dosage and Administration

Aerosol Administration

Solutions for inhalation should be prepared as described below and then used immediately.

Adults

Treatment of Pneumocystis Jiroveci (Carinii) Pneumonia – 600 mg/day for 21 days

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

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 to 10 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.

Children

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

Parenteral Administration

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.

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.

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.

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 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.

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.

Warnings and Precautions

Aerosol Use

Inhaled, nebulised pentamidine isethionate may induce bronchospasm or cough. This has been particularly noted in some patients with a history of smoking or asthma. An aerosolised bronchodilator should be used in conjunction with the administration of pentamidine once this reaction occurs and may be necessary prior to future treatment.

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

Pregnancy (Category B3)

There is no evidence of the safety of pentamidine isethionate in any form of administration, during human pregnancy. Pentamidine isethionate therefore should not be administered to pregnant patients unless it is considered essential.

Lactation

The use of pentamidine isethionate is contraindicated in breast-feeding women unless it is considered essential by the physician.

Pentamidine isethionate, especially when administered parenterally, should be used with particular caution in patients with hepatic and/or renal dysfunction, hypertension or hypotension, hyperglycaemia or hypoglycaemia, leucopenia, thrombocytopenia or anaemia.

Sudden, severe hypotension may occur in patients after a single dose of pentamidine isethionate has been given parenterally. The 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 the treatment is concluded.

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. Therefore, patients receiving pentamidine by inhalation should be closely monitored for the development of severe adverse reactions.

Laboratory monitoring

The following tests should be carried out before, during and after therapy:

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.
6. Urine analysis and serum electrolytes daily during therapy.
7. Electrocardiograms at regular intervals.

Adverse Effects

Aerosol Administration

The occurrence of cases of pneumothorax have been reported in patients presenting a history of *Pneumocystis jiroveci (carinii)* pneumonia. 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.

Local reactions involving the upper respiratory tract can occur ranging in severity from cough, shortness of breath, wheezing to bronchospasm. Other side effects reported with the use of aerosolised pentamidine were rash, fever, decrease in appetite, bad taste, fatigue, light-headedness, nausea, hypotension, hypoglycaemia, acute pancreatitis and renal insufficiency.

A miscarriage has been reported following prophylactic aerosolised administration.

Parenteral Administration (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.

A possible case of Stevens-Johnson syndrome has been reported.

Less severe reactions consisting of azotemia (elevated serum creatinine levels 2.4 to 6 mg/dL), abnormal liver function tests, leucopenia, anaemia, thrombocytopenia, hyperkalaemia, nausea and

vomiting, hypotension, dizziness, syncope, flushing, hypoglycaemia, hyperglycaemia, rash and taste disturbances may be observed.

Local reactions after parenteral administration ranging in severity from discomfort and pain to induration, abscess formation and muscle necrosis can occur. Raised serum creatinine phosphokinase (CPK) and lactic dehydrogenase levels have also been observed.

Rhabdomyolysis has been rarely reported following intramuscular administration of pentamidine isethionate.

Interactions

Nil information.

Overdosage

Treatment is symptomatic. However, no cases of overdosage have been recorded with pentamidine isethionate.

Pharmaceutical Precautions

This product should be reconstituted in a vertical laminar flow cabinet. 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.

Shelf Life

Store the dry product below 30°C.

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.

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.

Medicine Classification

Prescription medicine.

Package Quantities

300 mg vials available in packs of 5.

Further Information

Pentamidine isethionate is an aromatic diamidine. It is an antiprotozoal agent, which acts by interfering with DNA and folate transformation, and by the inhibition of RNA and protein synthesis.

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.

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

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