CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-789

MEDICAL REVIEW

MEDICAL OFFICER'S REVIEW

NDA 50-789: Tobramycin for Injection, USP
Applicant: American Pharmaceutical Partners, Inc.
Melrose Park, IL 60160-1002

Medical Reviewer: Alma C. Davidson, M.D.
Medical Officer
DAIDP, HFD-520

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A. Executive Summary

The current drug application for IV Tobramycin is a product by American Pharmaceutical Partners, Incorporated (APP). The reference-listed drug is Nebcin®(tobramycin), marketed by Eli Lilly and Company. The APP product, the subject of this review, is a sterile lyophilized powder for reconstitution intended solely for administration by injection and has the same active ingredient in the same concentration as the Lilly Nebcin® product. The main difference between APP tobramycin and Nebcin® is the use of [redacted] as a processing aid. APP claims that a [redacted] of not more than 1.1% w/w remains in the final APP product. Nebcin®does not use [redacted] during the manufacturing process.

The medical officer recommends approval of NDA 50-789 for APP's Tobramycin for Injection, USP. This recommendation is based on the following: FDA's findings of safety and efficacy of tobramycin (Nebcin®); APP's data which demonstrate that a similar amount of the active ingredient, tobramycin, is provided in their product; and safety for the [redacted] in the APP product based on animal toxicology data and published literature of human exposure.

B. Review of NDA 50-789

I. Introduction and Background

Tobramycin belongs to the class of aminoglycoside antibiotics. It is derived from the actinomycete *Streptomyces tenebrarius*. It acts by inhibiting synthesis of protein in bacterial cells. It has been shown to be active against most strains of aerobic gram-positive and aerobic gram-negative microorganisms both in vitro and in clinical infections.

The reference-listed drug (RLD), NEBCIN® (Tobramycin for Injection, USP) and its labeling were approved on June 11, 1975. It is indicated for the treatment of serious bacterial infections caused by susceptible strains of designated microorganisms including septicemia, lower respiratory tract infections, CNS infections (meningitis), intra-abdominal infections including peritonitis, skin, bone and skin structure infections, and complicated and recurrent urinary tract infections.

The applicant, APP, submitted the New Drug Application 50-789 for Tobramycin for Injection, USP on December 20, 2002 as a 505(b)(2) application. The APP Tobramycin for Injection is essentially identical to the approved RLD product (Nebcin®) except for the small amount of [redacted]

The applicant originally filed a 505(j) Abbreviated New Drug application (ANDA), 65-090 for Tobramycin for Injection, USP on April 17, 2001 with the Office of Generic Drugs. However, the applicant's request for a waiver of *in vivo* bioequivalence study requirements for their tobramycin was denied. The test product's composition was considered qualitatively different from that of the RLD because it uses [redacted] not used in the RLD. The RLD uses sulfuric acid and sodium hydroxide, as pH adjusters. The test product uses no pH adjusters. In addition, according to the Division of Bioequivalence, [redacted] and sodium hydroxide are not exception excipients. They do not fall under any of the three categories (buffers, antioxidants and preservatives) of excipients permitted for substitution under 21 CFR 314.94 (a)(9) (iii). Subsequently, a letter was issued from the Office of Generic Drugs indicating that the ANDA was not approvable on the basis of these differences from the RLD. The Office of Generics recommended that the product be reformulated to delete use of [redacted] or any other solvent unless it is removed during processing or it can be demonstrated to comply with 21 CFR 314.94(a)(9) (iii).

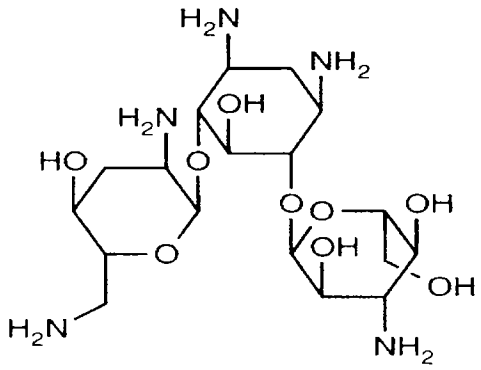
The applicant contacted the Division of Anti-Infective Drug Products about filing an NDA for this drug product. The Division received a formal request for a Type B meeting on November 26, 2001. In this meeting, held on Jan. 16, 2002, the Division agreed that Tobramycin for Injection, USP would be a suitable product for a 505(b)(2) NDA. This product would be considered an equivalent to the marketed IV formulation of tobramycin with the exception of Chemistry, Manufacturing, and Controls (CMC) data. Recommendations for the content and format of the CMC section of the application were

discussed at the meeting. No further clinical studies were required to support this new drug application.

Drug Established Name, Drug Class, Applicant's Proposed Indication(s), Dose, Regimens

Chemical Name: Tobramycin sulfate is *O*-3-amino-3-deoxy-α-D-glucopyranosyl-(1→4)-*O*-[2,6-diamino-2,3,6- trideoxy-α-D-*ribo*-hexopyranosyl-(1→6)]-2-deoxy-L-streptamine, sulfate (2:5)(salt).

Chemical structure:



Molecular formula: $(C_{18}H_{37}N_5O_9)_2 \cdot 5H_2SO_4$ **Molecular weight**: 1425.45

Drug class: Aminoglycoside antibiotic

Applicant's Proposed Indications: (Note: The indication statement below is from the package insert. This statement is identical to the Nebcin® label under the INDICATIONS AND USAGE section with the exception of the drug trade name.)

Tobramycin for Injection, USP is indicated for the treatment of serious bacterial infections caused by susceptible strains of the designated microorganisms in the diseases listed below:

Septicemia in the pediatric patient and adult caused by *P. aeruginosa, E. coli,* and *Klebsiella* spp
Lower respiratory tract infections caused by *P. aeruginosa, Klebsiella* spp, *Enterobacter* spp, *Serratia* spp, *E.coli,* and *S. aureus* (penicillinase- and non-penicillinase-producing strains).
Serious central-nervous-system infections (meningitis) caused by susceptible organisms.
Intra-abdominal infections, including peritonitis, caused by *E. coli, Klebsiella* spp, and *Enterobacter* spp.
Skin, bone, and skin structure infections caused by *P. aeruginosa, Proteus* spp, *E. coli, Klebsiella* spp, *Enterobacter* spp, and *S. aureus.*
Complicated and recurrent urinary tract infections caused by *P. aeruginosa, Proteus* spp, (indole-positive and indole-negative), *E. coli, Klebsiella* spp, *Enterobacter* spp, *Serratia* spp, *S. aureus, Providencia* spp, and *Citrobacter* spp.

Drug Formulation: 1.2 g of tobramycin sulfate, USP in a 50 mL vial, intended for reconstitution with 30 mL sterile water for injection, USP. This pharmacy bulk package would be used by hospital pharmacists for preparation of multiple doses of tobramycin.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics.

- **Chemistry**

The chemist, Dr. S. Pagay, reviewed the chemistry, manufacturing and controls data submitted by APP. Tobramycin for Injection, USP [redacted] The proposed acceptance criteria for [redacted] is 1.1% based on the applicant's manufacturing process as a [redacted] in the final drug product. The reader is referred to the chemistry review for details of the Chemistry, Manufacturing, and Controls.

- **Animal Pharmacology and Toxicology**

The pharmacology/toxicology reviewer, Dr. Amy Ellis, recommends approval of this NDA.

According to her review, the company submitted a toxicology report on [redacted] in this application. The report is a thorough discussion of the current information on the potential toxicities of [redacted]. The report included acute and repeat dose studies using different routes of administration (oral, IP, IV, and inhalation), and rodent carcinogenicity studies via the oral route. The acute dose studies, the effects of [redacted] included induction of anesthesia, narcosis and depression. In repeat dose studies, the target organs of toxicity included the kidney, ureter and urinary bladder. All these effects occur at doses higher (by orders of magnitude) than would be achieved in humans receiving tobramycin that had a 1.1% [redacted] The pharmacology reviewer agrees with the applicant that there are no toxicity or safety concerns regarding the [redacted] will be present in the final product if the limit (1.1% w/w) set in the chemistry specifications is followed. (Note: Please see the review of Dr. A. Ellis for details.)

Regarding the labeling of this product, the pharmacology/toxicology reviewer proposes that APP-Tobramycin for Injection, USP label be revised to be consistent with the current CDER practice in drug labeling.

- **Microbiology**

  According to the clinical microbiologist, Mr. Harold Silver, the **Microbiology** subsection and the **References** section for the Tobramycin for Injection, USP are identical to RLD (NEBCIN®) labeling. The microbiology reviewer recommended minor labeling revisions to the Applicant's proposed label for Tobramycin Injection, USP under the **Microbiology** subsection. In addition, the microbiologist recommended updating the **References** section.

- **Biopharmaceutics**

  The biopharmaceutics reviewer, Dr. Charles Bonapace, has found this application to be acceptable from the clinical pharmacology perspective. According to his review, the Office of Clinical Pharmacology/Biopharmaceutics believes that substantial evidence exists to support the in vivo bioavailability or bioequivalence of APP Tobramycin for Injection, USP and Nebcin® (Tobramycin for Injection, USP). (Note: Please see the review of Dr. C. Bonapace, for details.)

III. Human Pharmacokinetics and Pharmacodynamics

There are no pharmacokinetics and pharmacodynamics data provided by the applicant. The APP Tobramycin for Injection, USP is designed to deliver the same amount of active ingredient at the same concentration and the same pH as the RLD.

IV. Clinical Review

No clinical studies were required for this application. The Office of Clinical Pharmacology and Biopharmaceutics determined that substantial evidence exists to support the in vivo bioequivalence of Tobramycin for Injection, USP and the RLD, Nebcin®. Both products provide the same active ingredient, tobramycin, in a formulation for intravenous administration. Therefore, the recommendation for approval of this product is based on the FDA's findings of safety and efficacy for Nebcin®, together with animal toxicology data and published literature of human exposure to [redacted]. The labeling for this product will be similar to Nebcin's package insert, with differences in the chemistry and manufacturing of the APP product.

The difference between the APP Tobramycin and Nebcin is the use of [redacted]. The proposed acceptance criteria for [redacted] is 1.1% w/w was based on the applicant's manufacturing process as a [redacted] in the final drug product. This means that the 1.2 gm pharmacy bulk vial would contain no more than [redacted] person receiving

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✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

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