CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-789

CHEMISTRY REVIEW(S)

NDA 50-789

Tobramycin for Injection, USP
Review #2

American Pharmaceutical Partners, Inc.

Shrikant N. Pagay
Anti-Infective Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 50-789

2. REVIEW #: 2

3. REVIEW DATE: 6/7/04

4. REVIEWER: Shrikant N. Pagay

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	12/20/02
Amendment	8/20/03
Amendment	10/10/03

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	10/13/03
Amendment	1/12/04

7. NAME & ADDRESS OF APPLICANT:

Name:	American Pharmaceutical Partners, Inc.
Address:	2045 North Cornell Avenue, Melrose park, IL 60160
Representative:	Tony A. Glinsey
Telephone:	(708)- 486- 2115

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Tobramycin for Injection, USP
b) Non-Proprietary Name (USAN): Tobramycin for Injection, USP
c) Code Name/# (ONDC only): NA

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (2)

10. PHARMACOL. CATEGORY: Anti-infective

11. DOSAGE FORM: Injectable (lyophilized powder)

12. STRENGTH/POTENCY: 1.2 g/vial

13. ROUTE OF ADMINISTRATION: Injectable

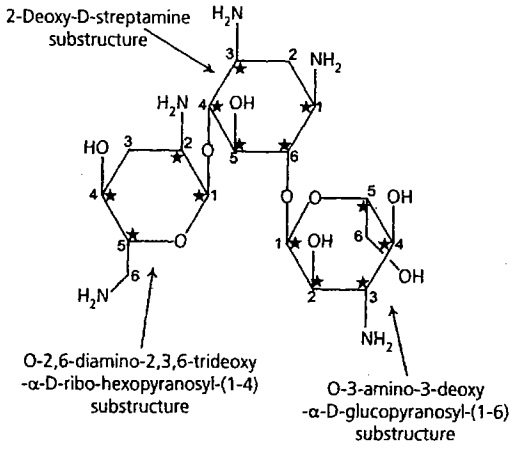
14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

O-3-Amino-trideoxy-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.
$(C_{18}H_{37}N_5O_9)_2.5H_2SO_4$, 1425.45.



*** Represents chiral centers**

17. RELATED/SUPPORTING DOCUMENTS:

Chemistry Review Data Sheet

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
1	II	[redacted]		1	Adequate	6/7/04	S.Pagay (3 reviews)
	III			3	Adequate	11/6/00	For IV drug product
	III			3	Adequate	8/5/03	For IV drug product
	III			3	Adequate	8/3/00	CVM reviewer

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: NA

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA	NA	NA

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Acceptable	1/9/04	J. Ambrogio
Pharm/Tox	NA		
Biopharm	NA		
LNC	NA		
Methods Validation	Pending	6/7/04	Philadelphia District Lab
OPDRA	NA		
EA	NA		
Microbiology	Approval	4/11/03	Paul Stinavage

19. COMMENTS:

Review #2 includes the assessment of the10/31/03 and 1/12/04 amendments. All other information is in Review # 1.

The initial CMC status of this application was approvable as of 10/24/03 due to the overall recommendation of "withhold" from the Office of Compliance for a facility inspection. Also, DMF [redacted] for the drug substance was deficient since the manufacturing facility for the drug substance under this DMF was also on "withhold" status. The DMF status is adequate as of 6/7/04 and the overall recommendation from the Office of Compliance is acceptable as of 6/15/04.

The Chemistry Review for NDA 050-789##-###

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended from CMC perspective as "approval" .

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

NA

II. Summary of Chemistry Assessments

The summary of chemistry assessment information was also submitted in Review 1.

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance

Tobramycin sulfate prepared by a [redacted] process is a white powder freely soluble in water and in mixtures of water and organic solvents. The drug is [redacted]

Based on the stability data presented (6 months under accelerated storage condition on 3 batches [redacted] months under long term storage condition on 1 batch an [redacted] months on 2 batches), the proposed expiration date of 36 months is acceptable. Tobramycin is inactive given orally but very effective as an injectable dosage form and an inhalation dosage form. Tobramycin is an old drug discovered in 1967 with the first NDA approved on 7/8/1975. Tobramycin sulfate is a class of compounds known as aminoglycoside antibiotics. It is a broad spectrum antibiotic with bactericidal activity on both the gram positive and gram negative micro-organisms. The mode of action of aminoglycoside exposure is generally attributed to inhibition of protein synthesis, misreading of genetic code, increased RNA synthesis, membrane damage (leaking of potassium ion) and ultimately cell death. Aminoglycosides are cleared through kidneys and have long post antibiotic effect (suppression of bacterial growth after concentrations fall below MIC levels). Aminoglycosides are toxic in kidney and ears.

Drug product:

The drug product is an injectable dosage form for intravenous administration. The injectable dosage form is a lyophilized powder of tobramycin sulfate. Prior to administration, it is reconstituted with water for injection. Tobramycin injection may be further diluted with either normal saline or 5% dextrose solution to administer as an IV infusion. Each vial contains 1.2 grams of tobramycin activity as tobramycin sulfate. The lyophilized powder is described as white to off-white powder and amorphous in nature.

The components of the drug product are: tobramycin sulfate, [redacted] It is used to enhance the powder characteristics to be free flowing and easily dispersible. The finished drug product contains [redacted] in this injectable dosage form has been considered to be safe as per evaluation by Pharm-Tox and Medical disciplines. [redacted]

The drug product is manufactured by [redacted] The stoppers are free of latex component. Based on the stability data presented (3 months under accelerated storage condition on one batch, 6 months under accelerated storage condition on 2 batches, 12 months under long term storage condition on 2 batches and [redacted] months under long term storage condition on one batch), the proposed 24 month shelf life is acceptable.

B. Description of How the Drug Product is Intended to be Used

Each vial is a Pharmacy Bulk Package for use in Hospital Pharmacy Admixture Service to dispense the required doses for individual patients. The vials are opened [redacted] in a suitable area, such as a [redacted]. The closure may be penetrated only one time after reconstitution using a suitable sterile device or dispensing set which allows measured amounts of the contents of the vial. The use of syringe or needle is not recommended as it may cause leakage. After entry, the entire contents of bulk vial should be dispensed within 24 hours.

The contents of each vial (1.2 gram dry powder) should be diluted with 30 mL sterile water for injection to prepare a 40 mg/mL solution. Prior to reconstitution, the vials should be stored at room temperature (15 - 30°C). After reconstitution, the vial should be stored up to 96 hours in a refrigerator or up to 24 hours at room temperature.

B. Basis for Approvability or Not-Approval Recommendation

The data provided to support the application is complete, i.e., a detailed list of specifications, manufacturing and in-process controls, new and improved (over USP

method) test method for the assay and impurities analysis, a complete package of the stability data to support the shelf life and CMC portion of the label which included appropriate directions for dispensing the drug product in a clinic. All facilities for manufacturing and testing the drug substance and drug product are acceptable to the Office of Compliance. Based on this review (Review #2), the application is recommended for approval from CMC considerations.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Shrikant N. Pagay
ChemistryTeamLeader Name/Date: James Vidra
Project Manager Name/Date: Raquel Peat

C. CC Block

5 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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

/s/

Shrikant Pagay
6/25/04 04:27:47 PM
CHEMIST
CMC approval for this NDA

Jim Vidra
6/25/04 04:32:09 PM
CHEMIST

NDA 50-789

Tobramycin for Injection, USP
Review #1

American Pharmaceutical Partners, Inc.

Shrikant N. Pagay
Anti-Infective Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 50-789

2. REVIEW #: 1

3. REVIEW DATE: 5/30/03

4. REVIEWER: Shrikant N. Pagay

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	12/20/02
Amendment	8/20/03
Amendment	10/10/03
Amendment	10/13/03

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Name:	American Pharmaceutical Partners, Inc.
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a) Proprietary Name: Tobramycin for Injection, USP
b) Non-Proprietary Name (USAN): Tobramycin for Injection, USP
c) Code Name/# (ONDC only): NA
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (2)

10. PHARMACOL. CATEGORY: Anti-infective

11. DOSAGE FORM: Injectable (lyophilized powder)

12. STRENGTH/POTENCY: 1.2 g/vial

13. ROUTE OF ADMINISTRATION: Injectable

14. Rx/OTC DISPENSED: _X__Rx ___OTC

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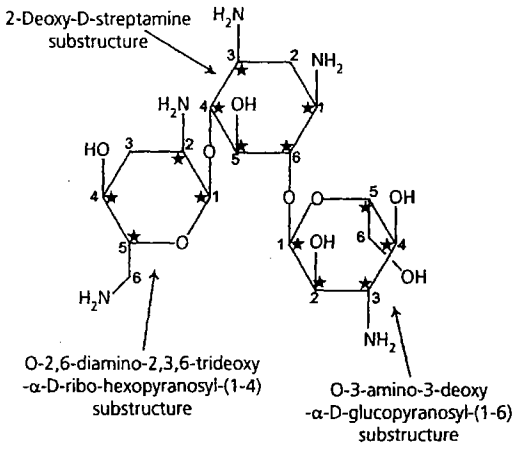
$(C_{18}H_{37}N_5O_9)_2.5H_2SO_4$, 1425.45.



*** Represents chiral centers**

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	[redacted]	1		9/24/03	S.Pagay
[redacted]	III			3	Adequate	11/6/00	For IV drug product
[redacted]	III			3	Adequate	8/5/03	For IV drug product
[redacted]	III			3	Adequate	8/3/00	CVM reviewer

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B. Other Documents: NA

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA	NA	NA

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Pending	1/10/03	
Pharm/Tox	NA		
Biopharm	NA		
LNC	NA		
Methods Validation	Pending	10/3/03	Philadelphia District Lab
OPDRA	NA		
EA	NA		
Microbiology	Pending	1/3/03	Paul Stinavage

19. COMMENTS:

The review includes the assessment of the original NDA and amendments. The amendments include stability update, responses to deficiencies and post-approval commitments by the sponsor based on the review of the deficiency response. The review notes format is as follows: The information from the submission is in regular font type, reviewer's comments are italicized. Each of the section in the assessment is evaluated either as adequate or inadequate at the beginning of the section..

The Chemistry Review for NDA 050-789##-###

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended from CMC perspective as "approvable" since the overall recommendation from the Office of Compliance is "withhold" due to the deficiencies in the drug substance manufacturing facility which will require corrective action.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

NA

II. Summary of Chemistry Assessments

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The components of the drug product are: tobramycin sulfate, [redacted]. It is used to enhance the powder characteristics to be free flowing and easily dispersible. The finished drug product contains [redacted] in this injectable dosage form has been considered to be safe as per evaluation by Pharm-Tox and Medical disciplines. [redacted] the vials. The container [redacted] The stoppers are free of latex component. Based on the stability data presented (3 months under accelerated storage condition on one batch, 6 months under accelerated storage condition on 2 batches, 12 months under long term storage condition on 2 batches and 24 months under long term storage condition on one batch), the proposed 24 month shelf life is acceptable.

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B. Basis for Approvability or Not-Approval Recommendation

The data provided to support the application is complete, i.e., a detailed list of specifications, manufacturing and in-process controls, new and improved (over USP method) test method for the assay and impurities analysis, a complete package of the stability data to support the shelf life and CMC portion of the label which included

appropriate directions for dispensing the drug product in a clinic. However, the overall recommendation from the Office of Compliance for the facility inspection was "withhold". Therefore, the CMC recommendation for this application is approvable (AE) status.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Shrikant N. Pagay
ChemistryTeamLeader Name/Date: James Vidra
Project Manager Name/Date: Raquel Peat

C. CC Block

36 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Medical Review 2 of 2

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/s/

Shrikant Pagay
10/24/03 02:13:32 PM
CHEMIST

Jim Vidra
10/24/03 02:15:49 PM
CHEMIST