

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205433Orig1s000**

**MEDICAL REVIEW(S)**

## Deputy Division Director Decisional Memo

|                                |  |
|--------------------------------|--|
| <b>Date</b>                    | (electronic stamp)   |
| <b>From</b>                    | Katherine Laessig, MD  |
| <b>Subject</b>                 | Deputy Division Director Decisional Memo   |
| <b>NDA #</b>                   | 205-433  |
| <b>Applicant Name</b>          | Pulmoflow, Inc. c/o Lachman Consulting Services, Inc.  |
| <b>Date of Submission</b>      | October 2, 2013  |
| <b>PDUFA Goal Date</b>         | August 23, 2014  |
| <b>Established (USAN) Name</b> | Tobramycin inhalation solution and PARI LC® Plus Reusable Nebulizer, trade name Kitabis™ Convenience Pak                   |
| <b>Dosage Forms / Strength</b> | Tobramycin inhalation solution, USP, 300 mg/5mL  |
| <b>Approved Indications</b>    | Management of cystic fibrosis in adults and pediatric patients 6 years of age and older with <i>Pseudomonas aeruginosa</i> |
| <b>Recommended Action:</b>     | Tentative Approval   |

| <b>Material Reviewed/Consulted</b><br>OND Action Package including: | <b>Names of discipline reviewers</b>   |
|---|--|
| Medical Officer Review  | Shrimant Mishra  |
| Pharmacology Toxicology Review                                      | Amy Ellis  |
| Product Quality Reviews   | Mark Seggel, Sandra Suarez Sharp, Stephen Donald                             |
| Microbiology Review   | Peter Coderre  |
| CDTL Review   | Benjamin Lorenz  |
| Labeling Reviews  | Jacqueline Sheppard, Aleksander Winiarski, Shawna Hutchins, Christine Corser |

OND=Office of New Drugs  
CDTL=Cross-Discipline Team Leader

## 1.0 Background

On October 2, 2013, Lachman Consultant Services, Inc., submitted NDA 205-433 on behalf of Pulmoflow, Inc., in support of Kitabis Convenience Pak. Kitabis Convenience Pak is a co-packaged product of tobramycin inhalation solution with the 510(k)-cleared device, the PARI LC Plus Reusable nebulizer. PARI Respiratory Equipment will maintain exclusive rights to distribute the product commercially in the US. This application is submitted under Section 505(b)(2) of the FD&C Act, and relies on the Agency's previous findings of safety and effectiveness for the reference listed product, TOBI® (NDA 50-753, approved in December 1997), as well as on recent published data and analyses regarding tobramycin. The applicant received an Unacceptable for Filing Letter on October 18, 2013, because the applicant had paid a

Fiscal Year 2013 User Fee instead of a Fiscal Year 2014 User Fee. On October 23, a full user fee was received and the application was accepted.

The applicant has certified that the patent for TOBI is currently in effect and will expire on October 19, 2014. The applicant will not market the proposed product until after this patent expires.

This memo will summarize elements of relevant reviews by discipline. No new clinical studies have been conducted and the majority of the information contained in this NDA is biopharmaceutics and product quality. As there were no new clinical trials submitted, there are no statistical or clinical pharmacology reviews. For detailed discussions of the other disciplines, please refer to the respective reviews.

## **2.0 Summary of Product Quality**

This NDA has been reviewed by multiple product quality reviewers. Dr. Mark Seggel conducted the review of the drug substance and drug product. Dr. Stephen Donald conducted the review of the product quality microbiology, and Dr. Suarez conducted the review of the biopharmaceutics. They have concluded that the applicant has provided sufficient information to assure the identity, strength, quality, purity, potency, and bioavailability of the drug product. The applicant had requested a biowaiver for conducting the in vivo bioequivalence studies on the basis that the tobramycin inhalation solution included with the Kitabis Pak is quantitatively equivalent to TOBI (contains the same NaCl content, pH, and osmolality) and has an equivalent droplet size distribution and emitted dose when using the PARI LC Plus nebulizer and the DeVilbiss® PulmoAide® compressor in accordance with the labeled instructions for use. Dr. Suarez has concluded that the in vitro characterization of the product and nebulizer adequately demonstrates the bioequivalence of the Kitabis Pak to the listed drug, TOBI. The drug product, tobramycin inhalation solution, has a 24-month expiration dating period when stored as directed. Three lots of drug product have been placed on stability under accelerated and long-term conditions with testing through 36 months. The final recommendation from CDRH-ODE and CDRH Office of Compliance regarding the PARI LC Plus nebulizer is acceptable. The current version of the PARI LC Plus nebulizer incorporates two new materials; however these are present in the 510(k)-cleared device, PARI LC Sprint nebulizer. The final overall CDER Office of Compliance recommendation is also acceptable.

## **2.0 Summary of Pharmacology/Toxicology**

Dr. Ellis reviewed the results of leachables testing for the drug product. Three lots were tested after approximately 17 months of storage at 5°C. With the exception of (b) (4), the listed chemicals were not detected, were below the level of quantitation, or were below the target limits proposed by the applicant. The proposed target limits appear reasonably safe. (b) (4)

(b) (4) is not mutagenic in Ames testing with *Salmonella typhimurium*. The applicant proposed a reporting threshold of (b) (4) in the tobramycin inhalation solution. As there are no special concerns regarding the toxicity of (b) (4), the proposed threshold is adequate. Dr. Ellis noted that in the three registration batches to determine stability, the concentrations of (b) (4) ranged from (b) (4). Dr. Ellis recommends approval.

### **3.0 Summary of Clinical Microbiology**

The clinical microbiology reviewer, Dr. Peter Coderre, has determined that the application may be approved contingent on the acceptance of changes to the Microbiology subsection of the product labeling. In this NDA, the applicant submitted tobramycin MIC data for *Pseudomonas aeruginosa* isolates from cystic fibrosis patients over the three year period from 2011 through 2013. Little change was seen in the susceptibility of *P. aeruginosa* to tobramycin in these clinical isolates. However, Dr. Coderre had concerns about the validity of the data because the Etest was used for the susceptibility methodology and a large number of specimen samples were throat swabs rather than sputum samples.

### **4.0 Summary of Clinical Safety**

The medical reviewer, Dr. Shrimant Mishra, recommends approval. The applicant submitted a postmarketing safety update that included a search of the recent published literature, as well as of the FDA Adverse Event Reporting System, and the Manufacturer and User Facility Device Experience database in order to evaluate for any new safety signals. One hundred four AERS reports were identified for tobramycin use via inhalation. Of these events, the reported terms generally fell into the categories either reflective of underlying disease (pneumonia, infective pulmonary exacerbation of cystic fibrosis, pulmonary function test decreased, etc.), adverse events already described in the product labeling (deafness, tinnitus, bronchospasm, etc.), or both. The Kitabis label has been updated to reflect what are believed to be adverse reactions, rather than the list of adverse events that are reflected in the TOBI label. The MAUDE search for the period of 2010-2013 did not identify any reports involving tobramycin use in combination with a nebulizer or any other inhalation device. The literature search identified 13 unique studies of tobramycin for inhalation that included information on adverse events. Most of these studies evaluated subjects with cystic fibrosis. Similar to the findings of the AERS review, the safety findings from these studies reflect what is already known about inhaled tobramycin as described in the package insert. No new safety signals have been identified.

## **5.0 Pediatrics**

Since Kitabis Pak is not a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, PREA is not triggered. Of note, the reference listed drug, TOBI, is labeled for use down to six years of age.

## **6.0 Advisory Committee**

A meeting of the Anti-infective Drugs Advisory Committee was not convened as there were no issues identified requiring advisory committee input.

## **7.0 Other Regulatory Issues**

As the application contained no new clinical trials, there was no need for any clinical inspections to be conducted by the Office of Scientific Investigations.

## **8.0 Labeling**

The proprietary name, Kitabis Pak, has been found acceptable by DMEPA and OPDP. The labeling, carton and container, and instructions for use have been found to be acceptable from the perspective of DMEPA, OPDP, Patient Labeling, and CDRH. Extensive labeling revisions were required as the label is in PLR format while the reference listed product label for TOBI is not. The applicant has agreed to all FDA proposed changes.

## **9.0 Benefit/Risk Assessment and Regulatory Action**

I concur with the recommendations of the review team that the benefit/risk assessment for this 505(b)(2) NDA for Kitabis Convenience Pak is favorable and that the application may be approved. However, since the listed drug, TOBI, upon which this application relies is subject to a period of patent protection, this application may be tentatively approved and the final approval of the application may not be made effective until the period of patent protection has expired. Two to six months prior to that date, the applicant must submit an amendment requesting final approval and providing the legal/regulatory basis for the request.

Katherine A. Laessig, MD

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/s/  
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KATHERINE A LAESSIG  
08/22/2014

## Cross-Discipline Team Leader Review

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|--|--|
| Date   | 18 August 2014   |
| From   | Benjamin Lorenz, MD  |
| Subject  | Cross-Discipline Team Leader Review  |
| NDA/BLA #<br>Supplement#                       | 205433   |
| Applicant                                      | Pulmoflow Inc.<br>c/o Lachman Consultant Services, Inc.                                |
| Date of Submission                             | 23 October 2013  |
| PDUFA Goal Date                                | 22 August 2014   |
|  |  |
| Proprietary Name /<br>Established (USAN) names | Kitabis™ / Tobramycin Inhalation Solution, USP and PARI LC®<br>Plus Reusable Nebulizer |
| Dosage forms / Strength                        | 300 mg/vial  |
| Proposed Indication(s)                         | For the management of cystic fibrosis patients with<br><i>Pseudomonas aeruginosa</i>   |
| Recommended:                                   | <i>Tentative Approval</i>  |

### 1. Introduction

On 2 October 2013, Pulmoflow Inc. submitted NDA-205433 for KITABIS PAK® (tobramycin inhalation solution, 300 mg / 5 mL), a co-packaged product of the inhaled aminoglycoside antibacterial drug with the PARI LC PLUS® Reusable Nebulizer. The Applicant is relying on FDA's previous findings of safety and efficacy for TOBI® Inhalation Solution (Novartis, NDA-050753) as well as recent published data and analysis regarding tobramycin. TOBI was approved on 22 December 1997 for the management of cystic fibrosis in adults and children six years of age and older with *Pseudomonas aeruginosa*. In view of the similarities between Kitabis Pak and TOBI, a biowaiver for conducting in vivo bioequivalence studies was requested by the Applicant on the basis that the tobramycin inhalation solution included with the Kitabis Pak is quantitatively equivalent to the TOBI (i.e. contains the same NaCl content, pH and osmolality) and has equivalent droplet size distribution and emitted dose when using the PARI LC Plus nebulizer and DeVilbiss® PulmoAide® compressor in accordance with the labeled instructions for use.

### 2. Background

Lachman Consultant Services, Inc. (Lachman Consultants) has submitted this NDA on behalf of Pulmoflow Inc., who is responsible for the development and funding of the submission and has authorized Lachman Consultants to act as the US agent. PARI Respiratory Equipment will maintain exclusive rights to distribute the product commercially in the US.

Tobramycin inhalation solution is currently available as TOBI as well as two recently approved generic versions. Tobramycin is also currently available in injectable dosage forms and in

formulations for topical ophthalmic use (tobramycin for injection was initially approved in 1975 and the ophthalmic solution was approved in 1980). Tobramycin inhalation solution is indicated for the management of cystic fibrosis patients 6 years of age and older with *P. aeruginosa*. A 300 mg dose is administered twice daily by oral inhalation using the PARI LC Plus Reusable Nebulizer and DeVilbiss Pulmo-Aide air compressor (b) (4)

Typically, tobramycin is administered in repeated cycles of 28 days on treatment followed by 28 days without treatment.

The PARI LC Plus Reusable Nebulizer is a 510(k)-cleared nebulizer. Bethkis® (tobramycin inhalation solution 300 mg / 4 mL) is a slightly different formulation approved on 12 October 2012 (Chiesi USA, NDA-201820) that requires the PARI LC Plus Nebulizer but a different air compressor. The Applicant has certified that the patent for TOBI is currently in effect and will expire 19 October 2014. Marketing for the proposed product (Kitabis Pak) is not intended to begin until after this patent expires.

No new clinical studies have been performed by the Applicant in support of this NDA. The majority of the material submitted in this NDA relate to biopharmaceutics and chemistry, manufacturing and controls (CMC). Sections submitted for clinical review include proposed labeling, a literature review of the safety of tobramycin and an analysis report of MIC data from isolates of 101 cystic fibrosis patients between 2011 and 2013.

Prior interactions between the Agency and the Applicant included preliminary recommendations sent on 21 September 2012 to the Applicant (PARI) regarding the proposed NDA package under IND 115904. A Type B pre-NDA meeting was held 27 September 2012 to further discuss the Agency's recommendations. Among the areas of discussion were details required for a biowaiver request as well as CMC and product quality microbiology requirements.

### 3. CMC/Device

Mark Seggel was the CMC Reviewer for this application. Steven Donald, M.S. was the Product Quality Microbiology Reviewer. Their reviews are summarized as follows.

The tobramycin inhalation solution included with the Kitabis Pak is manufactured (b) (4)

Critical quality attributes include pH (6 (b) (4)) and osmolality (130-200 mOsmol/kg), which were established for patient tolerability, and sterility. Other quality attributes include tobramycin assay and impurities, and an assay for sodium chloride. The specification is based on the current USP monograph for tobramycin inhalation solution.

No product quality microbiology deficiencies were identified based upon the information provided for the manufacturing process and process controls. The drug product, tobramycin inhalation solution, has a 24-month expiration dating period when stored as directed (identical to the RLD):

Store in a refrigerator at 2°-8°C (36°-46°F). Protect from intense light. Upon removal from the refrigerator, or if refrigeration is unavailable, tobramycin inhalation solution pouches (opened or unopened) may be stored at room temperature (up to 25°C/77°F) for up to 28 days.

Three lots of drug product (03312A, 03312B and 03312C) have been placed on the stability protocol under accelerated (25 °C, 60% RH) and long-term (2-8 °C, ambient RH) conditions with testing through 36 months. The Applicant commits to include the first three commercial batches to the stability protocol and one annual batch thereafter. Post-approval microbiological testing on the stability protocol is satisfactory.

Because the inhalation solution is packaged in single-dose, semi-permeable, LDPE ampules in laminated foil pouches (4 ampules / pouch), extractables testing was performed by the (b) (4). At the Agency's request, the applicant also initiated leachables testing on the registration stability samples at 17 months. This data was also reviewed and found to be acceptable by Dr. Amy Ellis, in her Pharmacology/Toxicology Review.

The materials of the LC Plus nebulizer are (b) (4) formulation and processing, and no other chemicals have been added (e.g., plasticizers, fillers, color additives, cleaning agents, mold release agents, etc.), with the following two exceptions: the (b) (4) material used to manufacture the cup and the (b) (4). PARI has confirmed that the changes in materials noted apply to all PARI LC Plus nebulizers, not just those provided in the convenience kit, and CDRH-ODE has confirmed that, from their perspective, the changes are acceptable since the materials are already qualified for use in the related nebulizer, PARI LC Sprint.

Although all facilities (drug substance manufacturing, drug product manufacturing and drug product testing) currently have acceptable CGMP status, the overall CDER Office of Compliance recommendation is still pending final inspection of the Catalent Woodstock site. A final device recommendation from CDRH-OC is also currently pending regarding the shelf-life of the nebulizer. Please refer to Mark Seggel's review dated 17 July 2014 for additional details. Although his preliminary recommendation is not to approve given the pending reports mentioned above, he anticipates submitting a final recommendation with additional labeling comments in an addendum.

## 4. Nonclinical Pharmacology/Toxicology

Amy Ellis Ph.D. was the Pharm/Tox Reviewer for this application. She concluded that from the nonclinical pharmacology standpoint the NDA can be approved. For details, please refer to her review dated 7 May 2014.

The applicant did not conduct any nonclinical studies in support of this NDA. Dr. Ellis stated that unless the impurity profile or leachables present in this formulation of tobramycin differs significantly from the previous formulation, there are no pharmacology/toxicology issues with this drug. In addition, the labeling does not differ from the listed drug and there are only a few editorial changes recommended from the pharmacology/toxicology perspective.

On 22 July 2014, upon receipt from the Applicant of the results of leachables testing for the drug product, Dr. Ellis submitted a follow-up review. With the exception of (b) (4), leachables were either not detected, below the level of quantitation, or below the target limits proposed by the Applicant. Dr. Ellis, however, had no special concerns regarding the toxicity of (b) (4) or the proposed reporting thresholds.

## 5. Clinical Pharmacology/Biopharmaceutics

Sandra Suarez Sharp, PhD was the Biopharmaceutics Reviewer and Ryan Owen, PhD was the Clinical Pharmacology Reviewer for this application.

Dr. Suarez's review focused on the acceptability of the biowaiver request supported by the following data:

- Comparative in vitro characterization (population BE analysis) for unit dose content, delivered dose and particle size distribution.
- Qualitative and quantitative formulation comparison between the proposed drug product and TOBI.
- Comparative physicochemical properties (e.g. pH, osmolarity).

The Applicant provided data to demonstrate that the conditions of use, route of administration, dosage form, strength, the components and composition, physicochemical properties and in vitro characterization of the proposed drug product are the same as those of TOBI. From the Biopharmaceutics perspective, Dr. Suarez concluded that the in vitro characterization of the product and nebulizer adequately demonstrates the bioequivalence of Kitabis Pak to the referenced drug TOBI and therefore recommended approval. For details, please refer to her review dated 14 July 2014.

Dr. Owen's review focused on proposed labeling. For additional details please also refer to Section 12 of this review and his Clinical Pharmacology Review dated 15 August 2014.

## 6. Clinical Microbiology

Peter Coderre, PhD was the Clinical Microbiology Reviewer for this application. His review focused on 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. Dr. Coderre was concerned, however, about the validity of the data due to the use of E-test for the susceptibility methodology and the number of the specimen samples that were taken as throat swabs rather than as sputum samples.

Dr. Coderre recommended approval contingent upon the Applicant's acceptance of his changes to the Microbiology subsection (12.4) of the Package Insert. For details, please refer to his review dated 03 June 2014.

## 7. Clinical/Statistical- Efficacy

Shrimant Mishra, MD, MPH was the Clinical Reviewer and Christopher Kadoorie, PhD was the Statistical Reviewer for this NDA. Dr. Kadoorie indicated that no statistical review was needed for this application as there were no clinical studies submitted in this NDA. As a 505(b)(2) application the Applicant is relying on the Agency's prior determination of efficacy and safety of the listed drug.

In his recommendation, Dr. Mishra stated that the risk/benefit assessment for this drug product has been demonstrated and was supported by prior evidence and experience with TOBI. In addition, based on a literature review of the safety of inhaled tobramycin, there is no substantial additional risk associated with this co-packaged product when used as prescribed for the proposed indications. Therefore, from the Clinical perspective, Dr. Mishra recommends approval for this application contingent upon several revisions to the proposed labeling. Please refer to his review for additional details.

## 8. Safety

As requested by the Agency at the 27 September 2012 pre-NDA meeting the Applicant submitted a post-marketing safety update that consisted of a search of recently published literature as well as the FDA Adverse Event Reporting Systems (FAERS) and Manufacture and User facility Device Experience (MAUDE) databases.

The FAERS review found 104 reports related to inhalational use of tobramycin. Many of these reports, however, appeared to either represent events often related to the underlying disease (e.g. pulmonary function test decreased) or events already described in the current prescribing information. There were no reports of AEs found in the MAUDE search for a nebulizer device that involved use of inhaled tobramycin.

In the Applicant's literature review, 13 unique studies of nebulized tobramycin or tobramycin for inhalation were found to have reported data for adverse events. Similar to the FAERS review, the findings in these studies largely represented events typical of the underlying disease or events that had previously been described.

For additional details regarding the safety assessment of the proposed drug product and recommended labeling revisions, refer to the Clinical review by Dr. Mishra.

## **9. Advisory Committee Meeting**

There was no Advisory Committee Meeting for this application.

## **10. Pediatrics**

Of note, the intended population is consistent with TOBI, which is approved for use in patients six years of age and older. The Applicant has requested a full waiver of the requirement for a pediatric assessment because Kitabis Pak does not represent a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration.

## **11. Other Relevant Regulatory Issues**

The Applicant has acknowledged that the patent for TOBI is currently in effect and will expire 19 October 2014. Marketing of Kitabis Pak would therefore not be permitted until after the TOBI patent expires.

No clinical studies/trials were conducted in support of this NDA. Therefore, no inspection request was sent to the Office of Scientific Investigations (OSI).

There are otherwise no additional relevant regulatory issues for this application.

## **12. Labeling**

DMEPA and OPDP recommended approval of the proprietary name, Kitabis Pak. The review team concurs.

Revisions to the Applicant's proposed label, however, were substantial. The initial proposed label was not submitted in PLR format and required resubmission. Sections 5 and 6, which were based on the current TOBI label, required additional updating in order to harmonize with other inhaled tobramycin products. In consultation with Bindi Nikhar, MD, Office of Combination Products, revisions were also proposed in order to improve consistency with other related combination products. Additional recommendations were provided from DMEPA by Aleksander Winiarski, PharmD, to help reduce risk of medication errors. Details are provided in his review dated 24 June 2014 for details. Please also refer to the OPDP review of the package insert by Christine Corser, PharmD, RAC dated 16 July 2014.

A review of Patient Labeling was done by Shawna Hutchins, MPH, BSN, RN (DMPP) and with suggested revisions provided to the Patient Package Insert (PPI) and Instructions for Use (IFU). Details are provided in her review dated 25 July 2014.

## 13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I concur with the assessments made by the review team and recommend the approval of this NDA contingent upon the finalization of device recommendations from CDRH-OC and an acceptable EES status following the Catalent Woodstock site inspection. Approval would be tentative pending the expiration of the TOBI patent on 19 Oct 2014.

- Risk Benefit Assessment

Since the application for this proposed co-package of a previously approved drug product and a cleared device consists of no new clinical studies, the risk-benefit assessment for this application focused on the establishment of bioequivalence, product quality and labeling. The rationale for the development of the Kitabis Pak is to limit the probability that an incorrect nebulizer is used with the tobramycin inhalation solution and improves convenience for patients. Substantial changes were made to the proposed package insert in order to comply with current labeling standards and improve consistency with other related combination products.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

Not applicable.

- Recommendation for other Postmarketing Requirements and Commitments

Not applicable.

- Recommended Comments to Applicant

No additional comments.

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/s/  
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BENJAMIN D LORENZ  
08/18/2014

## CLINICAL REVIEW

Application Type 505(b)(2)  
Application Number(s) NDA 205433  
Priority or Standard Standard

Submit Date(s) 10/2/2013  
Received Date(s) 10/23/2013  
PDUFA Goal Date 08/23/2014  
Division / Office DAIP

Reviewer Name(s) Shrimant Mishra, MD, MPH  
Review Completion Date 08/08/2014

Established Name Tobramycin inhalation  
solution/Pari LC Plus Reusable  
Nebulizer  
(Proposed) Trade Name Kitabis Pak  
Therapeutic Class Antimicrobial/Aminoglycoside  
Applicant Pulmoflow, Inc.

Formulation(s) Nebulized Solution  
Dosing Regimen 300MG/5ML BID  
Indication(s) Cystic Fibrosis patients with  
*P.aeruginosa*  
Intended Population(s) Ages 6 and up

## Table of Contents

|          |   |           |
|----------|---|-----------|
| <b>1</b> | <b>RECOMMENDATIONS/RISK BENEFIT ASSESSMENT .....</b>                                | <b>3</b>  |
| 1.1      | Recommendation on Regulatory Action .....   | 3         |
| 1.2      | Risk Benefit Assessment.....  | 3         |
| 1.3      | Recommendations for Postmarket Risk Evaluation and Mitigation Strategies ...        | 3         |
| 1.4      | Recommendations for Postmarket Requirements and Commitments .....                   | 3         |
| <b>2</b> | <b>INTRODUCTION AND REGULATORY BACKGROUND .....</b>                                 | <b>4</b>  |
| 2.1      | Product Information .....   | 4         |
| 2.2      | Tables of Currently Available Treatments for Proposed Indications .....             | 4         |
| 2.3      | Availability of Proposed Active Ingredient in the United States .....               | 4         |
| 2.4      | Important Safety Issues With Consideration to Related Drugs.....                    | 4         |
| 2.5      | Summary of Presubmission Regulatory Activity Related to Submission .....            | 4         |
| 2.6      | Other Relevant Background Information .....   | 5         |
| <b>3</b> | <b>ETHICS AND GOOD CLINICAL PRACTICES.....</b>                                      | <b>5</b>  |
| 3.1      | Submission Quality and Integrity .....  | 5         |
| 3.2      | Compliance with Good Clinical Practices .....                                       | 5         |
| 3.3      | Financial Disclosures.....  | 5         |
| <b>4</b> | <b>SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES .....</b> | <b>5</b>  |
| 4.1      | Chemistry Manufacturing and Controls .....  | 5         |
| 4.2      | Clinical Microbiology.....  | 5         |
| 4.3      | Preclinical Pharmacology/Toxicology .....   | 5         |
| 4.4      | Clinical Pharmacology .....   | 6         |
| <b>5</b> | <b>SOURCES OF CLINICAL DATA.....</b>  | <b>6</b>  |
| <b>6</b> | <b>REVIEW OF EFFICACY.....</b>  | <b>6</b>  |
|          | Efficacy Summary.....   | 6         |
| <b>7</b> | <b>REVIEW OF SAFETY.....</b>  | <b>6</b>  |
|          | Safety Summary .....  | 6         |
| <b>8</b> | <b>POSTMARKET EXPERIENCE.....</b>   | <b>6</b>  |
| <b>9</b> | <b>APPENDICES .....</b>   | <b>10</b> |
| 9.1      | Literature Review/References .....  | 10        |
| 9.2      | Labeling Recommendations .....  | 10        |
| 9.3      | Advisory Committee Meeting.....   | 10        |

## **1 Recommendations/Risk Benefit Assessment**

### **1.1 Recommendation on Regulatory Action**

The recommendation is for approval. This product is a co-package that includes a tobramycin inhalation solution that is (b) (4) Reference Listed Drug (RLD), TOBI, as well as the reusable nebulizer for which the solution is labeled for use, the Pari LC Plus. No new indications were proposed, no new clinical studies were performed and no significant new information was noted in the submitted safety update.

### **1.2 Risk Benefit Assessment**

The associated risks and benefits of this co-package are marginal compared to the individual components themselves. The rationale for marketing Kitabis Pak is to limit the probability that an incorrect nebulizer is used with the tobramycin inhalation solution and improves convenience for patients by having both the solution and nebulizer in one package. No significant new risk has been introduced with the co-package. It should also be noted that this co-package benefited from significant revision (at the division level) of the submitted label in order to bring it into conformance with current regulatory labeling standards; the original submitted label was simply a replica of the current TOBI label.

### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

None

### **1.4 Recommendations for Postmarket Requirements and Commitments**

None

## **2 Introduction and Regulatory Background**

### **2.1 Product Information**

This is a co-package of an inhalation solution of tobramycin and the Pari LC Plus nebulizer. The solution contains the same qualitative and quantitative characteristics as the RLD, TOBI, which itself is labeled for use with the LC Plus nebulizer. It is indicated for management of cystic fibrosis patients with *Pseudomonas aeruginosa*.

### **2.2 Tables of Currently Available Treatments for Proposed Indications**

Currently available similar therapies include the RLD (TOBI) itself, Bethkis (also a tobramycin inhalation solution with a slightly different concentration that requires the PARI LC Plus Nebulizer but a different air compressor), TOBI Podhaler (a tobramycin inhalation powder used with a specific inhaler), and Cayston (an aztreonam nebulized solution with a similar indication). (b) (4)

### **2.3 Availability of Proposed Active Ingredient in the United States**

Tobramycin is an aminoglycoside and available in the United States in inhalational form as discussed above. It is also available in parenteral form and as part of ophthalmic solutions.

### **2.4 Important Safety Issues With Consideration to Related Drugs**

With aminoglycosides as a class there are concerns about ototoxicity, nephrotoxicity, teratogenicity, and neuromuscular blockade. In particular, some TOBI subjects have suffered from tinnitus and hearing loss. Also, TOBI contains a warning for bronchospasm and has been associated with local oropharyngeal effects including voice alterations, taste alterations, and oropharyngeal pain. It should be noted that many of the adverse events listed for TOBI, such as cough or hemoptysis, can be both associated with the study drug and the underlying disease itself, and it is difficult to separate out such associations.

### **2.5 Summary of Presubmission Regulatory Activity Related to Submission**

A meeting was held between the applicant and DAIP on Sep. 27, 2012 (responses to premeeting questions had been provided to the applicant prior to the meeting). At this meeting, the plan and rationale for copackaging was explained. Also, the parameters of the safety update were outlined. The bulk of the discussion focused on CMC-related activities, including stability and cascade impaction testing.

## **2.6 Other Relevant Background Information**

None

## **3 Ethics and Good Clinical Practices**

### **3.1 Submission Quality and Integrity**

No clinical studies were submitted. Because the applicant based its proposed label on the outdated TOBI label, the review team had significant input for the revision and modernization of the proposed label so that it was in accordance with current PLR format and regulatory practices.

### **3.2 Compliance with Good Clinical Practices**

No clinical studies were performed

### **3.3 Financial Disclosures**

No clinical studies were performed

## **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

### **4.1 Chemistry Manufacturing and Controls**

*Please see the review performed by Dr. Mark Seggel*

### **4.2 Clinical Microbiology**

*Please see the review performed by Dr. Peter Coderre*

### **4.3 Preclinical Pharmacology/Toxicology**

*Please see the review performed by Dr. Amy Ellis*

#### **4.4 Clinical Pharmacology**

*Please see the review performed by Dr. Ryan Owen*

### **5 Sources of Clinical Data**

*No clinical studies were performed in support of this application.*

#### **5.1 Tables of Studies/Clinical Trials**

#### **5.2 Review Strategy**

#### **5.3 Discussion of Individual Studies/Clinical Trials**

### **6 Review of Efficacy**

#### **Efficacy Summary**

*No clinical studies were performed in support of this application.*

### **7 Review of Safety**

#### **Safety Summary**

*No new clinical studies were performed in support of this application.*

### **8 Postmarket Experience**

At a pre-NDA meeting held on Sept. 27, 2012, DAIP asked that the company submit a post marketing safety update for tobramycin inhalation solution. Specifically, the Division requested a search of the recent published literature as well as of the FDA Adverse Event Reporting Systems (AERS) and Manufacturer and User facility Device Experience (MAUDE) databases in order to highlight any potential new safety findings that may affect the review and/or labeling. The following brief summary highlights the applicant's findings. Of note, the applicant was also asked to submit a recent analysis of

changes in tobramycin MICs for relevant pathogens- please see the microbiology review by Dr. Peter Coderre for further details.

### **AERS Search**

The sponsor contracted out this safety review to another organization, (b) (4), using a specialized software known as CLAERITY, searched all AERS reports of tobramycin in a primary suspect drug role and with either route of administration specified as inhaled or with no specified dosage form noted, in all patients in the last 3 years of available data (July 1<sup>st</sup> 2009—Aug. 27<sup>th</sup>, 2012). A multitude of drug/trade names were included in the search including TOBI, tobramycin inhalation solution, and tobramycin powder for inhalation.

1059 AERS reports met the prespecified query, although only 104 of these reports specified the route to be inhalation. The mean age of subjects (when known) in the eligible reports was in the 40's however in the subset of reports where inhalation was actually specified, the median age was 30. The majority of reports came from the 10-30 and 60-80 year old age groups. Most cases originated in the US (all the inhaled cases did), with consumers (roughly 60%) and physicians being the primary reporters. Virtually all cases were classified as serious with hospitalizations, death, and other as the primary outcome.

When evaluating reported adverse events in the 104 inhalation subjects, the reported terms (reported by more than one subject) generally fell into one of three categories- potentially representative of underlying disease (pneumonia, infective pulmonary exacerbation of cystic fibrosis, pulmonary function test decreased, etc.), adverse events already reported/encompassed by current labeling (deafness, tinnitus, bronchospasm, etc.), or both. The division has attempted to revise the proposed labeling in order to strip out many preferred terms that are more likely to be related to underlying disease; the adverse event profile is much more abridged than in the current TOBI labeling. From the standpoint of this reviewer, the adverse event profile noted in these 104 inhalation reports is in line with the division's proposed labeling. The adverse event profile in the larger AERS subset (the 1059 reports which is inclusive of subjects where the route of administration is not specified) is difficult to interpret given uncertainty about the route of administration of drug and the underlying condition treated; this was not evaluated in great detail by this reviewer.

### **MAUDE Search**

For the MAUDE search, medical device AE reports submitted between April 29, 2010 and April 29, 2013 were evaluated. The database was queried using a search for the free-text term "tobramycin" and for the years 2010, 2011, 2012, and 2013. All reports from this query with a "Date Report Received" of April 29, 2010 or later were screened to identify any reports that mentioned tobramycin use in combination with a nebulizer device.

A total of 495 AE reports were retrieved for 2010–2013 from the MAUDE database, and of these, 477 were received during the last three years of available data (April 29, 2010–April 29, 2013). These 477 reports were screened to identify any reports involving tobramycin use in combination with a nebulizer device. None of the 477 medical device AE reports mentioning tobramycin also involved a nebulizer or any other inhalation device.

## Literature Review

The applicant contracted out its literature review to a company known as (b) (4). The review used PubMed and Embase to research the safety of tobramycin for inhalation in articles published between January 2011 and April 2013. Also, a manual check of the reference lists of all accepted papers was performed to supplement the above electronic searches. Citations and abstracts underwent initial screening for eligibility using the following criteria:

### Inclusion Criteria

- Published in the English language
  - Accepted study type with at least 1 outcome of interest:
    - Clinical trial or observational study investigating the use of tobramycin for inhalation (or no specific dosage form reported) with at least 1 safety outcome reported
- OR
- Case reports or case series of an adverse drug reaction thought to be potentially related to use of tobramycin for inhalation (or no specific dosage form reported)
- OR
- Nonclinical studies reporting pharmacokinetics or drug-drug interactions involving tobramycin for inhalation (or no specific dosage form reported)

### Exclusion Criteria

- Meta-analyses
- Reviews, editorials, or commentaries that do not contain safety-related case reports
- Animal or *in vitro* studies
- Treatment guidelines
- Articles on pathophysiology, etiology, or diagnosis
- Foreign-language studies
- No tobramycin treatment
- Dosage form of tobramycin specified as anything other than inhalation

- No safety data reported separately for patients using tobramycin for inhalation

Once this first round of screening was performed, the eligible papers were fully downloaded and evaluated by 2 independent reviewers. Papers deemed eligible after this second process underwent data extraction; the extracted data was used to summarize the important safety findings in each paper for the purposes of the submitted literature review.

Thirteen unique studies of tobramycin for inhalation were noted to have reported on adverse events. Almost all these studies included subjects with cystic fibrosis, and most were conducted outside of the US. Nine of the studies included data about nebulized tobramycin, while three studies exclusively studied tobramycin inhalation powder (a single study did not specify the route of inhalation). A few of the identified studies represented comparison trials used in the NDA submissions for other inhaled tobramycin products in this indication (such as studies supporting TOBI Podhaler and Bethkis).

Similar to the AERS review, the safety profile of nebulized/inhaled tobramycin as outlined in these studies either represented underlying disease or is essentially described in the draft labeling.

As has already been discussed, the division has currently taken the applicant's proposed label and revised it significantly in order to fit the PLR format and consolidate and harmonize disparate sections of the original label. In doing so, sections 5 and 6 of the originally proposed label (which was based on current TOBI labeling) have undergone significant revisions. Importantly, many reported adverse events in the original label were removed in the currently proposed iteration of the label in order to focus on adverse events that potentially have a more plausible connection with the drug itself rather than the underlying disease. In some cases, such as with adverse events like headache, dizziness, and vomiting, it can be difficult to know whether such events represent underlying disease or a drug effect, and thus the currently proposed labeling maintains a certain level of subjectivity. Despite this, nothing the sponsor has presented in its postmarketing safety update would require further alteration of the currently proposed label (as revised by the Division).

## **9 Appendices**

### **9.1 Literature Review/References**

Please see the current TOBI label for further information.

### **9.2 Labeling Recommendations**

Extensive labeling changes were made primarily to bring the originally proposed label (which was based on the current TOBI labeling) into conformance with current regulatory labeling practices. This significant editorial changes were made and the label was put into PLR format. Please see the draft label for further details.

### **9.3 Advisory Committee Meeting**

*No Advisory Committee meeting was held for this application*

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/s/  
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SHRIMANT MISHRA  
08/18/2014