



NDA 19-887/S-014

SUPPLEMENT APPROVAL

APP Pharmaceuticals
Attention: Brent Yurschak
Regulatory Scientist
1501 East Woodfield Road, Suite 300 East
Schaumburg, IL 60173

Dear Mr. Yurschak:

Please refer to your supplemental new drug application dated and received September 3, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for NebuPent[®] (pentamidine isethionate).

We also acknowledge receipt of your amendment dated December 14, 2010.

This supplemental new drug application provides for the following revisions to the labeling for NebuPent (additions are noted with underline and deletions are noted with ~~striketrough~~):

1. The **DESCRIPTION** section, is revised as follows:

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

2. The **CLINICAL PHARMACOLOGY/Microbiology** subsection, is revised as follows:

Microbiology
Mechanism of Action

~~Pentamidine isethionate, an aromatic diamidine, is known to have activity against Pneumocystis carinii. The mode of action is not fully understood. Studies suggest indicate~~ that the pentamidine isethionate interferes with microbial nuclear metabolism by inhibition of DNA, RNA, phospholipid and protein synthesis. However, the mode of action is not fully understood.

Activity in vitro and in vivo

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

3. The **PRECAUTIONS/Carcinogenesis, Mutagenesis and Impairment of Fertility** subsection is revised as follows:

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

No studies have been conducted to evaluate the potential ~~determine effects of~~ pentamidine isethionate as a carcinogen or mutagen or to determine its effects on carcinogenicity or fertility.

4. The **PRECAUTIONS/Pregnancy-Pregnancy Category C** is revised follows:

Animal reproduction studies have not been conducted with NebuPent. There are no adequate and well controlled studies of NebuPent in pregnant women. A literature report indicated that intravenously administered pentamidine in pregnant rats at 4 mg/kg/day was embryolethal; teratogenicity was not observed in this study. It is unknown whether pentamidine administered via the aerosolized route crosses the placenta at clinically significant concentrations. It is not known whether NebuPent can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. NebuPent should be given to a pregnant woman only if clearly needed. NebuPent should not be given to a pregnant woman unless the potential benefits are judged to outweigh the unknown risks.

5. Throughout the package insert the text “*Pneumocystis carinii* (PCP)” is replaced with the terminology “*Pneumocystis jiroveci* (PJP)”.

We have completed our review of this supplemental application, as amended. This supplement is approved, effective on the date of this letter, for use as recommended in the package insert attached to this letter, which is identical to the package insert submitted on December 14, 2010.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling (text for the package insert) and include the labeling changes proposed in any pending “Changes Being Effected” (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including pending “Changes Being Effected” (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format that includes the changes approved in this supplemental application.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Ms. June Germain, Regulatory Health Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, MD
Director
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: Package insert

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RENATA ALBRECHT

02/08/2011

Approval Letter