CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-789

MICROBIOLOGY REVIEW

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS (HFD-520)
Clinical Microbiology Review of NDA 50-789

NDA#: 50-789 **REVIEW #**: 1 **DATE COMPLETED**: 08/20/03

Clinical Microbiology Reviewer: Harold V. Silver

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
50-789	12/20/02	12/31/02	01/10/03

NAME & ADDRESS OF APPLICANT:

American Pharmaceutical Partners, Inc.
2045 North Cornell Avenue
Melrose Park, IL 60160-1002
Corona, CA 92880
Tel: (708) 343-6100 / Fax: (708) 343-4269

CONTACT PERSONS:

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DRUG PRODUCT NAME:

Proprietary:	Tobramycin for Injection, USP
Non-Proprietary/USAN:	tobramycin (as tobramycin sulfate)
Code Name:	#300351
CAS No:	*CAS-79645-27-5*

CHEMICAL NAME, STRUCTURE, MOLECULAR FORMULA, MOL. W.T.:

Tobramycin Sulfate:

Chemical Name/Structure	=	Tobramycin: See 2000 USAN (page 723)
Molecular Formula	=	$(C_{18}H_{37}N_5O_9)_2\ 5H_2SO_4$
Molecular Weight	=	1425.43

DOSAGE FORM: Injectable (lyophilized powder for reconstitution)

POTENCY: Each Pharmacy Bulk Package vial contains tobramycin sulfate equivalent to 1.2 g tobramycin / 50 mL.

ROUTE OF ADMINISTRATION: Intravenous, "Not for Direct Infusion".

DISPENSED: Rx

PHARMACOLOGICAL CATEGORY:

Aminoglycoside (oligosaccharide) antibiotic.

FDA Approved INDICATIONS AND USAGE:

Nebcin 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.

Aminoglycosides, including Nebcin, USP are not indicated in uncomplicated initial episodes of urinary tract infections unless the causative organisms are not susceptible to antibiotics having less potential toxicity. Nebcin may be considered in serious staphylococcal infections when penicillin or other potentially less toxic drugs are contraindicated and when bacterial susceptibility testing and clinical judgment indicate its use.

Bacterial cultures should be obtained prior to and during treatment to isolate and identify etiologic organisms and to test their susceptibility to tobramycin. If susceptibility tests show that the causative organisms are resistant to tobramycin, other appropriate therapy should be instituted. In patients in whom a serious life-threatening gram-negative infection is suspected, including those in whom concurrent therapy with penicillin or cephalosporin and an aminoglycoside may be indicated, treatment with Nebcin may be initiated before the results of susceptibility studies are obtained. The decision to continue therapy with Nebcin should be based on the results of susceptibility studies, the severity of the infection, and the important additional concepts discussed in the **WARNINGS** box above.

REMARKS / COMMENTS:

This is a Clinical Microbiology Review on American Pharmaceutical Partners, Inc. submission of NDA 50-789, Tobramycin for Injection, USP, 1.2 tobramycin / 50 mL vial

Initially, American Pharmaceutical Partners, Inc. submitted an Abbreviated New Drug Application (ANDA), ANDA 64-090, Tobramycin for Injection, USP, on April 17, 2001, to the Office of Generic Drugs (OGD). Bioequivalence deficiency letters were sent to the Applicant on July 3, 2001 and November 19, 2001. The Applicant was informed to submit the application as an NDA to achieve approval to market their drug product.

The Applicant submitted NDA 50-789 in response to the FDA/DAIDP Memorandum of the January 16, 2002 Teleconference and finalized on April 18, 2002; and the telephone call from

DAIDP/HFD-520 on September 3, 2002, respectively.
The Applicant states "the Agency views and agrees that the drug product is equivalent to the marketed IV formulation or Tobramycin, NEBCIN® by Eli Lilly and Company. The only exceptions are the Chemistry, Manufacturing, and Controls data portions of the application." Therefore, the "generic" is to use the innovator label.

NEBCIN®, tobramycin sulfate, USP, is manufactured by Eli Lilly & Company: N50477/005, N62008/004, N62-707/001, EQ 10 mg Base/mL, dated April 29, 1987; N62008/001, EQ 40 mg Base/mL; and N50519/001, EQ 1.2 g Base / vial, respectively.

Therefore, from the Clinical Microbiology Reviewer's perspective, the **MICROBIOLOGY** section and the **REFERENCES** section, for the Tobramycin for Injection, USP, NDA 50-789, package insert labeling are to be identical to the current NEBCIN® (tobramycin sulfate) labeling, 2.01 PA 2012-A AMP, Literature revised May 12, 2001. If appropriate, i.e., if it is a substantive scientific change, both package insert labeling need to be updated to reflect current content and format.

INTRODUCTION

NEBCIN, tobramycin sulfate, and its labeling were approved on June 11, 1975.

In the aforementioned labeling, under the **INDICATIONS AND USAGE** section, "*Proteus* sp. (indole-positive and indole-negative)" is indicated.

Under the **MICROBIOLOGY** section, "*Proteus* sp. (indole-positive and indole-negative), including *Proteus mirabilis*, *Pr. morganii*, and *Pr. vulgaris*" is stated.

In the submitted current NEBCIN labeling, dated March 25, 1999, under the **MICROBIOLOGY** section, "*Proteus mirabilis*, *Morganella morganii*, and *Proteus vulgaris*" are stated. *Morganella morganii* is the current nomenclature for *Proteus morganii*.

The susceptibility "MIC and Zone Diameter Interpretative Standards" and the "Acceptable Limits for Quality Control Strains" remains the same [NCCLS Supplemental Tables, M100-S13 (M7 and M2) January 2003].

PACKAGE INSERT

(45932 / Issued: September 2002)

Applicant's Proposed MICROBIOLOGY Section and REFERENCES Section of the Package Insert Labeling

DESCRIPTION Section (microbiology portion):

Tobramycin sulfate, a water-soluble antibiotic of the aminoglycoside group, is derived from the actinomycete *Streptomyces tenebrarius.*

Clinical Microbiology Reviewer's Comments:

The microbiology labeling for the **DESCRIPTION** section is acceptable.

MICROBIOLOGY Section:

Microbiology

Tobramycin acts by inhibiting synthesis of protein in bacterial cells. *In vitro* tests demonstrate that tobramycin is bactericidal.

Tobramycin has been shown to be active against most strains of the following organisms both *in vitro* and in clinical infections as described in **INDICATIONS AND USAGE**:

Clinical Microbiology Reviewer's Comments:

Under the aforementioned ***Microbiology***, 2nd paragraph, found in ITEM 3, line 6, on Page 9, in the application, revise the labeling statement: "…..as described in **INDICATIONS AND USAGE**:" to read as:

"…..as described in the **INDICATIONS AND USAGE** section:"

Aerobic Gram-positive microorganisms
Staphylococcus aureus

Aerobic Gram-negative microorganisms
Citrobacter species
Enterobacter species
Escherichia coli
Klebsiella species
Morganella morganii
Pseudomonas aeruginosa
Proteus mirabilis
Proteus vulgaris
Providencia species
Serratia species

Aminoglycosides have a low order of activity against most gram-positive organisms, including *Streptococcus pyogenes, Streptococcus pneumoniae,* and enterococci.

Although most strains of enterococci demonstrate *in vitro* resistance, some strains in this group are susceptible. *In vitro* studies have shown that an aminoglycoside combined with an antibiotic that interferes with cell-wall synthesis affects some enterococcal strains synergistically. The combination of penicillin G and tobramycin results in a synergistic bactericidal effect *in vitro* against certain strains of *Enterococcus faecalis.* However, this combination is not synergistic against other closely related organisms, eg, *Enterococcus faecium.* Speciation of enterococci alone cannot be used to predict susceptibility. Susceptibility testing and tests for antibiotic synergism are emphasized.

Cross resistance between aminoglycosides may occur.

***Susceptibility Tests* Section:**

Susceptibility Tests

Diffusion Techniques

Quantitative methods that require measurement of zone diameters give the most precise estimates of susceptibility of bacteria to antimicrobial agents. One such procedure is the National Committee for Clinical Laboratory Standards (NCCLS)-approved procedure.[1] This method has been recommended for use with disks to test susceptibility to tobramycin. Interpretation involves correlation of the diameters obtained in the disk test with minimum inhibitory concentrations (MIC) for tobramycin.

Reports from the laboratory giving results of the standard single-disk susceptibility test with a 10-mcg tobramycin disk should be interpreted according to the following criteria:

Zone Diameter (mm)	Interpretation
≥15	(S) Susceptible
13-14	(I) Intermediate
≤12	(R) Resistant

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood levels. A report of "Intermediate" suggests that the organism would be susceptible if high dosage is used or if the infection is confined to tissues and fluids in which high antimicrobial levels are obtained. A report of "Resistant" indicates that achievable concentrations are unlikely to be inhibitory and other therapy should be selected.

Standardized procedures require the use of laboratory control organisms. The 10-mcg tobramycin disk should give the following zone diameters:

Organism		Zone Diameter (mm)
E. coli	ATCC 25922	18-26
P. aeruginosa	ATCC 27853	19-25
S. aureus	ATCC 25923	19-29

Dilution techniques

Broth and agar dilution methods, such as those recommended by the NCCLS[2], may be used to determine MICs of tobramycin. MIC test results should be interpreted according to the following criteria:

MIC (mcg/mL)	Interpretation
≤ 4	(S) Susceptible
8	(I) Intermediate
≥ 16	(R) Resistant

As with standard diffusion methods, dilution procedures require the use of laboratory control organisms. Tobramycin laboratory reagent should give the following MIC values:

Organism		MIC Range (mcg/mL)
E. faecalis	ATCC 29212	8-32
E. coli	ATCC 25922	0.25-1
P. aeruginosa	ATCC 27853	0.25-1
S. aureus	ATCC 29213	0.12-1

Clinical Microbiology Reviewer's Comments:

The Applicant's aforementioned microbiology labeling for the **Microbiology - *Susceptibility Tests*** section is acceptable.

REFERENCES Section:

REFERENCES:

1. National Committee for Clinical Laboratory Standards, Performance Standards for Antimicrobial Disk Susceptibility Tests—Sixth Edition. Approved Standard NCCLS Document M2-A6, Vol. 17, No. 1, NCCLS, Wayne, PA, 1997.

2. National Committee for Clinical Laboratory Standards, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically—Fourth Edition. Approved Standard NCCLS Document M7-A4, Vol. 17, No. 2, NCCLS, Wayne, PA, 1997.

Clinical Microbiology Reviewer's Comments:

The Applicant's aforementioned microbiology labeling for the **REFERENCES** section is identical to Eli Lilly's NEBCIN labeling. However, to maintain current scientific procedural susceptibility and quality control testing, the **REFERENCES** section is to be updated. Additions are shown with a single-underline and deletions are shown with a ~~strikethrough.~~

REFERENCES:

1. NCCLS. *Performance Standards for Antimicrobial Disk Susceptibility Tests; Approved Standard—Eighth Edition.* NCCLS document M2-A8 (ISBN 1-56238-485-6). NCCLS, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2003.

2. NCCLS. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard—Sixth Edition.* NCCLS document M7-A6 (ISBN 1-56238-486-4). NCCLS, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2003.

CLINICAL MICROBIOLOGY REVIEWER'S CONCLUSIONS and RECOMMENDATIONS on NDA 50-789

From the Clinical Microbiology Reviewer's perspective, the **DESCRIPTION** (microbiology portion) labeling is acceptable. When final labeling is negotiated with the Applicant on the Agency's recommended **MICROBIOLOGY** and **REFERENCES** portions of the package insert labeling, an "approval" letter can be issued for NDA 50-789, Tobramycin for Injection, USP.

The following, as stated on Page 4 and Page 6 in this Clinical Microbiology Review, are to be conveyed to the Applicant (and under **Note:** to the innovator, Eli Lilly and Company):

1. In the labeling, under the aforementioned ***Microbiology***, 2nd paragraph, in ITEM 3, line 6, on Page 9, in the application, revise the labeling statement: ".....as described in **INDICATIONS AND USAGE**:" to read as:

   ".....as described in the **INDICATIONS AND USAGE** section:"

2. To maintain current scientific procedural susceptibility and quality control testing, the **REFERENCES** section is to be updated to read:

REFERENCES:

1. NCCLS. *Performance Standards for Antimicrobial Disk Susceptibility Tests; Approved Standard—Eighth Edition*. NCCLS document M2-A8 (ISBN 1-56238-485-6). NCCLS, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2003.

2. NCCLS. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard—Sixth Edition*. NCCLS document M7-A6 (ISBN 1-56238-486-4). NCCLS, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2003.

Note: The aforementioned recommended updated "**REFERENCES**" are also to be conveyed to the innovator, Eli Lilly and Company, for the drug product NEBCIN®, Tobramycin Injection, USP.

Harold V. Silver
Clinical Microbiology Reviewer
DAIDP/HFD-520

cc: Orig. NDA 50-789
HFD-520/TLMO/J.Alexander
HFD-520/MO/A.Davidson
HFD-520/BioPharm/C.Bonapace
HFD-520/Chem/S.Pagay
HFD-520/PM/R.Peat
HFD-520/Micro/H.V.Silver
Filename: 50789FIN
APPROVAL

Concurrence Only:
HFD-520/TLMicro/A.T.Sheldon
RD#2 and Final Initialed 8/25/03 ATS
HFD-520/DepDir/L.Gavrilovich

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

/s/

Harold Silver
8/25/03 04:10:10 PM
MICROBIOLOGIST

Please sign off on the Clinical Microbiology Labeling Review for NDA 50-789.

Albert Sheldon
8/26/03 07:09:40 AM
MICROBIOLOGIST

Lillian Gavrilovich
8/29/03 03:45:21 PM
MEDICAL OFFICER