

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205433Orig1s000

PHARMACOLOGY REVIEW(S)

Tobramycin Inhalation Solution. Twice daily, patients nebulize 5 ml of the solution for inhalation; a total of 10 ml potentially providing up to a (b) (4)/day exposure to (b) (4). This is (b) (4) to the qualification threshold proposed by the Product Quality Research Institute for leachables in orally inhaled and nasal drug products, based on safety thresholds for known toxicants. As there are no special concerns regarding the toxicity of (b) (4) (e.g., neither mutagen nor potent respiratory sensitizer), the proposed threshold that would allow up to (b) (4) (b) (4)/day exposure is considered adequate. Of note, the 3 registration batches to determine stability of the Tobramycin Inhalation Solution to be included in Kitabis™ contained concentrations of (b) (4) ranging from (b) (4).

Stability Testing on Tobramycin 300 mg/5 mL Inhalation Solution Drug Product		
Company: PARI Pharma GmbH	Protocol No.: TTP-PCT-M0002.02	Phase: Ad Hoc Leachables Testing
Product: Tobramycin Inhalation Solution	Lot No.: 03312A Manufacture Date: 13 Nov 2012	Timepoint: 17 Months (Approximately)
Strength: 300 mg/5 mL (60 mg/mL)	Packaging: 4 x 5 mL LDPE vials in a foil pouch	Condition/Orientation: 5°C/Ambient RH/Random Pull Date: 06 Jun 2014
Method: PDR-ATM-PCT-0001 v1.0, "Analysis of Leachables in Tobramycin Inhalation Solution by GC-MS"		
Specifications: Report Results		
Component Name	Test Date	Results
Methyl-2,2-dimethyl-3-hydroxypropionate (221139)	6 June 14	ND
[REDACTED]		<LOQ
N-Butylbenzenesulfonamide (NBSA)		ND
[REDACTED]		ND
Bis(2-ethylhexyl)phosphate (DEHP)		ND
Bis(2-ethylhexyl)phosphate, also referred to as dioctyl phosphate (DDOP)		BL
[REDACTED]		ND
[REDACTED]		BL
[REDACTED]		BL
[REDACTED]		AL

ND = Not Detected

LOQ = Limit of Quantitation

Target Limit = [REDACTED]

BL = Below Limit

AL = Above Limit

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/s/

AMY L ELLIS
07/24/2014

WENDELYN J SCHMIDT
07/25/2014

PHARMACOLOGY/TOXICOLOGY REVIEW
NDA 205433 Kitabis™
(Tobramycin Inhalation Solution and PARI LC® Plus Reusable Nebulizer)

DATE: 5/7/14

TO: Frances LeSane
Chief Project Manager, DAIP
and
File, NDA 205433

FROM: Amy L. Ellis, Ph.D.
Pharmacologist, DAIP

THROUGH: Wendelyn Schmidt, Ph.D.
Supervisory Pharmacologist, DAIP

RE: Pharmacology/Toxicology Review of NDA 205433, Kitabis™
(Tobramycin Inhalation Solution and PARI LC® Plus Reusable Nebulizer)

This NDA is for a Convenience Kit containing one PARI LC® Plus Reusable Nebulizer (an approved device) and Tobramycin Inhalation Solution. The Tobramycin Inhalation Solution is manufactured to (b) (4) TOBI® and contains (b) (4) tobramycin in sodium chloride solution (b) (4) water for injection), (b) (4)

The PARI LC® Plus Reusable Nebulizer is the same as that approved for TOBI® administration. The sponsor, Pulmoflow, Inc. (Richmond, VA) represented by Lachman Consultant Services, Inc. (Westbury, NY), is requesting approval for the same indication as the reference listed drug TOBI®, management of cystic fibrosis patients with *Pseudomonas aeruginosa*. The sponsor also followed the monograph "Tobramycin Inhalation Solution USP" and used it to set product specifications. The inhalation solution will be packaged in vials made of low density polyethylene (b) (4) which is used to manufacture containers for other products administered via inhalation and marketed in the U.S.

NDA 205433 does not require a pharmacology/toxicology review. The sponsor did not conduct any additional nonclinical toxicology studies to support the current NDA. The Division agreed that nonclinical studies would not be necessary as long as there are no impurities or degradation products in Tobramycin Inhalation Solution packaged with the PARI LC® Plus Reusable Nebulizer that exceed ICH qualification threshold levels or the levels in comparable marketed products such as TOBI® or generic solutions of tobramycin for inhalation. Thus far, it appears that there are no impurities or degradation products in the current product that require qualification via nonclinical testing, according to the Chemistry Reviewer. The sponsor has requested that the Agency rely on its findings of safety and effectiveness for the approved product TOBI® to support NDA 205433 for Tobramycin Inhalation Solution and PARI LC® Plus Reusable Nebulizer, as permitted under section 505(b)(2) of the FD&C Act.

The pharmacologist has no objection to the approval of NDA 205433 for Tobramycin Inhalation Solution and PARI LC® Plus Reusable Nebulizer, provided that the Chemistry Reviewer agrees with the sponsor's assessment that the product contains no impurities or degradation products that need to be qualified via nonclinical testing. The label for this product should, as appropriate, be consistent with the labels for TOBI® (NDA 050753) and the TOBI Podhaler (NDA 201688). The label for Tobramycin Inhalation Solution and PARI LC® Plus Reusable Nebulizer was written in PLR format, so a few editorial changes were made to the nonclinical data discussions in Sections 8.1 and 13 for clarity. None were scientifically substantive. The first paragraph of Section 8.1 contains clinical information; the Medical Officer may want to consider adding some additional language here, or refer to the Warnings section regarding the congenital deafness observed in offspring from women who received streptomycin.

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/s/

AMY L ELLIS
05/08/2014

WENDELYN J SCHMIDT
05/22/2014