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RESEARCH**

*APPLICATION NUMBER:*

**201688s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	August 20, 2012
<b>From</b>	Eileen Navarro, MD
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA #</b>	NDA 201, 688 (IND 64409)
<b>Supplement#</b>	S000
<b>Applicant</b>	Novartis Pharmaceuticals Corporation
<b>Date of Submission</b>	21-DEC-2011
<b>PDUFA Goal Date</b>	19-OCT-2012
<b>GRMP Goal Date</b>	16-SEP-2012
<b>Proprietary / Established (USAN) names</b>	TOBI Podhaler™ Tobramycin
<b>Dosage forms / Strength</b>	Four - 28 mg capsules administered twice daily, in two inhalations per tablet for a total of 4 capsules (8 inhalations) per dose in a 28 day cycle of treatment followed by 28 days off treatment.
<b>Proposed Indication(s)</b>	Treatment of CF patients with chronic <i>P. aeruginosa</i> infections.
<b>Recommended:</b>	<i>Approval with Postmarketing Requirements</i>

- **Summary:**

The drug product proposed in this NDA505b(1) submission, TOBI® Podhaler™ (tobramycin inhalation powder), is a dry powder formulation, intended as alternative to the currently marketed product tobramycin solution in saline. It is the first antimicrobial powder developed for any respiratory indication. At issue is whether the this alternative formulation, delivered via a novel device, affords similar benefits and assures similar safety as the identical drug substance marketed as a liquid solution, so as to serve as a treatment alternative for cystic fibrosis in patients ages 6 and older, who are chronically colonized with *Pseudomonas aeruginosa*. One of two placebo controlled trials concludes significant benefit using the FEV1 increment endpoint at 1 month, whereas the other trial failed recruitment goals and the difference favoring the new drug was not statistically conclusive of a benefit. In a large comparative safety study, cough and upper airway adverse reactions, none serious, were seen with TIP compared to TOBI. A similar increment in FEV1 was seen with TIP compared to the standard of care, and notwithstanding a greater need for rescue oral antimicrobial, rates of hospitalization and intravenous antibiotic therapy were similar between the two study arms. Three deaths, all in the TIP arm are attributed to breakthrough infectious exacerbation of CF. Following treatment, more resistant *P. aeruginosa* isolates were seen in the TIP arm; the increment in MIC for this small number of isolates was disproportionately higher than seen with TOBI. There are no minimum inhibitory concentrations (MIC) standards established for resistance in *P. aeruginosa* airway infections; resistance as defined by MICs for systemic infections has not been shown to correlate with treatment failures in CF and other airway infections. Increased adherence was not seen with TIP, compared to TOBI, despite the shorter drug administration time, and the portability and simplified maintenance of the inhaler. A single placebo-controlled (2301) study provides a direct measure of treatment effect in this drug development program, for an endpoint demonstrated to correlate in the long term with increased survival. The applicant also concludes noninferior efficacy of TIP relative to TOBI,

using the same pulmonary function endpoint, in a comparative trial (2302) although the margin of benefit was not justified sufficiently *apriori*. The Agency, however, has adequate experience in placebo controlled trials for this endpoint in this indication, to put this proposed margin for a treatment effect in context, as it has in the past<sup>1</sup>. Nonetheless, data from the NDA provides little information on pulmonary drug delivery from the inhaler in patients with limited pulmonary flows (such as in pediatric patients with FEV1 <40% of predicted or the frail elderly). As well there is limited long term follow up to assess impact of resistance development, no instructions for use demonstrated to predictably limit errors of use, limited long terms outcome assessment for clinically relevant endpoints such as exacerbation rate, hospitalization, rescue antimicrobial use and death. Given the limits of information in the drug development program, the Division should require postmarketing studies that fill the gap in information, and craft a label that conveys these gaps. Foreign regulators in the EU required a postmarketing study in pediatric patients that would assess usability in the younger age group and assess long term efficacy of the product over 48 weeks (6 cycles). The applicant plans a “real world study in the US (Study C2407), contingent upon US approval that would compare safety ( (b)(4) ) and other clinical efficacy endpoints (b)(4) with an approved inhaled product”. I recommend that the (b)(4) also be assessed in this study and that the comparator be TOBI .

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<sup>1</sup> Response to GAO inquiry – NI margins for antifungal agents

## Cross Discipline Team Leader Review Template

### 1. Introduction

The drug product proposed in this NDA505b(1) submission, TOBI® Podhaler™ (tobramycin inhalation powder), is a dry powder formulation is intended as an alternative to the currently marketed inhalation solution TOBI® with the same active ingredient, tobramycin. The applicant of this New Drug Application (NDA) presents two placebo controlled trials conducted mainly in pediatric patients and one comparative safety trial largely in adults, to provide evidence of the safety and efficacy of TOBI Podhaler (referred to as TIP in the rest of this document), a powder formulation of tobramycin for the management of cystic fibrosis patients with *Pseudomonas aeruginosa*. TIP is a dry powder packaged in a hard capsule. Drug delivery for this new powder formulation of tobramycin is via a handheld, manually operated, breath-activated T-326 dry powder inhaler (DPI). The inhaler is intended for replacement every 7 days. TIP is to be administered as four capsules equaling 112 mg of tobramycin twice daily for repeated cycles of 28 days on drug and 28 days off drug. TIP is marketed in Canada, Chile, Colombia, Germany, The Netherlands, Norway, Denmark, Ireland, and the UK countries.

### 2. Background

CF is an orphan disease, there are 30 000 patients in the US with this autosomal recessive disease. The ion transport defects in cystic fibrosis (CF) lead to low volumes of fluids essential to the function of mucosal surfaces and secretory organs. In the lung, the small volumes of thick viscid mucus predispose to chronic infections with *Pseudomonas aeruginosa*. Antibiotics to treat *P. aeruginosa* pulmonary infections have resulted in improved pulmonary function (as measured by FEV1) and a corollary increase in survival in patients with CF. As treatment of episodic exacerbations of CF with antipseudomonal antibiotics has proven beneficial, the chronic intermittent use of antibiotics for chronic suppression of *P. aeruginosa* is standard of care. CFF guidelines strongly recommend chronic use of inhaled tobramycin in CF patients 6 years and older with FEV1% predicted <40 to 69<sup>2</sup> and persistent *P. aeruginosa* in airway cultures. The CFF also recommends inhaled tobramycin use in asymptomatic CF patients 6 year older; however, the evidence supporting this recommendation is weaker. The duration of 'chronic' therapy is not defined. In clinical practice, patients generally remain on cycled inhaled antibacterial drugs indefinitely.

Three drugs, belonging to three different antimicrobial classes, are approved for the treatment of *Pseudomonas aeruginosa* in CF.

Ciprofloxacin, a fluoroquinolone antimicrobial, is approved for the treatment of acute pulmonary exacerbations in CF patients 5-17 years, based on a comparative study demonstrating improved symptoms of exacerbation in 67 patients who receive d ciprofloxacin 10mg/kg/dose q8h IV for one week followed by ciprofloxacin tablets 20mg/kg/dose q12h to

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<sup>2</sup> Flume PA, O'Sullivan BP, Robinson KA, et al Cystic Fibrosis Pulmonary Guidelines: Chronic Medications for Maintenance of Lung Health Am J Respir Crit Care Med 176:957-969, 2007

complete 10-21 days treatment. Concerns regarding chondrotoxicity limit long term use of this drug class in pediatric patients.

For the chronic suppression of *P. aeruginosa*, liquid formulations of the aminoglycoside tobramycin (TOBI<sup>®</sup>) and the monobactam aztreonam (Cayston<sup>®</sup>) are approved for use by inhalation with nebulizers. TOBI<sup>®</sup> (NDA 50 753) is specifically indicated for use with the Pari LC Plus nebulizer and Pulmo-aide air compressor. The treatment dose is 300 mg inhaled delivered in 15 minutes twice daily for repeated cycles of 28 days on drug and 28 days off drug. Cayston<sup>®</sup> (NDA 50814) is formulated for inhalation via the Altera nebulizer (75mg delivered in 2-3 minutes per dose TID). Although the indication of use for Cayston differs from TOBI<sup>c</sup> (to improve respiratory symptoms in CF patients with *P. aeruginosa* for a single 28 day cycle of therapy), in the clinical setting, it is often used in a manner similar to TOBI<sup>®</sup>. The intravenous formulations of both drugs are also used off-label to treat acute exacerbations of CF. Cayston was filed as a 505b2, allowing FDA to rely in part on the finding of effectiveness of the parenteral formulation aztreonam; in the EU, the drug is labeled for use only in patients 18 and older. In the current NDA, the applicant similarly references the effectiveness of TOBI although studies supporting TIP efficacy were conducted and stand on their own.

Given the microenvironment in thick dry mucus secretions of the CF patient, the chronic use of inhaled hypertonic saline is recommended by the CF foundation to improve lung function and to reduce exacerbations (<sup>ibid Flume</sup>). A concern regarding the use of this tobramycin powder formulation, is that the powder may be less efficacious than TOBI<sup>®</sup> which is a liquid solution in saline. While the serum pharmacokinetic studies indicate that absorption of the powder TIP is more efficient than that of the inhaled solution, activity at the endobronchial and peripheral airways is not known to correlate with serum PK of topically acting products in CF (<sup>ibid Flume</sup>).

### 3. CMC/Device

TIP is the first antimicrobial powder formulation developed for inhalation and similar to TOBI, is intended for chronic use. Dr. Mark Seggel finds that sufficient information is provided in the NDA to assure the identity, strength, quality, purity, and potency of the drug product and that the labels have provide requisite information (e.g., description, how supplied, storage statements). He recommends approval pending favorable GMP inspections as reflected in a recommendation from the Office of Compliance. The quality product microbiology reviewer Stephen E. Langille, Ph.D. likewise recommends approval.

Drug Substance: The drug substance, tobramycin, is identical to that used to manufacture the approved TOBI (NDA 50-753, referenced by the applicant, who also provides references the DMF of the two drug substance manufacturers, (b) (4) (DMF (b) (4)) and (b) (4) (DMF (b) (4)). There are no inspectional issues related to the drug substance.

Drug Product: The API Tobramycin is a (b) (4) antibiotic mixed (b) (4) with sulfuric acid (salt forming and pH adjustment), DSPC and calcium chloride (wall forming) and perflubron (poreforming agent (b) (4)). Spray drying yields (b) (4) particles with porous structure which is dispensed into capsules. TOBI<sup>®</sup> Podhalert<sup>™</sup> capsules each contain 28 mg of tobramycin powder (corresponds to a target delivered dose of 25.5 mg tobramycin per capsule).

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