

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205433Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

Division of Anti-Infective Products

Tobramycin Inhalation Solution
 Pulmoflow
 NDA 205—433 SN000

Clinical Microbiology Review #1
 Peter Coderre, PhD
 03 June 2014

Applicant:

Pulmoflow Inc.

Contact:

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 Senior Associate
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Submission Reviewed: NDA 205—433 SN000

Indication: Management of Cystic Fibrosis (CF) patients infected with *Pseudomonas aeruginosa*

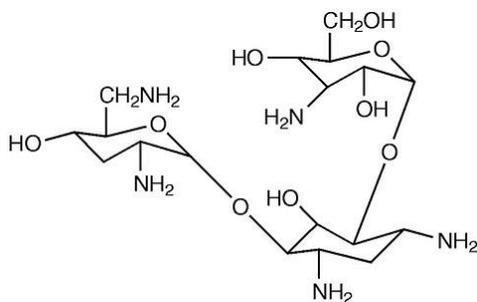
Product Names:

Proprietary: Kitabis™

Non-proprietary/USAN: Tobramycin Inhalation Solution (TIS)

Chemical Name: *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

Molecular Formula: C₁₈ H₃₇ N₅ O₉; MW: 467.52

Structural Formula:

Dosage Form and Duration of Treatment: The 300 mg dose of tobramycin is the same for patients regardless of age or weight. Tobramycin inhalation solution has not been studied in patients less than 6 years old. Doses should be inhaled as close to 12 hours apart as possible and not less than 6 hours apart.

Route of Administration: Inhalation by PARI LC® Plus Reusable Nebulizer using TIS

Dispensed: Rx

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Initial Submission Dates:

Received by CDER: 26 September 2013
Received by Reviewer: 26 September 2013
Review Completed: 03 June 2014

Remarks:

Pursuant to Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, and in compliance with 21 CFR §314.50, Lachman Consultant Services, Inc. (Lachman Consultants), as United States Agent on behalf of the Applicant (Pulmoflow Inc.), submits an original New Drug Application for Kitabis™ (Rx Only) (Tobramycin Inhalation Solution, USP and PARI LC® Plus Reusable Nebulizer).

The Applicant is 100% responsible for the development and funding of the NDA submission 205—433. The Applicant will grant PARI Respiratory Equipment, Inc. exclusive rights to distribute the product commercially in the United States. In addition, the Applicant requested PARI to perform certain tasks associated with the development of the product based on PARI Respiratory Equipment's well established connections with the drug manufacturer, Catalent, and other key contacts.

This review describes the findings and the recommendations of the Microbiology Reviewer. These recommendations are for evaluation by the Division Director for the determination of a decision whether this New Drug Application should be approved.

CONCLUSIONS AND RECOMMENDATION

The Applicant submits a NDA for Tobramycin Inhalation Solution (Kitabis™) in accordance with Section 505(b)(2) of the Federal Food, Drugs and Cosmetic Act. Overall, there is limited Microbiology data included, only a small surveillance study.

In this study, the Applicant presents tobramycin MIC data of *P. aeruginosa* isolates from CF patients over a recent three year period 2011—2013. Little change was seen in the susceptibility of *P. aeruginosa* to tobramycin in clinical isolates taken from cystic fibrosis patients. However, the validity of the data is questionable due to the use of Etest for the susceptibility methodology and due to the methodology for sample collection since a large number of the specimen samples were taken as throat swaps rather than as sputum samples.

From a Microbiology standpoint, this Reviewer deems the application “approvable” contingent upon the acceptance of the changes made by this Reviewer to the Microbiology subsection of the Package Insert. The modified Package Insert is presented below.

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MICROBIOLOGY SUBSECTION OF THE PACKAGE INSERT

Note: Recommended modifications to verbiage are indicated as follows: added text is shown as blue, underlined text and deleted text is shown as ~~red, strikethrough text~~.

12.4 Microbiology

Mechanism of Action

Tobramycin is an aminoglycoside (b) (4) produced by *Streptomyces tenebrarius*. It acts primarily by disrupting protein synthesis, leading to altered cell membrane permeability, progressive disruption of the cell envelope, and eventual cell death.

Tobramycin has *in vitro* activity against (b) (4) Gram-negative bacteria (b) (4) including *Pseudomonas aeruginosa*. It is bactericidal *in vitro* at peak concentrations equal to or slightly greater than the minimum inhibitory concentration (b) (4).

Susceptibility Testing

(b) (4)

Interpretive criteria for inhaled antibacterial products are not defined. (b) (4) *in vitro* antimicrobial susceptibility test methods used to determine the susceptibility for parenteral tobramycin therapy can be used to monitor the susceptibility of *P. aeruginosa* isolated from cystic fibrosis patients ^(1, 2, 3). The relationship between *in vitro* susceptibility test results and clinical outcome with TOBRAMYCIN Inhalation Solution therapy is not clear. A single sputum sample from a cystic fibrosis patient may contain multiple morphotypes of *P.* (b) (4) *aeruginosa* and each morphotype may (b) (4) require a different concentration of tobramycin to inhibit its growth *in vitro*. Patients should be monitored for changes in tobramycin susceptibility. (b) (4)

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~~susceptibility to tobramycin. If decreased susceptibility is noted, the results should be reported to the clinician.~~

(b) (4)

REFERENCES

(b) (4)

1. [Clinical and Laboratory Standards Institute \(CLSI\). Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically – Ninth Edition; Approved Standard. CLSI Document M07-A9. Clinical and Laboratory Standards Institute, 950 West Valley Road., Suite 2500, Wayne, Pennsylvania, 19087, 2012.](#)
2. [Clinical and Laboratory Standards Institute \(CLSI\). Performance Standards for Antimicrobial Disk Diffusion Susceptibility Tests; Approved Standard – Eleventh Edition. CLSI document M02-A11, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania, 19087, USA, 2012.](#)
3. [Clinical and Laboratory Standards Institute \(CLSI\). Performance Standards for Antimicrobial Susceptibility Testing; Twenty-fourth Informational Supplement, CLSI document M100-S24, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania, 19087, USA, 2014.](#)

Reviewer's comments: The following verbiage present in the TOBI Podhaler label was not included in the present label:

Development of Resistance

In clinical studies, some increases from baseline to the end of the treatment period were observed in the tobramycin MIC for *P. aeruginosa* morphotypes. In general, a higher percentage of patients treated with TOBI Podhaler had increases in tobramycin MIC compared with placebo or patients treated with TOBI inhalation solution.

The clinical significance of changes in MICs for *P. aeruginosa* has not been clearly established in the treatment of cystic fibrosis patients.

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Cross-Resistance

Some emerging resistance to aztreonam, ceftazidime, ciprofloxacin, imipenem, or meropenem were observed in the TOBI Podhaler clinical trials. As other anti-pseudomonal antibiotics were concomitantly utilized in many patients in the clinical trials, the association with TOBI Podhaler is not clear.

Other

No trends were observed in the isolation of treatment-emergent bacterial respiratory pathogens (*Burkholderia cepacia*, *Stenotrophomonas maltophilia*, *Staphylococcus aureus* and *Achromobacter xylosoxidans*).

This verbiage was not included in the present label because no clinical studies were conducted to support such statements. This additional verbiage was pertinent to the TOBI podhaler label whose Applicant conducted the relevant clinical studies which serve as the basis for this verbiage. To include this verbiage would be confusing.

SURVEILLANCE STUDIES

At the pre-IND meeting with the Division, the Applicant was asked to supply recent (within the last three years) updated tobramycin MIC data from 100 *Pseudomonas aeruginosa* isolates from cystic fibrosis patients. The Applicant was reminded that this data could be acquired from the literature. Here, the Applicant presents tobramycin MIC data from the University Of Washington School Of Medicine, Division of Infectious Diseases on *Pseudomonas aeruginosa* isolates from 101 cystic fibrosis patients (2011 – 2013).

For tobramycin, a value of less than or equal to 4 µg/mL is considered susceptible; a value of 8 µg/mL is considered intermediate; a value greater than or equal to 16 µg/mL is considered resistant. This is based on the CLSI (NCCLS) standards referenced in the protocol.

From the specimens taken from each subject, the MIC values of the mucoid and non-mucoid morphotypes were determined. If more than one morphotype of *P. aeruginosa* was isolated from a single sample, each one was evaluated separately and given its own designation (e.g. Subject #1, *P. aeruginosa* #3).

A summary of those results is provided in [Table 1](#).

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Table 1: Summary of Tobramycin MIC Values Determined in Clinical Isolates from Cystic Fibrosis Patients

Year	No. Subjects	Morphotype	No. Isolates Tested	No. Samples (No. Patients)		
				S	I	R
				MIC: ≤ 4 $\mu\text{g/mL}$	MIC: 6 - 12 $\mu\text{g/mL}$	MIC: ≥ 16 $\mu\text{g/mL}$
2011	30	Non-Mucoid	47	26 (20)		9 (5)
		Mucoid	21	17 (6) ¹	4 (4) ²	0 (0)
2012	33	Non-Mucoid	58	48 (17)	7 (7)	3 (3)
		Mucoid	14	11 (8) ¹	0 (0)	3 (3) ³
2013	38	Non-Mucoid	39	26 (26)	4 (4)	9 (5)
		Mucoid	35	27 (17) ¹	5 (5)	3 (2) ⁴

1 Several patients had a clinical isolate with a MIC value for susceptibility in a non-mucoid morphotype

2 One patient also had a clinical isolate with a MIC value for intermediate resistance in a non-mucoid morphotype

3 One patient also had a clinical isolate with a MIC value for resistance in a non-mucoid morphotype

4 Both patients also had clinical isolates with MIC values for resistance in a non-mucoid morphotypes

Source: Table 1, Non-Clinical Section, NDA 205—433.

In this dataset, the number of non-mucoid and mucoid isolates of *Pseudomonas aeruginosa* evaluated varied from between patients. The majority of the clinical isolates (mucoid and non-mucoid morphotypes) were susceptible to tobramycin. The incidence of tobramycin intermediate plus resistant clinical isolates of *Pseudomonas aeruginosa* taken from cystic fibrosis patients appears to have decreased between 2011 and 2013, although the number of patients having resistant clinical isolates was the same in 2011 and 2013. Please note that the two patients with mucoid clinical isolates resistant to tobramycin in 2013 also showed resistance to the non-mucoid morphotype.

These results indicate that susceptibility of *Pseudomonas aeruginosa* to tobramycin in clinical isolates taken from cystic fibrosis patients based on MIC values has essentially not changed between 2011 and 2013.

Reviewer's comments: The Applicant presents tobramycin MIC data of *P. aeruginosa* isolates from CF patients over a recent three year period 2011—2013. Little change was seen in the susceptibility of *P. aeruginosa* to tobramycin in clinical isolates taken from cystic fibrosis patients. However, the validity of the data is questionable due to the use of Etest for the susceptibility methodology and due to the methodology for sample collection since a large number of the specimen samples were taken as throat swabs rather than as sputum samples.

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Peter Coderre, Ph.D., M.B.A.
Microbiology Reviewer

For concurrence only,
Microbiology Team Leader, HFD-520
Kerry Snow, M.S.
5 June 2014

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

/s/

PETER E CODERRE
06/12/2014

KERRY SNOW
06/13/2014

Product Quality Microbiology Review

2/28/2014

NDA: 205433

Drug Product Name

Proprietary: Kitabis

Non-proprietary: Tobramycin

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
10/02/2013	10/02/2013	11/04/2013	11/04/2013
2/24/2014	2/24/2014	N/A	N/A

Submission History (for 2nd Reviews or higher)

None

Applicant/Sponsor

Name: Pulmoflow Inc.

Address: 3900 Westerre Parkway, Suite 300, Richmond, VA 23233

Representative: Lachman Consultants, Donald H. Chmielewski
1600 Stewart Ave , Westbury NY 11590

Telephone: 516 222-6222

Name of Reviewer: Steven P. Donald, M.S.

Conclusion: Recommended for Approval

Product Quality Microbiology Data Sheet

- A. 1. **TYPE OF SUBMISSION:** Original NDA
2. **SUBMISSION PROVIDES FOR:** The manufacturing and marketing of a sterile drug product
3. **MANUFACTURING SITE:** Catalent Pharma Solutions, 2210 Lake Shore Dr., Woodstock IL 60098
4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
- Dosage Form: Sterile solution
 - Route of Administration: Inhalation
 - Strength/Potency: 300 mg/5 mL
 - Container: Single use LDPE ampoule. Intended for use with PARI LC PLUS® Reusable Nebulizer
5. **METHOD(S) OF STERILIZATION:** (b) (4)
6. **PHARMACOLOGICAL CATEGORY:** Antibiotic
- B. **SUPPORTING/RELATED DOCUMENTS:** None
- C. **REMARKS:** None

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Executive Summary

I. Recommendations

- A. Recommendation on Approvability** - Recommended for Approval
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – N/A

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – The bulk drug solution is (b) (4) filled into a 5ml LDPE vial using (b) (4), heat sealed and packaged within a foil overwrap.
- B. Brief Description of Microbiology Deficiencies** – No product quality microbiology deficiencies were identified based upon the information provided.
- C. Assessment of Risk Due to Microbiology Deficiencies** – N/A
- D. Contains Potential Precedent Decision(s)**- Yes No

III. Administrative

- A. Reviewer's Signature** _____
Steven P. Donald, M.S.
Microbiology Reviewer
- B. Endorsement Block** _____
Stephen Langille, Ph.D.
Senior Microbiology Reviewer
- C. CC Block**
N/A

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/s/

STEVEN P DONALD
03/07/2014

STEPHEN E LANGILLE
03/09/2014