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2 45847D/Revised: December 2010



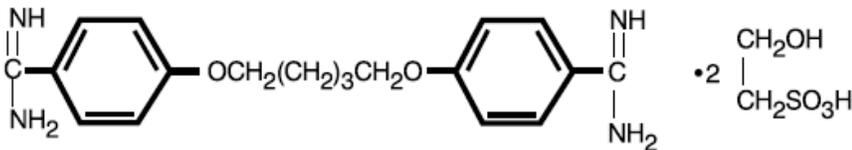
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4 **For Oral Inhalation Only**

5 **DESCRIPTION:**

6 NebuPent (pentamidine isethionate), an antifungal agent, is a nonpyrogenic
7 lyophilized product. After reconstitution with Sterile Water for Injection, USP,
8 NebuPent is administered by inhalation via the Respigard[®] II nebulizer [Marquest,
9 Englewood, CO] (see **DOSAGE AND ADMINISTRATION**).

10 Pentamidine isethionate, 4,4'-[1,5-pentane-diylbis(oxy)]bis-
11 benzenecarboximidamid, is a white crystalline powder soluble in water and glycerin
12 and insoluble in ether, acetone, and chloroform.



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14 **C₁₉H₂₄N₄O₂•2C₂H₆O₄S**

592.68

15 Each vial contains 300 mg pentamidine isethionate.

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1 **CLINICAL PHARMACOLOGY:**

2 *Microbiology*

3 **Mechanism of Action**

4 Studies suggest that the pentamidine isethionate interferes with microbial nuclear
5 metabolism by inhibition of DNA, RNA, phospholipid and protein synthesis.
6 However, the mode of action is not fully understood.

7 **Activity *in vitro* and *in vivo***

8 Pentamidine isethionate, an aromatic diamidine, is known to have activity against
9 *Pneumocystis jiroveci*.

10 **Pharmacokinetics**

11 In 5 AIDS patients with suspected *Pneumocystis jiroveci* pneumonia (PJP), the mean
12 concentrations of pentamidine determined 18 to 24 hours after inhalation therapy
13 were 23.2 ng/mL (range 5.1 to 43.0 ng/mL) in bronchoalveolar lavage fluid and 705
14 ng/mL (range 140 to 1336 ng/mL) in sediment after administration of a 300 mg
15 single dose via the Respirgard[®] II nebulizer. In 3 AIDS patients with suspected PJP,
16 the mean concentrations of pentamidine determined 18 to 24 hours after a 4 mg/kg
17 intravenous dose were 2.6 ng/mL (range 1.5 to 4.0 ng/mL) in bronchoalveolar
18 lavage fluid and 9.3 ng/mL (range 6.9 to 12.8 ng/mL) in sediment. In the patients
19 who received aerosolized pentamidine, the peak plasma levels of pentamidine were
20 at or below the lower limit of detection of the assay (2.3 ng/mL).

21 Following a single 2-hour intravenous infusion of 4 mg/kg of pentamidine
22 isethionate to 6 AIDS patients, the mean plasma C_{max}, T_{1/2} and clearance were
23 612 ± 371 ng/mL, 6.4 ± 1.3 hr and 248 ± 91 L/hr respectively. In another study of

1 aerosolized pentamidine in 13 AIDS patients with acute PJP who received 4
2 mg/kg/day administered via the Ultra Vent[®] jet nebulizer, peak plasma levels of
3 pentamidine averaged 18.8 ± 11.9 ng/mL after the first dose. During the next 14
4 days of repeated dosing, the highest observed C_{max} averaged 20.5 ± 21.2 ng/mL. In
5 a third study, following daily administration of 600 mg of inhaled pentamidine
6 isethionate with the Respigard[®] II nebulizer for 21 days in 11 patients with acute
7 PJP, mean plasma levels measured shortly after the 21st dose averaged
8 11.8 ± 10.0 ng/mL. Plasma concentrations after aerosol administration are
9 substantially lower than those observed after a comparable intravenous dose. The
10 extent of pentamidine accumulation and distribution following chronic inhalation
11 therapy are not known.

12 In rats, intravenous administration of a 5 mg/kg dose resulted in
13 concentrations of pentamidine in the liver and kidney that were 87.5 and 62.3-fold
14 higher, respectively, than levels in those organs following 5 mg/kg administered as
15 an aerosol.

16 No pharmacokinetic data are available following aerosol administration of
17 pentamidine in humans with impaired hepatic or renal function.

18 **INDICATIONS AND USAGE:**

19 NebuPent is indicated for the prevention of *Pneumocystis jiroveci* pneumonia (PJP)
20 in high-risk, HIV-infected patients defined by one or both of the following criteria:

- 21 i. a history of one or more episodes of PJP
- 22 ii. a peripheral CD4⁺ (T4 helper/inducer) lymphocyte count less than or equal to
23 200/mm³.

1 These indications are based on the results of an 18-month randomized, dose-
2 response trial in high risk HIV-infected patients and on existing epidemiological
3 data from natural history studies.

4 The patient population of the controlled trial consisted of 408 patients, 237
5 of whom had a history of one or more episodes of PJP. The remaining patients
6 without a history of PJP included 55 patients with Kaposi's sarcoma and 116
7 patients with other AIDS diagnoses, ARC or asymptomatic HIV infection. Patients
8 were randomly assigned to receive NebuPent via the Respigard[®] II nebulizer at one
9 of the following three doses: 30 mg every two weeks (n=135), 150 mg every two
10 weeks (n=134) or 300 mg every four weeks (n=139). The results of the trial
11 demonstrated a significant protective effect (p<0.01) against PJP with the 300 mg
12 every four week dosage regimen compared to the 30 mg every two week dosage
13 regimen. The 300 mg dose regimen reduced the risk of developing PJP by 50 to 70%
14 compared to the 30 mg regimen. A total of 293 patients (72% of all patients) also
15 received zidovudine at sometime during the trial. The analysis of the data
16 demonstrated the efficacy of the 300 mg dose even after adjusting for the effect of
17 zidovudine.

18 The results of the trial further demonstrate that the dose and frequency of
19 dosing are important to the efficacy of NebuPent prophylaxis in that multiple
20 analyses consistently demonstrated a trend toward greater efficacy with 300 mg
21 every four weeks as compared to 150 mg every two weeks.

22 No dose-response was observed for reduction in overall mortality; however,
23 mortality from PJP was low in all three dosage groups.

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1 **CONTRAINDICATIONS:**

2 NebuPent is contraindicated in patients with a history of an anaphylactic reaction to
3 inhaled or parenteral pentamidine isethionate.

4 **WARNINGS:**

5 The potential for development of acute PJP still exists in patients receiving
6 NebuPent prophylaxis. Therefore, any patient with symptoms suggestive of the
7 presence of a pulmonary infection, including but not limited to dyspnea, fever or
8 cough, should receive a thorough medical evaluation and appropriate diagnostic
9 tests for possible acute PJP as well as for other opportunistic and nonopportunistic
10 pathogens. The use of NebuPent may alter the clinical and radiographic features of
11 PJP and could result in an atypical presentation, including but not limited to mild
12 disease or focal infection.

13 Prior to initiating NebuPent prophylaxis, symptomatic patients should be
14 evaluated appropriately to exclude the presence of PJP. The recommended dose of
15 NebuPent for the prevention of PJP is insufficient to treat acute PJP.

16 **PRECAUTIONS:**

17 **IMPORTANT: DO NOT MIX THE NEBUPENT SOLUTION WITH ANY**
18 **OTHER DRUGS. DO NOT USE THE RESPIRGARD® II NEBULIZER TO**
19 **ADMINISTER A BRONCHODILATOR.** (See **DOSAGE AND**
20 **ADMINISTRATION**).

21 *Pulmonary*

22 Inhalation of NebuPent may induce bronchospasm or cough. This has been noted
23 particularly in some patients who have a history of smoking or asthma. In clinical

1 trials, cough and bronchospasm were the most frequently reported adverse
2 experiences associated with NebuPent administration (38% and 15%, respectively of
3 patients receiving the 300 mg dose); however less than 1% of the doses were
4 interrupted or terminated due to these effects. For the majority of patients, cough
5 and bronchospasm were controlled by administration of an aerosolized
6 bronchodilator (only 1% of patients withdrew from the study due to treatment-
7 associated cough or bronchospasm). In patients who experience bronchospasm or
8 cough, administration of an inhaled bronchodilator prior to giving each NebuPent
9 dose may minimize recurrence of the symptoms.

10 ***General***

11 The extent and consequence of pentamidine accumulation following chronic
12 inhalation therapy are not known. As a result, patients receiving NebuPent should be
13 closely monitored for the development of serious adverse reactions that have
14 occurred in patients receiving parenteral pentamidine, including hypotension,
15 hypoglycemia, hyperglycemia, hypocalcemia, anemia, thrombocytopenia,
16 leukopenia, hepatic or renal dysfunction, ventricular tachycardia, pancreatitis,
17 Stevens-Johnson syndrome, hyperkalemia and abnormal ST segment of ECG.

18 Extrapulmonary infection with *P. jiroveci* has been reported infrequently.
19 Most, but not all, of the cases have been reported in patients who have a history of
20 PJP. The presence of extrapulmonary pneumocystosis should be considered when
21 evaluating patients with unexplained signs and symptoms.

22 Cases of acute pancreatitis have been reported in patients receiving
23 aerosolized pentamidine. NebuPent should be discontinued if signs or symptoms of
24 acute pancreatitis develop.

1 ***Drug Interactions***

2 While specific studies on drug interactions with NebuPent have not been conducted,
3 the majority of patients in clinical trials received concomitant medications, including
4 zidovudine, with no reported interactions. Because the nephrotoxic effects may be
5 additive, the concomitant or sequential use of NebuPent and other nephrotoxic drugs
6 such as aminoglycosides, amphotericin B, cisplatin, foscarnet, or vancomycin
7 should be closely monitored and avoided, if possible.

8 ***Carcinogenesis, Mutagenesis and Impairment of Fertility***

9 Literature reports indicate that pentamidine was not mutagenic in the Ames bacterial
10 (*S. typhimurium*) test and did not induce an increase in chromosomal aberrations in
11 Chinese Hamster Ovary (CHO) cell or in human lymphocytes *in vitro*.

12 No studies have been conducted to determine effects of pentamidine
13 isethionate on carcinogenicity or fertility.

14 ***Pregnancy–Pregnancy Category C***

15 There are no adequate and well controlled studies of NebuPent in pregnant women.
16 A literature report indicated that intravenously administered pentamidine in pregnant
17 rats at 4 mg/kg/day was embryolethal; teratogenicity was not observed in this study.
18 It is unknown whether pentamidine administered via the aerosolized route crosses
19 the placenta at clinically significant concentrations. It is not known whether
20 NebuPent can cause fetal harm when administered to a pregnant woman. NebuPent
21 should be given to a pregnant woman only if clearly needed.

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1 ***Nursing Mothers***

2 It is not known whether NebuPent is excreted in human milk. Because of the
3 potential for serious adverse reactions in nursing infants from NebuPent, a decision
4 should be made whether to discontinue nursing or to discontinue the drug, taking
5 into account the importance of the drug to the mother. Because many drugs are
6 excreted in human milk, NebuPent should not be given to a nursing mother unless
7 the potential benefits are judged to outweigh the unknown risks.

8 ***Pediatric Use***

9 The safety and effectiveness of NebuPent in pediatric patients (birth to 16 years of
10 age) have not been established.

11 **ADVERSE REACTIONS:**

12 The most frequently reported unsolicited adverse events (1 to 5%) in clinical trials,
13 regardless of their relation to NebuPent therapy were as follows (n=931):

14 *Body as a Whole:* Night sweats.

15 *Gastrointestinal:* Diarrhea and nausea.

16 *Hematologic:* Anemia.

17 *Infection:* Bronchitis, non-specific herpes, herpes zoster, non-specific influenza,
18 oral Candida, pharyngitis, sinusitis, and upper respiratory tract.

19 *Nervous System:* Headache.

20 *Respiratory System:* Chest pain, cough, and wheezing.

21 *Special Senses:* Bad taste.

22 Adverse events of less than 1% incidence were as follows (No causal relationship to
23 treatment has been established for these adverse events):

- 1 *Body as a Whole:* Allergic reaction, non-specific allergy, body odor, facial edema,
2 fever, leg edema, lethargy, low body temperature, and temperature abnormality.
- 3 *Cardiovascular:* Cerebrovascular accident, hypotension, hypertension, palpitations,
4 poor circulation, syncope, tachycardia, vasodilatation and vasculitis.
- 5 *Gastrointestinal:* Abdominal cramps, abdominal pain, constipation, dry mouth,
6 dyspepsia, gastritis, gastric ulcer, gingivitis, hiatal hernia, hypersalivation, oral
7 ulcer/abscess, splenomegaly, and vomiting.
- 8 *Hematological:* Eosinophilia, neutropenia, non-specific cytopenia, pancytopenia,
9 and thrombocytopenia.
- 10 *Hepatic:* Hepatitis, hepatomegaly, and hepatic dysfunction.
- 11 *Infection:* Bacterial pneumonia, central venous line related sepsis, cryptococcal
12 meningitis, cytomegalovirus (CMV) colitis, CMV retinitis, esophageal Candida,
13 histoplasmosis, Kaposi's sarcoma, non-specific mycoplasma, oral herpes, non-
14 specific otitis, non-specific pharyngitis, pharyngeal herpes, non-specific serious
15 infection, tonsillitis, tuberculosis, and viral encephalitis.
- 16 *Metabolic:* Hyperglycemia, hypoglycemia, and hypocalcemia.
- 17 *Musculoskeletal:* Arthralgia, gout, and myalgia.
- 18 *Neurological:* Anxiety, confusion, depression, drowsiness, emotional lability,
19 hallucination, hypesthesia, insomnia, memory loss, neuralgia, neuropathy, non-
20 specific neuropathy, nervousness, paranoia, paresthesia, peripheral neuropathy,
21 seizure, tremors, unsteady gait, and vertigo.
- 22 *Reproductive:* Miscarriage.

1 *Respiratory system:* Asthma, bronchitis, bronchospasm, chest congestion, chest
2 tightness, coryza, cyanosis, eosinophilic or interstitial pneumonitis, gagging,
3 hemoptysis, hyperventilation, laryngitis, laryngospasm, non-specific lung
4 disorder, nasal congestion, pleuritis, pneumothorax, rales, rhinitis, shortness of
5 breath, non-specific sputum, and tachypnea.

6 *Skin:* Desquamation, dry and breaking hair, dry skin, erythema, non-specific
7 dermatitis, pruritus, rash, and urticaria.

8 *Special senses:* Blepharitis, blurred vision, conjunctivitis, contact lens discomfort,
9 eye pain or discomfort, hemianopsia, loss of taste, non-specific odor, and smell.

10 *Urogenital:* Flank pain, incontinence, nephritis, renal failure, and renal pain.

11 In a clinical trial where some adverse events were solicited by investigators, the
12 incidences were as follows:

13 Cough (62.7%)
14 Decreased appetite (50.0%)
15 Dizziness or light-headedness (45.1%)
16 Fatigue (65.7%)
17 Fever (51.0%)
18 Non-specific serious infection (15.2%)
19 Shortness of breath (48.3%)
20 Wheezing (32.4%)

21 From post-marketing clinical experience with NebuPent the following spontaneous
22 adverse events have been reported: anaphylaxis, colitis, diabetes, dyspnea,
23 esophigitis, hematochezia, increased blood urea nitrogen (BUN) and serum

1 creatinine levels, melena, pancreatitis (see **WARNINGS**), syndrome of
2 inappropriate antidiuretic hormone (SIADH), and torsade de pointes.

3 **OVERDOSAGE:**

4 Overdosage has not been reported with NebuPent. The symptoms and signs of
5 overdosage are not known.

6 A serious overdosage, to the point of producing systemic drug levels similar
7 to those following parenteral administration, would have the potential of producing
8 similar types of serious systemic toxicity. (See **PRECAUTIONS**).

9 Available clinical pharmacology data (see **CLINICAL**
10 **PHARMACOLOGY**) suggest that a dose up to 40 times the recommended
11 NebuPent dosage would be required to produce systemic levels similar to a single
12 4 mg/kg intravenous dose.

13 **DOSAGE AND ADMINISTRATION:**

14 **IMPORTANT: NEBUPENT MUST BE DISSOLVED ONLY IN STERILE**
15 **WATER FOR INJECTION, USP. DO NOT USE SALINE SOLUTION FOR**
16 **RECONSTITUTION BECAUSE THE DRUG WILL PRECIPITATE. DO**
17 **NOT MIX THE NEBUPENT SOLUTION WITH ANY OTHER DRUGS. DO**
18 **NOT USE THE RESPIRGARD® II NEBULIZER TO ADMINISTER A**
19 **BRONCHODILATOR.**

20 ***Reconstitution***

21 The contents of one vial (300 mg) must be dissolved in 6 mL Sterile Water for
22 Injection, USP. Place the entire reconstituted contents of the vial into the
23 Respigard® II nebulizer reservoir for administration.

1 ***Dosage***

2 The recommended adult dosage of NebuPent for the prevention of *Pneumocystis*
3 *jiroveci* pneumonia is 300 mg once every four weeks administered via the
4 Respirgard® II nebulizer.

5 The dose should be delivered until the nebulizer chamber is empty
6 (approximately 30 to 45 minutes). The flow rate should be 5 to 7 liters per minute
7 from a 40 to 50 pounds per square inch (PSI) air or oxygen source. Alternatively, a
8 40 to 50 PSI air compressor can be used with flow limited by setting the flowmeter
9 at 5 to 7 liters per minute or by setting the pressure at 22 to 25 PSI. Low pressure
10 (less than 20 PSI) compressors should not be used.

11 ***Stability***

12 Freshly prepared solutions for aerosol use are recommended. After reconstitution
13 with sterile water, the NebuPent solution is stable for 48 hours in the original vial at
14 room temperature if protected from light.

15 **HOW SUPPLIED:**

16 Product	NDC	
17 No.	No.	
18 87715	63323-877-15	NebuPent® (pentamidine isethionate) 300 mg
19		lyophilized product in single dose vials, indivi-
20		dually packaged.

21 Store dry product at 20° to 25°C (68° to 77°F) [see USP Controlled Room
22 Temperature].

23 Protect the dry product and the reconstituted solution from light.



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