PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

# [Pr]Pentamidine Isetionate for Injection BP

Pentamidine Isetionate for Injection

Powder for Solution, 300 mg per vial,

Intramuscular, Intravenous

BP

Antiparasitic Agent

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JUL 02, 2021

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**RECENT MAJOR LABEL CHANGES**

| | |
|---|---|
| 7 WARNINGS AND PRECAUTIONS | 08/2022 |

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**Sections or subsections that are not applicable at the time of authorization are not listed.**

## PART I: HEALTH PROFESSIONAL INFORMATION

## 1 INDICATIONS

Pentamidine Isetionate for Injection BP is indicated for the treatment of pneumonia due to *Pneumocystis jirovecii* (*Pneumocystis carinii* Pneumonia or PCP).

### 1.1 Pediatrics

**Pediatrics (<18 years of age):** The safety and efficacy of pentamidine isetionate has not been established in the pediatric population, and pharmacokinetic data are extremely limited. Pentamidine Isetionate for Injection BP should be considered only if there is no other appropriate treatment (see **4 DOSAGE AND ADMINISTRATION**).

### 1.2 Geriatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

## 2 CONTRAINDICATIONS

Pentamidine Isetionate for Injection BP is contraindicated in:

- Patients who are hypersensitive to this drug, to any ingredient in the formulation or component of the container. For a complete listing, see the **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING** section of the Prescribing Information with Patient Information.

## 3 SERIOUS WARNINGS AND PRECAUTIONS BOX

**Serious Warnings and Precautions**

- **Pentamidine Isetionate for Injection BP should be used with caution in patients with hypertension, hypotension, hypoglycemia, hyperglycemia, hypocalcemia, leukopenia, thrombocytopenia, anemia and hepatic or renal dysfunction.**
- **Pentamidine Isetionate for Injection BP 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 7 WARNINGS AND PRECAUTIONS: Monitoring and Laboratory Tests).**
- **Profound severe hypotension may result after a single dose (see 7 WARNINGS AND PRECAUTIONS: Cardiovascular)**
- **Severe hypotension, hypoglycemia, acute pancreatitis, renal impairment and cardiac arrhythmias resulting in death (see 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS)**
- **Extravasation reactions may result in ulceration, tissue necrosis and long-term sequelae (see 8 ADVERSE REACTIONS)**

## 4 DOSAGE AND ADMINISTRATION

### 4.1 Dosing Considerations

Pentamidine Isetionate for Injection BP may be administered intravenously or intramuscularly. When administered intravenously, Pentamidine Isetionate for Injection BP must be given only by slow infusion (i.e. over a period of 2 to 3 hours). Intramuscular administration should be reserved for patients with adequate muscle mass and for whom a slow intravenous infusion is not practical. Intramuscular administration is normally not recommended because of poor local tolerance (see **7WARNINGS AND PRECAUTIONS**).

Since severe hypotension reactions may occur, patients receiving Pentamidine Isetionate for Injection BP should be in a supine position and blood pressure should be closely monitored during administration of the drug and several times thereafter until blood pressure is stable.

### 4.2 Recommended Dose and Dosage Adjustment

Adults: The recommended regimen is 4 mg/kg once a day for 14 to 21 days. The benefits and risks of therapy for longer than 14 doses are not well defined.

Patients with Renal Failure (creatinine clearance < 35 mL/min):

- Life-threatening infections: 4 mg/kg once daily for 7 to 10 days, followed by 4 mg/kg on alternate days to complete the course of 14 doses.
- Less severe infections: 4 mg/kg on alternate days for 14 doses.

Children: Clinical and pharmacokinetic data are extremely limited and further investigation is necessary to fully characterize the pharmacokinetics of pentamidine isetionate in this age group. However, a dosage of 4 mg/kg has been used in children. Pentamidine Isetionate for Injection BP should be considered only if there is no other appropriate treatment.

### 4.3 Reconstitution

**Parenteral Products:**
**Preparation for Use and Reconstitution**

For Intravenous Infusion: RECONSTITUTE ONLY WITH STERILE WATER FOR INJECTION.

**RECONSTITUTION TABLE**

| Vial size | Volume to be added to vial | Approximate available volume | Approximate average concentration |
|---|---|---|---|
| 300 mg | 3 mL | 3.15 mL | 100 mg / mL |

Further dilute the appropriate volume of reconstituted solution with 50 to 500 mL of 5% dextrose injection or 0.9% sodium chloride injection. The reconstituted solution should not be mixed with anyother injection solution.

For Intramuscular Injection: Reconstitute as for intravenous injection and do not further dilute.

**As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discolouration and leakage prior to administration whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discolouration or leakage should not be used.**

### 4.4 Administration

Intravenous infusion: The reconstituted and further diluted solution should be administered over a period of at least 60 minutes and preferably over a period of 2 to 3 hours.

Intramuscular injection: The appropriate volume of reconstituted solution should be administered well within the body of a relatively large muscle mass.

## 5 OVERDOSAGE

There are apparently no reports of acute toxicity associated with overdosage of pentamidine isetionate. In general, overdosage would be expected to produce effects that are an extension of common adverse effects or of the serious metabolic sequelae observed. In case of suspected overdosage, treatment should be symptomatic and supportive. Neither peritoneal dialysis nor hemodialysis appear to remove the drug rapidly enough to cause a precipitous decline in the plasmaconcentration of pentamidine isetionate.

For management of a suspected drug overdose, contact your regional poison control centre.

## 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

**Table – Dosage Forms, Strengths, Composition and Packaging**

| Route of Administration | Dosage Form / Strength/Composition | Non-medicinal Ingredients |
|---|---|---|
| Intravenous<br>Intramuscular | Lyophilized powder for solution<br>300 mg per vial | The formulation does not contain any non-medicinal ingredients. |

Pentamidine Isetionate for Injection BP is supplied as a sterile, lyophilized powder/cake and supplied in single-dose vials, packages of 5 products.

Each vial contains: Pentamidine isethionate USP….300 mg

The Container closure system of Pentamidine Isetionate for Injection BP consist of a 20 ml clear glass vial stoppered with 20 mm dark grey rubber stopper and sealed with 20 mm red MT flip off seal.

## 7 WARNINGS AND PRECAUTIONS

Please see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX**.

### General

Pentamidine Isetionate for Injection BP should only be administered under close medical supervision, and the patient should be very carefully monitored for the development of serious adverse reactions (see **8 ADVERSE REACTIONS**). The administration of Pentamidine Isetionate for Injection BP 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 Pentamidine Isetionate for Injection BP. In such cases, the prophylactic use of an antiemetic and/or acetaminophenmay be considered.

**Cardiovascular**

Patients may develop sudden, severe hypotension after receiving a single intramuscular or intravenous dose of pentamidine isetionate. Therefore, patients receiving Pentamidine Isetionate for Injection BP 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. Pentamidine Isetionate for Injection BP should be infused overa period of at least 60 minutes and preferably over 2 to 3 hours to minimize the risk of hypotension.

Severe hypotension with accompanying bradycardia has been observed in a patient after the sixth dose of pentamidine isetionate. 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 Isetionate for Injection BP. ECG's may be required at regular intervals if signs of cardiotoxicity develop

Phlebitis can occur after intravenous injection.

**Endocrine and Metabolism**

Pentamidine isetionate can produce hypoglycemia, 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 isetionate-induced hypoglycemia has been associated with pancreatic islet cell necrosis and inappropriately high plasma insulin concentrations. Hyperglycemia and diabetes mellitus, with orwithout preceding hypoglycemia, have also occurred, sometimes several months after termination of therapy with pentamidine isetionate.

Hypoglycemia induced by pentamidine isetionate 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 isetionate treatment.

**Hematologic**

Leukopenia and thrombocytopenia, which can be severe (e.g. leukocyte count less than 1,000/$mm^3$, platelet count less than 20,000/$mm^3$), occur occasionally in patients receiving pentamidine isetionate. Cases of anemia have been observed. In a few cases, pentamidine isetionate therapy has beenassociated with neutropenia.

**Hepatic/Biliary/Pancreatic**

Abnormal liver function tests may occur. Liver function should be routinely monitored in patients receiving Pentamidine Isetionate for Injection BP (see **7 WARNINGS AND PRECAUTIONS: Monitoringand Laboratory Tests**). Cases of acute pancreatitis have been observed with pentamidine isetionate treatment.

**Immune**

Hypersensitivity reactions at the injection site, such as skin rash and erythema, may occur (see **7 WARNINGS AND PRECAUTIONS: Skin** and **8 ADVERSE REACTIONS**).

**Monitoring and Laboratory Tests**

In order to monitor for possible toxicity, the following tests should be carried out before, during and after therapy:

a) Daily determinations of blood urea nitrogen (BUN), serum creatinine and serum electrolytes.
b) Daily blood glucose determinations during therapy and continuing several times after completion of therapy as required by the clinical condition.
c) Twice weekly complete blood count and platelet count.
d) Liver function tests including bilirubin, alkaline phosphatase, ALT (SGPT) and AST (SGOT), weekly or every 3-5 days if values are elevated.
e) Weekly serum calcium determinations.
f) Electrocardiograms at regular intervals.

**Renal**

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 agentsor previous evidence of renal disease.

**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.

### 7.1 Special Populations

#### 7.1.1 Pregnant Women

In a teratogenicity study in rabbits, the drug was embryotoxic as evidenced by the number of post- implantation losses and by delayed ossification. It is not known whether pentamidine isetionate cancause fetal harm when administered to pregnant women. Pentamidine Isetionate for Injection BP should not be used during pregnancy, unless the benefits outweigh the risks and this medication recommended by the overseeing health professional.

#### 7.1.2 Breast-feeding

Since it is not known whether pentamidine isetionate is excreted into breast milk, the drug should be used with caution in nursing mothers and cessation of nursing should be considered.

## 8 ADVERSE REACTIONS

### 8.1 Adverse Reaction Overview

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

The following life-threatening reactions have been reported in patients receiving pentamidine isetionate. They require immediate corrective measures and withdrawal of treatment: cardiac arrhythmias (including QT interval prolongation and torsade de pointes), hypotension, hypoglycemia,acute pancreatitis, hypocalcemia, leukopenia

(less than 1,000/mm$^3$), thrombocytopenia (less than 20,000/mm$^3$) and acute renal failure.

### 8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared tothe rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Adverse reactions (characterized as likely related to drug-therapy) occurring in ≥ 1% of pentamidine isetionate-treated patients are shown in **Table 1** below. The table provides the frequency of adverseeffects, which occurred in two prospective uncontrolled trials involving immunosuppressed patientswith pneumonitis caused by *Pneumocystis jirovecii* treated with parenteral pentamidine isetionate 4mg/kg/day for 12 to 14 days.

**Table 1: Common (≥ 1%) Adverse Reactions Reported in patients treated with pentamidine isethionate**

| System/Organ Class | Adverse Reactions | Number of patients (%)[1] Western et al. (1970) | Number of patients (%)[2] Walzer et al. (1974) |
|---|---|---|---|
| Cardiovascular | Hypotension<br>Tachycardia | 6 (3.7)<br>4 (2.4) | 39 (9.6)<br>- |
| Gastrointestinal | Nausea, vomiting | 4 (2.4) | - |
| Hematologic | Anemia<br>Depressed serum folate<br>Hematologic disturbances<br>Thrombocytopenia | 3 (1.8)<br>2 (1.2)<br>-<br>2 (1.2) | -<br>-<br>17 (4.2)<br>- |
| Hepatic | Abnormal liver function (hepatic dysfunction) | 12 (7.3) | 39 (9.6) |
| Metabolic | Hypocalcemia<br>Hypoglycemia | 4 (2.4)<br>15 (9.1) | 5 (1.2)<br>25 (6.2) |
| Renal and urogenital | Azotemia<br>Impaired renal function | 31 (18.9)<br>- | -<br>39 (9.6) |
| Skin | Abscess and/or necrosis<br>Pain at injection site<br>Abscess and/or pain at injection site<br>Facial flushing<br>Itching<br>Rash | 11 (6.7)<br>16 (9.8)<br>-<br>3 (1.8)<br>2 (1.2)<br>4 (2.4) | -<br>-<br>74 (18.3)<br>-<br>-<br>6 (1.5) |
| Special senses | Unpleasant taste | 2 (1.2) | - |

[1] Adverse reactions were observed in 42% of the patients treated with pentamidine isetionate (N=164). Some patients had more than one adverse effect. Refer to Western, K.A., Perera, D.R., and Schultz, M.G. Pentamidine isetionate in the treatment of *Pneumocystis carinii* pneumonia. 1970. Annals Intern. Med. 73: 695.

[2] Adverse reactions were observed in 46.8% of the patients treated with pentamidine isetionate (N=404). Refer to Walzer, P.D., Perl, D.P, Kragstad, D.J. et al. *Pneumocystis carinii* pneumonia in the United States. 1974. Annals Intern. Med. 80: 83.

### 8.3 Less Common Clinical Trial Adverse Reactions

The following other reactions were observed less frequently or only occasionally in patients receiving pentamidine isetionate: Less common adverse reactions occurring in <1% of pentamidine isetionate- treated patients are shown in **Table 2** below.

**Table 2: Less Common (<1%) Adverse Reactions Reported in patients treated with pentamidine isetionate**

| System/Organ Class | Adverse Reactions |
|---|---|
| Body as a whole | Death |
| Metabolic | Hyperglycemia, hyperkalemia |
| Neurologic | Dizziness, hallucinations, syncope |
| Skin | Alopecia, erythema multiforme |
| Renal and urogenital | Albuminuria, glycosuria |
| Vascular | Venous thrombosis |

Preliminary evidence suggests that the frequency of adverse effects due to pentamidine isetionate is higher in patients with acquired immunodeficiency syndrome (AIDS) than in non-AIDS patients. In onestudy, 20 of 24 (83%) AIDS patients treated with pentamidine isetionate experienced some kind of adverse effect. Hepatic abnormalities (58%), nausea and vomiting (46%), hypoglycemia (33%), azotemia (25%) and pain at injection site (25%) were the most commonly seen.

## 9 DRUG INTERACTIONS

### 9.4 Drug-Drug Interactions

Since nephrotoxic effects may be additive, the concurrent or sequential use of pentamidine isetionate with drugs having a nephrotoxic potential (e.g. aminoglycosides, amphotericin B, cisplatin, methoxyfluorane or vancomycin) should be undertaken with caution. Pentamidine Isetionate for Injection BP should be administered with caution to patients who are receiving drugs with hepatotoxicpotential or medication that can impair the hematopoietic system.

### 9.5 Drug-Food Interactions

Interactions with food have not been established.

### 9.6 Drug-Herb Interactions

The effects of herbal products on the pharmacokinetics of pentamidine isetionate have not been studied.

### 9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

## 10 CLINICAL PHARMACOLOGY

### 10.1 Mechanism of Action

Pentamidine isetionate is a member of a class of compounds known as aromatic diamidines. The exact mechanism of antiprotozoal action of pentamidine isetionate has not been fully elucidated. Several mechanisms of action may

be involved, and the role of the mechanism(s) may vary for different types of protozoa. *In vitro*, pentamidine isetionate appears to have a direct cidal effect on *Pneumocystis jirovecii*. Pentamidine isetionate is believed to act by inhibiting glucose metabolism, interfering with DNA and folate transformation, and by inhibiting RNA, protein synthesis and intracellular amino acidtransport.

**10.3 Pharmacokinetics**

**Absorption:**
Following daily intramuscular administration of single 4 mg/kg doses of pentamidine isetionate, the plasma pentamidine isetionate concentration has been reported in an early study to average 0.3 to 0.5mcg/mL (range: 0.3 - 1.4 mcg/mL) after 1 to 10 days of therapy. In these patients, plasma drug concentrations did not vary appreciably throughout the day, did not increase with successive doses, and generally did not increase immediately after administration of a dose.

Significant differences in the pharmacokinetic parameters of pentamidine isetionate between intramuscularly and intravenously treated patients with the Acquired Immunodeficiency Syndrome (AIDS) have been reported. The mean peak concentration in plasma after intramuscular and intravenous administration (2 hour infusion) of a single 4 mg/kg dose (calculated as salt) were 209 ng/mL and 612 ng/mL, respectively. Plasma concentrations, which declined bi-exponentially, were detectable throughout the 24-hour post-dose interval and fell to <25 ng/mL after 8 hours. The mean plasma clearance, elimination half-life, apparent volume of distribution, and apparent volume at steadystate for intramuscularly treated patients were 305 L/h, 9.36 hours, 924 liters, and 2,724 liters, respectively. These parameters for the intravenously treated patients were 248 L/h, 6.40 hours, 140 liters, and 821 liters respectively. Renal clearance of pentamidine isetionate was 5.0% of the plasma clearance for intramuscularly treated patients and 2.5% for intravenously treated patients.

**Distribution:**
Distribution of pentamidine isetionate into human body tissues and fluids has not been well characterized, but the drug appears to be rapidly and extensively distributed and/or bound to tissues. Following parenteral administration, highest concentrations have been found in the liver, followed by the kidneys, adrenals, spleen, lungs and pancreas. It is believed that continued parenteral administration beyond the first week of therapy may not substantially increase accumulation of the drug. Pentamidine isetionate penetrates the central nervous system (CNS) only very poorly after prolonged therapy. *In vitro*, pentamidine isetionate is reportedly 69% bound to serum proteins. It is not known whether pentamidine isetionate crosses the placenta or is distributed into breast milk.

**Elimination:**
Little is known about the elimination of pentamidine isetionate in humans. Plasma concentrations of pentamidine isetionate have been found to decline in a biphasic manner following a single intramuscular injection or intravenous infusion in patients with normal renal function. The mean elimination half-life was found to be 54 and 18 minutes in the initial phase, respectively, and 9.4 and 6.4 hours in the terminal phase, respectively. Pentamidine isetionate appears to be eliminated very slowly from tissues in which the drug principally accumulates. (e.g. liver, lungs). Limited data suggest that the elimination half-life of pentamidine isetionate is not substantially altered in patients with mildto moderate renal impairment, but may be prolonged up to 2 days or longer in patients with severe renal impairment. In humans, pentamidine isetionate is excreted in urine apparently as unchanged drug. It is not known is the drug is excreted in feces.

Urinary excretion has been found to occur mostly within the first 6 to 8 hours following administration of a dose, although decreasing amounts of pentamidine isetionate have been found to be excreted slowly for up to 6 to 8 weeks following discontinuation of the drug in several patients. Limited data suggest that pentamidine isetionate is not appreciably removed by haemodialysis orperitoneal dialysis.

## 11 STORAGE, STABILITY AND DISPOSAL

The unopened vials should be stored between 15°C and 25°C, protected from light.

Reconstituted solutions that have been further diluted in 5% dextrose injection or 0.9% sodium chloride injection to a concentration of approximately 2 mg / mL are stable for up to 24 hours at roomtemperature.

## 12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

## PART II: SCIENTIFIC INFORMATION

## 13 PHARMACEUTICAL INFORMATION

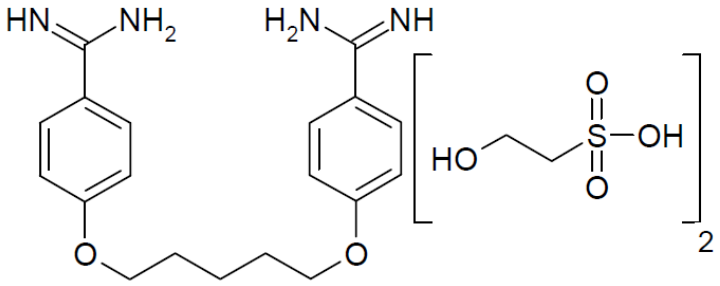
**Drug Substance**

Proper Name: Pentamidine isetionate USP

Chemical Name: Ethanesulfonic acid, 2-hydroxy-, compd. with 4,4'- [1,5-pentanediylbis (oxy)] bis [benzenecarboximidamide]; 4,4'-(Pentane-1,5-diylbis(oxy)) dibenzimidamide bis (2 hydroxyethanesulfonate)

Molecular Formula and molecular mass: $C_{19}H_{24}N_4O_2.(C_2H_6O_4S)_2$ ; 592.68 g/mol (Pentamidine Isetionate)
$C_{19}H_{24}N_4O_2$ ; 340.42 g/mol (Pentamidine)

Chemical Structure:




Physicochemical properties: White or almost white powder or colourless crystals. Pentamidine Isetionate for Injection BP is a sterile lyophilized powder for injection. It contains no preservative.

## 14 CLINICAL TRIALS

Not applicable.

## 15 MICROBIOLOGY

Pentamidine isetionate is active *in vitro* and/or *in vivo* against a variety of protozoa, including the genera of Trypanosomatidae pathogenic to humans. *In vitro* studies have not yet quantified the effectsof pentamidine isetionate on *Pneumocystis jirovecii*, an organism generally considered a protozoan; however, several have compared the activity of the drug with that of trimethoprim/sulphamethoxazole.

*In Vitro* Activity: Pentamidine isetionate in concentrations of 0.3 to 9 mg/L decreased the viability of *Pneumocystis jirovecii* to a similar extent as did trimethoprim / sulphamethoxazol (trimethoprim 1.8 to 54 mg/L plus sulphamethoxazole 9 to 270 mg/L) in experimental models in chick embryo lung epithelialcells, and in the lung cells of rats with pneumonia which was induced by corticosteroids. Although bothdrugs inhibited the organism, pentamidine isetionate, unlike trimethoprim/ sulphamethoxazole, was demonstrated to be directly lethal to *Pneumocystis jirovecii* in its non-replicating state.

*In Vivo* Activity: Induction of *Pneumocystis jirovecii* pneumonia in rats given corticosteroids, a method first described by Frenkel et al. (1966), has served as the model of the *in vivo* activity of pentamidine isetionate. However, since *Pneumocystis jirovecii* is likely a species-specific organism, it is unclear whether these *in vivo* results have clinical applications. Using this rat model, Western et al. (1975) demonstrated that pentamidine isetionate 10 or 20 mg/kg subcutaneously or 4 mg/kg intramuscularly in daily or thrice weekly doses for 2 weeks prolonged survival time beyond that seen in control animals,but did not decrease mortality nor prevent proliferation of the organism. Pentamidine isetionate and trimethoprim/sulphamethoxazole decreased indices of disease severity to a similar extent, but only 14 to 52% of animals to which pentamidine isetionate was administered, recovered, in contrast to 64 to 79% of those receiving the combination antimicrobial agent. Further, unlike trimethoprim/ sulphamethoxazole, pentamidine isetionate was not shown to be useful prophylactically. Combination drug regimens of pentamidine isetionate plus trimethoprim/sulphamethoxazole, rifampicin or clindamycin in rat models have not improved the treatment success rate achieved with pentamidine isetionate alone.

## 16 NON-CLINICAL TOXICOLOGY

**Acute toxicity:**

The $LD_{50}$ for pentamidine isetionate in mice by the intravenous and subcutaneous routes was 28 mg/kg and 64 mg/kg, respectively. Near lethal acute doses of pentamidine isetionate have produced a hyperglycemic effect in rabbits. In the guinea pig, toxic concentrations of pentamidine isetionate have produced fatty degeneration of the liver and cloudy swelling of the kidney. In a variety of anesthetizedanimals, a sharp fall in blood pressure followed the intravenous administration of pentamidine isetionate.

**Subacute toxicity:**

In a subacute 6-week I.V. toxicity study in rats, pentamidine isetionate was administered at dose levels of 0, 2, 6 and 18 mg/kg/day. This study included a 3-week recovery period for some of the animals. Significant clinical and laboratory findings included a reduction $K^+$ in all treated animals, whereas total bilirubin levels were raised in all male treated groups. At the 18 mg/kg/day dose level, local irritation atthe injection site, as well as reduction in body weight were observed in both sexes. At study termination, the relative kidney and liver weights were increased in both sexes dosed at 18 mg/kg/day and remained higher than those of the controls at the end of the recovery period.

There was evidence of some renal impairment at the18 mg/kg dose level. This consisted of increased plasma urea levels in association with increases in urinary volume, decreases in urinary specific gravityand increases in urine enzyme levels at termination of dosing.

An I.V. toxicity study was also done in Beagle dogs. Pentamidine isetionate was administered daily for 2 weeks at dose levels of 0, 2, 4 and 8 mg/kg/day. Weight gain was adversely affected in both sexes at the 8 mg/kg dose level, and reductions in food intake occurred in all treated animals. Elevation of plasma urea and creatinine, and of urinary LDH, NAG and lysozyme, together with the presence of renaltubular cells in the urine of dogs given 8 mg/kg pointed to the kidney as the target organ. No toxicologically significant macroscopic post-mortem findings or treatment related histopathological changes were recorded except for lesions at the injection site.

**Reproductive and Developmental Toxicology:**

Pentamidine isetionate was assessed for feto-toxic and teratogenic activity in mated female New Zealand white rabbits at dose levels of 1, 2, 3 and 8 mg/kg intravenously once daily from the fifth to the twentieth day post-coitum. A degree of maternal toxicity (severe central nervous system, somatomotor, respiratory and cardiovascular reactions) was evident at 8 mg/kg. A dose-related decreased body weight and food consumption was also noted in the dams.

Litter data parameters (viable fetuses, litter weight and fetal weight, sex ratio) remained largely unaffected by treatment except for a mild feto-toxic effect in all dosage groups as indicated by increased post-implantation loss and increased incidence of minor fetal skeletal anomalies which mayhave been linked to maternal toxicity.

## 17 SUPPORTING PRODUCT MONOGRAPHS

1. Pentamidine Isetionate for Injection BP, Sterile Powder for Solution, 300 mg per vial, Submission control number 255613, Product Monograph, Pfizer Canada ULC, January 31, 2022.

## PATIENT MEDICATION INFORMATION

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**
**[Pr] Pentamidine Isetionate for Injection BP**
**Pentamidine Isetionate for Injection**

Read this carefully before you start taking **Pentamidine Isetionate for Injection BP** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Pentamidine Isetionate for Injection BP**.

**Serious Warnings and Precautions**

- **This medicine may cause serious reactions, sometimes leading to death, including:**
  - **very low blood pressure, even after 1 dose**
  - **very low blood sugar**
  - **irregular heartbeat**
  - **inflamed pancreas**
  - **leakage of the medicine outside the vein which can cause:**
    - **tissue irritation and sores**
    - **cell death**
    - **other complications**

- **Your doctor will only use this product in hospital setting with the facilities to test:**
  - **blood sugar**
  - **blood cell count**
  - **kidney and liver function**
  - **heart rate**

- **Your doctor will consider the following conditions you may have before deciding that this medicine is right for you:**
  - **high or low blood pressure**
  - **high or low blood sugar**
  - **low number of white or red blood cells, platelets**
  - **any liver or kidney problem**

**What is Pentamidine Isetionate for Injection BP used for?**
Pentamidine Isetionate for Injection BP is a medicine used to treat infection in the lung (pneumonia).

**How does Pentamidine Isetionate for Injection BP work?**
Pentamidine isetionate prevents the growth of the microbe and causes its death.

**What are the ingredients in Pentamidine Isetionate for Injection BP?**
Medicinal ingredients: Pentamidine isetionate.
Non-medicinal ingredients: The formulation does not contain any non-medicinal ingredients.

**Pentamidine Isetionate for Injection BP comes in the following dosage forms:**
Powder for solution: 300 mg / vial.

**Do not use Pentamidine Isetionate for Injection BP if:**

- You are hypersensitive to this drug or to any part of the container.

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Pentamidine Isetionate for Injection BP. Talk about any health conditions or problems you may have, including if you:**

- Have liver, pancreas or kidney problems
- Have high or low blood pressure
- Have high or low blood sugar level
- Have low white blood cells (leukopenia)
- Have low red blood cells (anemia)
- Have low blood platelets (thrombocytopenia)
- Have low blood calcium levels (hypocalcemia)
- Have irregular heart rate or rhythm
- Are pregnant or planning to become pregnant
- Are breastfeeding or planning to breastfeed.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**The following may interact with Pentamidine Isetionate for Injection BP:**

- Drugs that are potentially toxic to the kidneys:
  - Aminoglycosides
  - Amphotericin B
  - Cisplatin
  - Methoxyfluorane
  - Vancomycin
- Drugs that are potentially harmful to the liver or blood cells.

**How to take Pentamidine Isetionate for Injection BP:**

Pentamidine Isetionate for Injection BP will always be prepared and given to you by a doctor or a healthcare professional. You may receive the medicine through a vein in the hand or arm, or injected into a muscle of the upper leg or buttock.

**Usual adult dose:**

The usual dose is 4 mg/kg once a day for 14 to 21 days, or as decided by your doctor. Your doctor may order blood tests before, during and after treatment.

**Overdose:**

If you think you, or a person you are caring for, have taken too much Pentamidine Isetionate for Injection BP, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

**Missed Dose:**

If you missed a scheduled dose, contact your doctor for instruction.

**What are possible side effects from using Pentamidine Isetionate for Injection BP?**

Like all medicines, Pentamidine Isetionate for Injection BP can cause side effects. If any side effects

occur, most are likely to be minor and temporary. However, some may be serious and need medical attention.
These are not all the possible side effects you may feel when taking Pentamidine Isetionate for Injection BP. If you experience any side effects not listed here, contact your healthcare professional. Please also see the Serious Warnings and Precautions section above.
Common side effects include:

- Local reactions at the site of injection (pain, swelling and accumulation of pus, change in colour or appearance of the skin)
- Low folate blood level
- Low calcium blood (hypocalcemia)
- Low number of red blood cells (anemia)
- Low number of platelets in the blood (thrombocytopenia)
- Abnormal liver blood tests
- Nausea
- Vomiting
- Skin redness (flushing)
- Unpleasant taste
- Rash, itching
- Pain or tenderness at the injection side.

Less common side effects include:

- High level of blood sugar (hyperglycemia)
- High level of blood urea nitrogen and serum creatinine
- High level of potassium in the blood (hyperkalemia)
- High level of albumin in the urine (albuminuria)
- High level of glucose in the urine (glycosuria)
- Red spots on the skin (erythema multiforme)
- Dizziness
- Fainting (or loss of consciousness)
- Hair loss (alopecia)
- Hallucinations
- Blood clot in vein
- Death.

| **Serious side effects and what to do about them** | | | |
|---|---|---|---|
| **Symptom / effect** | **Talk to your healthcare professional** | | **Stop taking drug and get immediate medical help** |
| | **Only if severe** | **In all cases** | |
| **VERY COMMON** | | | |
| Kidney problems, less urine, change in the colour of your urine | | | √ |
| Low blood pressure | | | √ |
| **COMMON** | | | |
| Low blood sugar levels | | | √ |

| | | | |
|---|---|---|---|
| Low white blood cells count (less than 1,000/mm3), low blood platelets count (less than 20,000/mm3) | | | √ |
| Low calcium levels in the blood serum | | | √ |
| **RARE** | | | |
| Acute inflammation of the pancreas | | | √ |
| Irregular heart rate or rhythm (a condition called QT interval prolongation and/or torsade de pointes) | | | √ |

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

**Reporting Side Effects**

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how toreport online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

**Storage:**

The healthcare professional will store the product according to the professional product information.

**If you want more information about Pentamidine Isetionate for Injection BP:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; Marcan Pharmaceutical Inc.'s website www.marcanpharma.com or by calling 1-855-627-2261.

This leaflet was prepared by Marcan Pharmaceuticals Inc.

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