CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-789

PHARMACOLOGY REVIEW

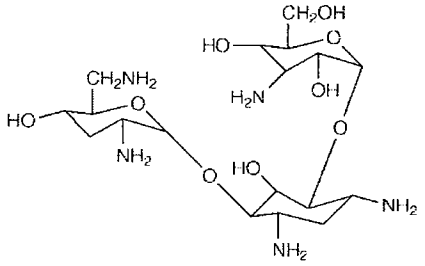
PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 50,789
Review number: 1
Sequence number/date/type of submission: 000; 12/31/02; original NDA 505(b)(2) submission
Information to sponsor: Yes (x) No ( )
Sponsor and/or agent: American Pharmaceutical Partners, Inc.; Melrose Park, IL
Manufacturer for drug substance: [redacted]

Reviewer name: Amy L. Ellis
Division name: Anti-Infective Drug Products
HFD #: 520
Review completion date: 2/10/03

Drug:

Trade name: none
Generic name (list alphabetically): Tobramycin for Injection, USP
Code name: none
Chemical name: O-3-amino-3-deoxy-α-D-glycopyranosyl-(1→4)-O-[2,6-diamino-2,3,6-trideoxy-α-D-*ribo*-hexopyranosyl-(1→6)]-2-deoxy-L-streptamine sulfate
Molecular formula/molecular weight: $(C_{18}H_{37}N_5O_9)_2 \cdot 5H_2SO_4$/1425.45
Structure:



Relevant INDs/NDAs/DMFs: PIND 60,234; NDA 50,753 (TOBI); NDAs 50,477 and 50,519 (Nebcin®)

Drug class: Aminoglycoside antibiotic

Indications: Treatment of serious bacterial infections (caused by susceptible strains of microorganisms) including septicemia, lower respiratory tract infections, CNS infections including meningitis, intra-abdominal infections including peritonitis, skin, bone and skin structure infections, complicated and recurrent urinary tract infections.

Clinical formulation: 1.2 g of tobramycin sulfate, USP in a 50 ml vial, intended for reconstitution with 30 ml sterile water for injection, USP.

Route of administration: Intravenous

Proposed use: see Indications above

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

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On Original

Appears This Way
On Original

Executive Summary

I. Recommendations

A. Recommendation on Approvability: The pharmacologist has no objection to the approval of this NDA.

B. Recommendation for Nonclinical Studies: None.

C. Recommendations on Labeling: The sponsor is proposing to use the same wording as the Nebcin® label. This is not acceptable because the Nebcin® label is relatively old and no longer consistent with current Center practice. A section describing *Carcinogenesis, Mutagenesis, Impairment of Fertility* needs to be added and the *Pregnancy* section should be expanded. These can be based on the TOBI® label.

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings: Tobramycin for Injection is essentially identical to the approved drug product Nebcin®. No new nonclinical studies were necessary for the current product. In toxic amounts, aminoglycoside antibiotics, including tobramycin, are known to damage the kidneys, cochlear hair cells (which can lead to hearing loss and/or vestibular toxicity), and 8th cranial nerve. The plasma concentration of this class of drugs is monitored during therapy due to these toxicities. Tobramycin for Injection contains a small amount of the [redacted] The sponsor has included a toxicology report on this substance and the pharmacology reviewer agrees with the sponsor that there are no toxicity or safety concerns regarding the [redacted] that will be present in the product if the limit (1.1%, w/w) set in the chemistry specifications is followed.

B. Pharmacologic Activity: Tobramycin is bactericidal and inhibits protein synthesis in bacterial cells.

C. Nonclinical Safety Issues Relevant to Clinical Use: Nothing new; renal, cochlear, and neurotoxicities have been observed in both laboratory animals and humans. Appropriate warnings, based on those found in the Nebcin® label, have been included in the label for this product.

III. Administrative

A. Reviewer signature: _____

B. Supervisor signature: Concurrence (TL)- _____

Concurrence (Deputy Div Dir)- _____

Non-Concurrence - _____
(see memo attached)

C. cc: list:

PM/Peat
MO/Davidson
Chem/Pagay
Micro/Silver
Stat/Lin
Biopharm/Bonapace

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PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY:

Tobramycin is bactericidal and inhibits protein synthesis in bacterial cells.

II. SAFETY PHARMACOLOGY:

No safety pharmacology studies were necessary.

III. PHARMACOKINETICS/TOXICOKINETICS:

Tobramycin is given intravenously or intramuscularly because it is poorly absorbed from the GI tract. It does not undergo significant metabolism and is excreted almost entirely by the kidney.

IV. GENERAL TOXICOLOGY:

Tobramycin for Injection is essentially identical to the approved drug product Nebcin®. No new nonclinical studies were necessary for the current product. In toxic amounts, aminoglycoside antibiotics, including tobramycin, are known to damage the kidneys, cochlear hair cells (which can lead to hearing loss and/or vestibular toxicity), and 8th cranial nerve.

Tobramycin for Injection contains a small amount of the [redacted]. The sponsor has included a toxicology report on this substance and the pharmacology reviewer agrees with the sponsor that there are no toxicity or safety concerns regarding the [redacted] that will be present in the product if the limit (1.1%, w/w) set in the chemistry specifications is followed. A more extensive discussion of the [redacted] issue may be found in the review of PIND 60,234 and in the Conclusions/Recommendations section below.

V. GENETIC TOXICOLOGY:

According to the label for TOBI® (tobramycin for inhalation), the Ames bacterial reversion test failed to show a significant increase in revertants with or without metabolic activation in all strains. Tobramycin was negative in the mouse lymphoma forward mutation assay, did not induce chromosomal aberrations in Chinese hamster ovary cells, and was negative in an *in vivo* mouse micronucleus test. These data will be included in the label for Tobramycin for Injection as permitted under 505 (b)(2).

VI. CARCINOGENICITY:

A rat inhalation carcinogenicity study performed with TOBI® showed no evidence of treatment-related neoplasms. Although the respiratory tract receives the most exposure when an inhalational route of administration is used, serum concentrations measured in the rats following dosing demonstrated that systemic exposure to tobramycin occurred in this study. This information has not yet been included in the TOBI® label, however, so it may not be possible to

include it in the label for Tobramycin for Injection. If the TOBI® label is updated before approval of the current NDA, results of this study should be included in the label of Tobramycin for Injection.

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

Reproduction toxicity studies were conducted by Lilly to support the Nebcin® NDA. The reports of these studies were shared with the sponsor of the TOBI® NDA and included in the TOBI® label, although the information is not in the Nebcin® label. Both Nebcin® and TOBI® have been assigned Pregnancy Category D based upon human experience with aminoglycosides. Tobramycin for Injection will also receive this designation.

As stated in the TOBI® label, subcutaneous administration of up to 100 mg/kg of tobramycin did not affect mating behavior or cause impairment of fertility in male or female rats. Subcutaneous administration of tobramycin at doses of 100 or 20 mg/kg/day during organogenesis was not teratogenic in rats or rabbits, respectively. Doses of tobramycin ≥40 mg/kg/day were severely maternally toxic to rabbits and precluded the evaluation of teratogenicity. Ototoxicity was not evaluated in offspring during nonclinical reproduction toxicity studies with tobramycin. Aminoglycosides can cause fetal harm (e.g., congenital deafness) when administered to a pregnant woman.

VIII. SPECIAL TOXICOLOGY STUDIES:

None.

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

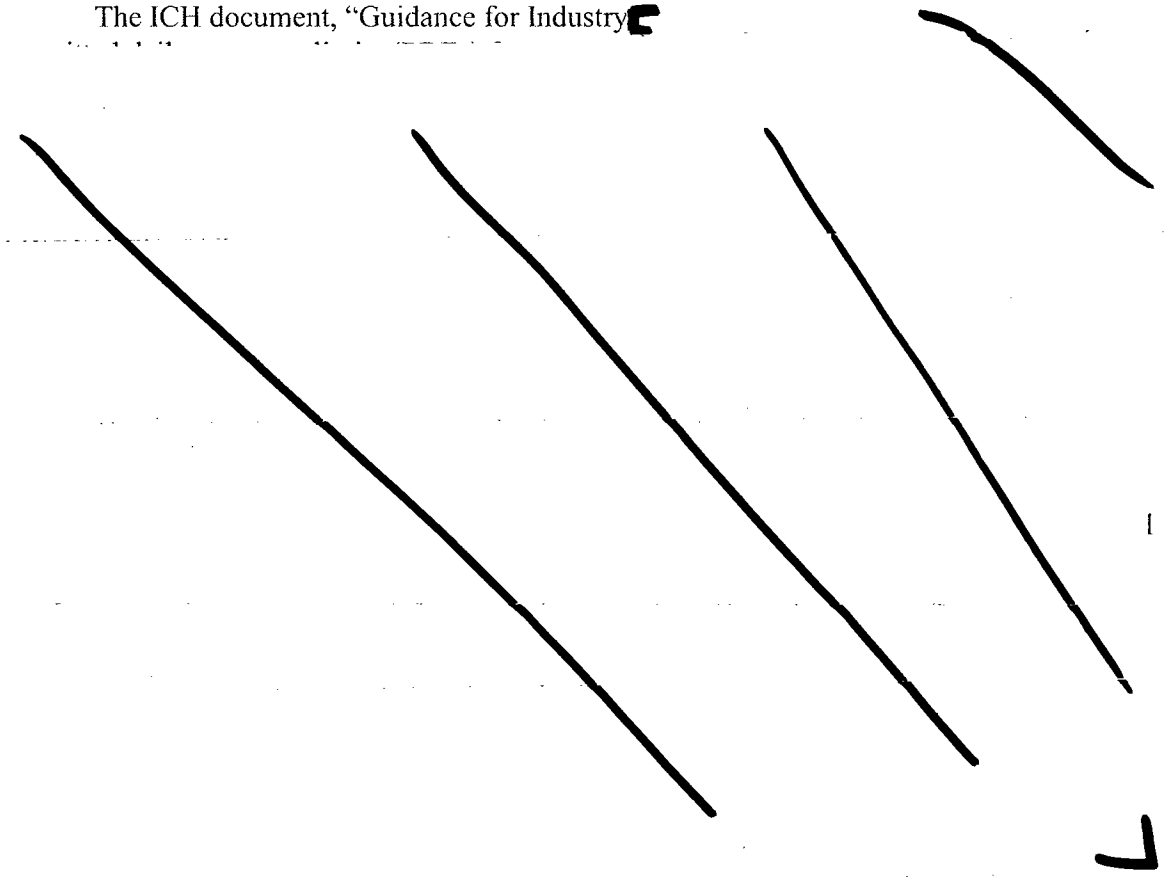
Conclusions:

Tobramycin for Injection would have been considered a generic drug product if it did not contain a small amount of the [redacted] Thus, the Division agreed that no nonclinical or clinical studies would be needed for the NDA submission provided that the sponsor could justify the limit for [redacted] (1.1%, w/w) in their product. In PIND 60,234, the sponsor submitted a toxicology report on [redacted]. This report was also included in the current NDA.

The toxicology report on [redacted] submitted by the sponsor is a thorough discussion of the current information on the potential toxicities of this compound. Original references were used and cited to provide data from a number of animal toxicology and kinetic studies and *in vitro* genotoxicity assays that have been conducted with this compound. These included acute and repeat dose studies using a variety of routes of administration (oral, IP, IV, inhalation) and rodent carcinogenicity studies via the oral route. [redacted] can induce anesthesia as well as narcosis and depression; there is little difference between anesthetic and lethal doses of this solvent. It is about 2-5 times more toxic than ethanol in acute animal studies. Target organs of toxicity identified in repeat dose studies included the kidney, ureter, and urinary bladder (hyperplasia of transitional epithelium of kidney, inflammation, dilatation, thickening, calculi). All of these effects occur at doses orders of magnitude higher than would be achieved in a human receiving tobramycin that had a 1.1% [redacted]. Regardless of metabolic activation, [redacted] was

not genotoxic to *S. typhimurium* (NTP study) or mouse lymphoma cells and it did not induce sister chromatid exchange or chromosome aberrations in CHO cells. A report from the literature showed that [redacted] was weakly mutagenic to *S. typhimurium* strain TA102 in the absence of S-9 with a small increase in mutagenic potency when rat or human S-9 was included. The investigators suggested that this was the result of oxidative damage to DNA, to which this strain of bacteria is especially sensitive.

The ICH document, "Guidance for Industry[redacted]



The author of the sponsor's toxicology report used the NOEL in males from the rat carcinogenicity study to calculate a PDE for [redacted]; the same study and dose that had been chosen by the CDER ICH representative. However, the sponsor's consultant arrived at a PDE of 90 mg by using a factor of 1 instead of 10 for F4. The consultant believed that the kidney tumors observed in the male rats may have been species specific, secondary to accumulation of α-2-microglobulin. The NTP interpreted the findings of the study to show "some evidence of carcinogenicity" to male rats and the CDER ICH representative used this as the basis for choosing 10 for F4.

Despite the disagreement regarding a PDE for[redacted] The 5 mg/kg dose of tobramycin is reserved for severe infections, the usual dose in adults is 3 mg/kg/day. It is noted that the labeled dose for premature infants and neonates is 4 mg/kg/day and for pediatric patients > 1 week old the dose is 6-7.5 mg/kg/day. Patients with severe cystic fibrosis may receive up to 10 mg/kg/day. The exposure to [redacted] following any of these doses will remain below the 9 mg

PDE. It is important to consider that the PDE was calculated based upon data from a chronic study, but tobramycin would rarely be used on a chronic basis in the clinic.

General Toxicology Issues: None, this product is essentially identical to the approved product, Nebcin®.

Recommendations:

The pharmacologist has no objection to the approval of NDA 50,789 for Tobramycin for Injection, USP.

Labeling with basis for findings:

X. APPENDIX/ATTACHMENTS:

Addendum to review: None.

Other relevant materials (Studies not reviewed, appended consults, etc.): Nothing to report.

Any compliance issues: No.

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

/s/

Amy Ellis
5/13/03 08:13:07 AM
PHARMACOLOGIST
The pharmacologist has no objection to the approval of this NDA.
Bob- You signed the paper copy of this review on 5/6/03.

Robert Osterberg
5/14/03 07:10:39 AM
PHARMACOLOGIST

Lillian Gavrilovich
5/14/03 04:07:06 PM
MEDICAL OFFICER