

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

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**PHARMACOLOGY REVIEW(S)**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION**

Application number: 201,688  
Supporting document/s: SD-0  
Applicant's letter date: 12/20/11  
CDER stamp date: 12/21/11  
Product: TOBI® Podhaler™ (tobramycin inhalation powder)  
Indication: Management of cystic fibrosis patients with *P. aeruginosa*  
Applicant: Novartis Pharmaceuticals Corporation  
Review Division: Anti-Infective Products  
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# 1 Executive Summary

## 1.1 Introduction

The TOBI® Podhaler™ is a dry powder for inhalation (DPI) formulation of tobramycin. It is intended to be used in the same manner as the marketed product TOBI®, which is a saline solution of tobramycin administered using a nebulizer. The DPI would be more convenient for patients than the nebulizer currently approved for use with TOBI® (e.g., increased portability, decreased maintenance). The sponsor conducted repeat dose studies in rats (up to 26 weeks) and dogs (up to 4 weeks) to bridge this new formulation to the original TOBI®. In addition, they have provided data on the DPI excipient DSPC to demonstrate its safety when given via inhalation.

## 1.2 Brief Discussion of Nonclinical Findings

The data from repeat dose toxicity studies in rats and dogs suggest that TIP (Tobramycin Inhalation Powder) is unlikely to cause greater systemic or pulmonary toxicity related to tobramycin than the currently marketed drug TOBI®. There were no clinical signs of tobramycin toxicity in either species in any of the inhalation toxicity studies conducted with TIP. Histopathologic findings in the respiratory tissues and kidneys of the rats dosed with TIP for up to 26 weeks were similar to those observed following chronic treatment with TOBI® solution given by nebulization. Some of these (minimal squamous hyperplasia in the larynx and at the broncho-alveolar junction, nasal inflammation) are not uncommonly observed in rats after inhalation of aerosols. Other respiratory findings included accumulation of alveolar macrophages containing pigment/basophilic debris, degeneration of olfactory epithelium, and minimal respiratory metaplasia of the olfactory mucosa. Kidney changes identical to those observed in older rats as age-related nephropathy were observed at a greater incidence in TIP-treated rats than controls. There were fewer findings in dogs dosed with TIP for up to 4 weeks. Inflammation of the mucosa in the nasal turbinates was mostly minimal to mild. Minimal tubular degeneration/regeneration was observed in the kidney and was associated with inflammation.

The highest inhaled dose of tobramycin base used in the 26-week rat study was approximately 38 mg/kg/day and the highest inhaled dose of tobramycin base used in the 4-week dog study was approximately 28 mg/kg/day. The pulmonary deposited doses for rats and dogs are assumed to be 10% and 20% of the inhaled dose, respectively. In humans, the dose regimen is to inhale the contents of 4 capsules of TIP twice daily. Each capsule contains 28 mg of tobramycin base, for a total of 224 mg daily. This is an inhaled dose of 11.2 mg/kg in a child weighing 20 kg.

## 1.3 Recommendations

### 1.3.1 Approvability

The pharmacologist has no objection to the approval of the TOBI® Podhaler™.

### 1.3.2 Additional Non Clinical Recommendations

None.

### 1.3.3 Labeling

The Pregnancy (8.1) and Carcinogenesis, Mutagenesis, Impairment of Fertility (13.1) sections of the label for this product will follow the TOBI® label. This is appropriate because both products contain the same active ingredient given by the same route of administration using the same schedule. Clinical exposure appears similar between the products when they are used as described in the label.

## 2 Drug Information

### 2.1 Drug

CAS Registry Number: 32986-56-4 (for tobramycin)

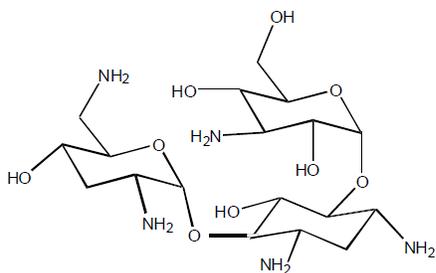
Generic Name: Tobramycin Inhalation Powder

Code Names: TIP (Tobramycin Inhalation Powder), TPI (Tobramycin Powder for Inhalation), TBM100C, TBM100

Chemical Name: O-3-amino-3-deoxy- $\alpha$ -D-glycopyranosyl-(1 $\rightarrow$ 4)-O-[2,6-diamino-2,3,6-trideoxy- $\alpha$ -D-ribo-hexopyranosyl-(1 $\rightarrow$ 6)]-2-deoxy-L-streptamine

Molecular Formula/Molecular Weight: C<sub>18</sub>H<sub>37</sub>N<sub>5</sub>O<sub>9</sub> / 467.52 (as free base)

Structure of Free Base



Pharmacologic Class: Aminoglycoside antimicrobial

### 2.2 Relevant INDs, NDAs, and DMFs

IND 64,409 (TIP); NDA 50-753 and IND 46,945 (both for TOBI); DMFs (b) (4) and (b) (4) (held by both current manufacturers of the drug substance)

### 2.3 Drug Formulation

Each capsule of TIP contains (from the submission):

**Table 2-1 Composition of one TBM100 28 mg Inhalation powder hard capsule**

| Ingredient                                        | Theoretical amount per capsule (mg) <sup>2</sup> | Function                              | Reference to standards                                |
|---------------------------------------------------|--------------------------------------------------|---------------------------------------|-------------------------------------------------------|
| <b>Capsule fill</b>                               |                                                  |                                       |                                                       |
| Tobramycin                                        | 28.0                                             | Active pharmaceutical ingredient      | USP, Ph.Eur., Novartis monograph [3.2.S.4.1]          |
| Sulfuric acid                                     | (b) (4)                                          | Salt forming agent and pH adjuster    | NF, Ph.Eur.                                           |
| 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) | (b) (4)                                          | Wall forming agent                    | Novartis monograph [3.2.P.4.1]                        |
| Calcium chloride                                  | (b) (4)                                          | Wall forming agent                    | Added as calcium chloride dihydrate, USP, Ph.Eur., JP |
| Water for Injection <sup>1</sup>                  | (b) (4)                                          | Processing aid                        | USP, Ph.Eur.                                          |
| Perflubron <sup>1</sup>                           | (b) (4)                                          | Processing aid and pore forming agent | USP                                                   |
| <b>Capsule fill weight</b>                        |                                                  |                                       |                                                       |
| (b) (4)                                           | (b) (4)                                          | (b) (4)                               | See Table 2-2, Novartis monograph [3.2.P.4.1]         |
| <b>Total capsule weight</b>                       | <b>105.6<sup>2</sup></b>                         |                                       |                                                       |

<sup>1</sup> Processing aid removed to residual levels. (b) (4)

**Table 2-2 Capsule shell composition**

| Capsule shell component | Percentage per capsule | Function | Reference to standards                                                                         |
|-------------------------|------------------------|----------|------------------------------------------------------------------------------------------------|
| Hypromellose<br>(b) (4) | (b) (4)                | (b) (4)  | USP, Ph.Eur.<br>USP, Ph.Eur.<br>NF, 2009/10/EC<br>USP, Ph.Eur.<br>See Table 2-3<br>NF, Ph.Eur. |
| (b) (4)                 |                        |          |                                                                                                |

**Table 2-3 Qualitative composition of Printing Ink - Blue**

| Printing ink component | Reference to standards                                                                            |
|------------------------|---------------------------------------------------------------------------------------------------|
| (b) (4)                | USP/NF, Ph.Eur.<br>21CFR, 2008/128/EC<br>NF<br>21CFR, 2008/128/EC<br>USP, Ph.Eur.<br>USP, Ph.Eur. |

## 2.4 Comments on Novel Excipients

This appears to be the first product for inhalation to contain the excipients DSPC (1, 2-distearoyl-SN-glycero-3-phosphocholine) and calcium chloride. According to FDA's public database of inactive ingredients, DSPC is present in an approved IV solution containing liposomes and calcium chloride is present in a variety of approved oral, ophthalmic, and topical products as well as solutions for injection. In addition to the repeat dose toxicity studies in rats and dogs that have vehicle control groups and TIP groups where these excipients are present, the sponsor also conducted genotoxicity studies with DSPC alone and repeat dose toxicity studies with the DPI vehicle containing both DSPC and calcium chloride. DSPC was negative in the Ames assay at concentrations up to 5000 µg/plate, did not induce chromosome aberrations in Chinese Hamster ovary cells at concentrations up to 1000 µg/ml, and did not induce micronucleus formation in the bone marrow of mice given up to 25 mg/kg via IP injection. In repeat dose toxicity studies with TIP, dogs received the DSPC/CaCl vehicle daily for 4 weeks and rats received it daily for 26 weeks (at inhaled doses of about 12 mg/kg/day for both species) without apparent toxicity. In addition, dogs that received the vehicle weekly for 26 weeks (about 80 mg/kg inhaled dose on the first day and about 14 mg/kg for the rest of the study) demonstrated no histopathologic changes in respiratory tissues and no changes in clinical chemistry parameters. DSPC and calcium chloride appear to be reasonably safe for repeated inhalation at the levels used in TIP.

## 2.5 Comments on Impurities/Degradants of Concern

The sponsor has proposed a specification for S-lyso-PC of not more than (b) (4) (w/w) in the TIP drug product. S-lyso-PC is a lyso-lecithin and a degradation product of DSPC that forms spontaneously during storage. It was of concern because lyso-lecithins can induce bronchoconstriction. The sponsor provided data from guinea pigs demonstrating that S-lyso-PC had a similar potency for inducing bronchoconstriction as the better characterized P-lyso-PC (an endogenous substance) and there was a no-effect level for this activity. One of the phase 3 clinical trials of TIP was on hold for several months due to the level of S-lyso-PC in the placebo powder that the sponsor wanted to use. The sponsor chose to qualify the level of S-lyso-PC in the placebo by conducting a 2 week study in rats (to prevent having to manufacture additional placebo powder). The placebo powder used for the rat study was spiked to a level of (b) (4) S-lyso-PC and the TIP contained (b) (4) S-lyso-PC. These test articles were well tolerated by the rats and not associated with biologically significant differences in respiratory function. Microscopic changes in respiratory tract tissues of the animals that received TIP with (b) (4) S-lyso-PC were consistent with those seen in rats exposed to tobramycin alone (e.g., TOBI®). The Division agreed that the sponsor could resume the clinical trial using placebo powder that contained (b) (4) S-lyso-PC and that the TIP drug product could be qualified at a level of S-lyso-PC (b) (4) (a specification that the sponsor asked the Division to consider when the rat study report was submitted).

## 2.6 Proposed Clinical Population and Dosing Regimen

TIP will be labeled for use by cystic fibrosis patients  $\geq 6$  years of age with *P. aeruginosa*. The recommended daily dose of TIP is to inhale the contents of 4 capsules twice daily for 28 days using the Podhaler device. After a 28-day period off drug, the on/off cycle is repeated chronically.

## 2.7 Regulatory Background

IND 64,409 for the TIP drug product (now called the TOBI® Podhaler™) was first submitted in May 2003 by Chiron Corporation. This sponsor was also the holder of approved NDA 50-753 for TOBI® (tobramycin solution for inhalation) after obtaining it from the original applicant, PathoGenesis. Chiron was acquired by Novartis Pharmaceuticals Corporation, the current sponsor of this application and holder of the original TOBI® NDA. An advisory committee for the TOBI® Podhaler™ is scheduled for 9/5/12 to discuss clinical issues regarding the product. The nonclinical data for TIP have not suggested any particular safety concerns.

# 3 Studies Submitted

## 3.1 Studies Reviewed

Pharmacokinetic Study of Inhaled and Intravenous Tobramycin in the Rat (Study No. N002938B)

Summary of 14 Day Inhalation Toxicity Study in Rats of Vehicle Dry Powder Aerosol (DSPC and Calcium Chloride) Compared to Air Control (Study No. 26088)

Summary of 14 Day Inhalation Toxicity Study in Dogs of Vehicle Control Dry Powder Aerosol (DSPC and Calcium Chloride) Compared to Air Control (Study No. 26089)

Summary of Six Month Inhalation Toxicity Study in Dogs of Vehicle Dry powder Aerosol (DSPC and Calcium Chloride) Compared to Air Control (Study No. LS\_2005\_021\_S)

### **3.2 Studies Not Reviewed**

All nonclinical pharmacology/toxicology studies submitted in the NDA were reviewed.

### **3.3 Previous Reviews Referenced**

The following studies were reviewed under IND 64,409:

Original IND (SD-6) and SD-9:

28-Day Inhalation Toxicity Study of Tobramycin Dry Powder in the Rat (Study No. MN103741) (Draft report in SD-6, final report in SD-9)

Pilot Dose Range-Finding Inhalation Toxicity and Pharmacokinetic Study of Tobramycin Dry Powder in Dogs (Study No. MN103742) (SD-9)

7-Day Inhalation Toxicity Study of Tobramycin Dry Powder in Dogs (Study No. MN103743) (Draft report in SD-6, final report in SD-9)

Evaluation of a Test Article (DSPC) in the *Salmonella typhimurium/Escherichia coli* Plate Incorporation Mutation Assay in the Presence and Absence of Induced Rat Liver S-9 (Study No. 0745-2140) (SD-6)

Test for Chemical Induction of Chromosome Aberrations in Cultured Chinese Hamster Ovary (CHO) Cells With and Without Metabolic Activation (Study No. 0745-3110) (SD-6)

*In Vivo* Test for Chemical Induction of Micronucleated Polychromatic Erythrocytes in Mouse Bone Marrow Cells (Study No. 0745-1521) (SD-6)

SD-36:

6-Month Inhalation Toxicity Study of TPI in the Rat (Study No. N103748)

28-Day Inhalation Toxicity Study of TPI in Dogs (Study No. N103749)

SD-96:

TBM100C: Pulmosphere placebo powder spiked with (b) (4) S-lyso-PC: A 2-week inhalation toxicity study of a powder formulation in the rat with a 4-week recovery period (Study No. N0670618)

## 4 Pharmacology

### 4.1 Primary Pharmacology

Antimicrobial activity mediated by perturbation of protein synthesis. Tobramycin binds to the 30 S subunit of the ribosomal complex, causing misreading of mRNA and premature termination of translation.

### 4.2 Secondary Pharmacology

N/A

### 4.3 Safety Pharmacology

Safety pharmacology studies were not conducted with this product. Tobramycin, like other aminoglycosides, is known to cause neuromuscular blockade at high doses.

## 5 Pharmacokinetics/ADME/Toxicokinetics

Tobramycin is not well absorbed when given orally. Some drug is absorbed through the lung when it is administered via inhalation, but in human cystic fibrosis patients, blood levels are not as great as if the same dose was given parenterally. Bioavailability of aerosolized drug appears to be higher in healthy rats than human CF patients. Tobramycin is excreted unchanged by the kidney.

### 5.1 PK/ADME

**Pharmacokinetic Study of Inhaled and Intravenous Tobramycin in the Rat** (Study No. N002938B)

**Summary:** This GLP study was conducted at (b) (4) in 1998 with the TOBI solution for nebulization (Lot No. PT-96-0064-B) and not TIP. It compared serum pharmacokinetic parameters between tobramycin given intravenously with inhaled tobramycin.

Sprague-Dawley rats were assigned to receive a single dose of tobramycin via inhalation or IV. Three rats were sampled at each time point. The tables below illustrate the sampling scheme for rats at each targeted dose (one lower, one higher) for each route of administration:

| <b>Inhalation</b>          |                                         |                    |                          |
|----------------------------|-----------------------------------------|--------------------|--------------------------|
| <b>Target Dose (mg/kg)</b> | <b>Blood Sampling Times</b>             | <b>Lung Tissue</b> | <b>Number of Animals</b> |
| 1.7                        | <b><i>5 min.</i></b>                    | <b>5 min.</b>      | 3                        |
|                            | <b><i>10 min. (End of Exposure)</i></b> | <b>10 min.</b>     | 3                        |
|                            | 5 min., 60 min.                         | 60 min.            | 3                        |
|                            | 10 min., 2 hrs.                         | 2 hrs.             | 3                        |
|                            | 15 min., 4 hrs.                         | 4 hrs.             | 3                        |
|                            | 30 min., 8 hrs.                         | 8 hrs.             | 3                        |
|                            | 12 hrs.                                 | 12 hrs.            | 3                        |
|                            | 24 hrs.                                 | 24 hrs.            | 3                        |
| 14.9                       | <b><i>10 min.</i></b>                   | <b>10 min.</b>     | 3                        |
|                            | <b><i>40 min.</i></b>                   | <b>40 min.</b>     | 3                        |
|                            | <b><i>90 min. (End of Exposure)</i></b> | <b>90 min.</b>     | 3                        |
|                            | 5 min., 60 min.                         | 60 min.            | 3                        |
|                            | 10 min., 2 hrs.                         | 2 hrs.             | 3                        |
|                            | 15 min., 4 hrs.                         | 4 hrs.             | 3                        |
|                            | 30 min., 8 hrs.                         | 8 hrs.             | 3                        |
|                            | 12 hrs.                                 | 12 hrs.            | 3                        |
|                            | 24 hrs.                                 | 24 hrs.            | 3                        |

Italicized and bold font timepoints represent blood collection during the inhalation period. All other timepoints were post inhalation.

| <b>Intravenous</b>         |                             |                    |                          |
|----------------------------|-----------------------------|--------------------|--------------------------|
| <b>Target Dose (mg/kg)</b> | <b>Blood Sampling Times</b> | <b>Lung Tissue</b> | <b>Number of Animals</b> |
| 1.7                        | 5 min., 60 min.             | 60 min.            | 3                        |
|                            | 10 min., 2 hrs.             | 2 hrs.             | 3                        |
|                            | 15 min., 4 hrs.             | 4 hrs.             | 3                        |
|                            | 30 min., 8 hrs.             | 8 hrs.             | 3                        |
|                            | 12 hrs.                     | 12 hrs.            | 3                        |
|                            | 24 hrs.                     | 24 hrs.            | 3                        |
| 14.9                       | 5 min., 60 min.             | 60 min.            | 3                        |
|                            | 10 min., 2 hrs.             | 2 hrs.             | 3                        |
|                            | 15 min., 4 hrs.             | 4 hrs.             | 3                        |
|                            | 30 min., 8 hrs.             | 8 hrs.             | 3                        |
|                            | 12 hrs.                     | 12 hrs.            | 3                        |
|                            | 24 hrs.                     | 24 hrs.            | 3                        |

Serum and lung tissue were shipped to the study sponsor (PathoGenesis Corporation, Seattle, WA) for analysis. Tobramycin levels were measured using a validated HPLC assay with UV detection.

The pulmonary deposited doses in the table below were estimated using the following equation:

$$\frac{\text{Aerosol concentration of test article (mg/L)} \times \text{Minute Volume (L/min)} \times \text{Exposure Duration (min)}}{\text{Body Weight (kg)}} \times \text{Deposition Fraction}$$

The rats that received the lower dose of tobramycin via inhalation were exposed to nebulized drug for 10 minutes and the animals that received the higher dose were exposed for 90 minutes.

Other parameters were determined based on data collected during the study (e.g., analysis of test atmosphere, body weights). Minute Volume was determined by the equation  $MV = 0.8 \text{ mL/min/g body weight}$ . Mean particle size ranged from (b) (4) with a geometric standard deviation range of 1.9-2.2. The mean concentration of tobramycin base in the test atmosphere was 0.57 mg/L (mean total mass concentration was 1.02 mg/L).

The sponsor used a deposition fraction of 0.5. The FDA generally uses a more conservative deposition fraction of 0.1 for rats. Regardless, the data demonstrated significant absorption of tobramycin after administration via inhalation.

### Serum Pharmacokinetics of Tobramycin in Rats after IV or Inhalational Dosing

| Parameter                 | Low Dose    | High Dose    | Low Dose    | High Dose    |
|---------------------------|-------------|--------------|-------------|--------------|
|                           | Intravenous |              | Inhalation  |              |
| Dose (mg/kg)              | 1.80        | 15.26        | 2.40        | 21.60        |
| $t_{1/2\lambda}$ (hr)     | 0.28 ± 0.01 | 0.69 ± 0.13  | 0.24 + 0.00 | 1.09 + 0.09  |
| $C_{\text{max}}$ (µg/mL)  | 6.28 ± 0.18 | 53.47 ± 4.40 | 4.21 ± 0.57 | 19.72 ± 1.47 |
| $AUC_{\infty}$ (µg·hr/mL) | 3.19 ± 0.08 | 31.03 ± 0.62 | 3.45 ± 0.24 | 32.72 ± 1.46 |

Serum half life of tobramycin is relatively short. The maximum concentrations achieved in lung tissues were 12.90 µg/g (low) and 293.07 µg/g (high). These came 0.4 hours (low) and 1.54 hours (high) after dosing was completed. These maximum lung concentrations fell to steady state levels about 2 hours after  $C_{\text{max}}$  was achieved. Lung levels were similar after these time points through 24 hours after the end of dosing (last sample time in this study). The mean levels were 7.21 and 31.89 µg/g for the low and high dose group, respectively. Other studies have demonstrated that tobramycin accumulates in the lung after repeated inhalational dosing and its half life in this tissue is long. The data in this single dose study are consistent with these observations.

The sponsor estimated that the bioavailability of tobramycin given via inhalation was approximately 0.81 at the low dose and 0.74 at the high dose. Tobramycin is not orally bioavailable, so absorption of tobramycin given via inhalation must have occurred in respiratory tissues.

Although the DPI dosage form of TOBI may not share identical PK parameters with the nebulized solution, experimental data in rats and dogs suggests that they are similar, with significant levels of tobramycin remaining in the lungs several weeks after dosing ends.

## 6 General Toxicology

### 6.1 Single-Dose Toxicity

Single dose studies were not conducted with TIP and were not necessary.

### 6.2 Repeat-Dose Toxicity

#### Summary of 14 Day Inhalation Toxicity Study in Rats of Vehicle Dry Powder Aerosol (DSPC and Calcium Chloride) Compared to Air Control

|                                     |                                                                                                                                         |
|-------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| Study no.:                          | LS-2005-048                                                                                                                             |
| Study report location:              | Testing laboratory archives                                                                                                             |
| Conducting laboratory and location: |  (b) (4)                                              |
| Date of study initiation:           | 1/22/02                                                                                                                                 |
| GLP compliance:                     | OECD                                                                                                                                    |
| QA statement:                       | Yes                                                                                                                                     |
| Drug, lot #, and % purity:          | DPI Vehicle (93.4% DSPC and 6.6% CaCl), Lot No. A1290. No information regarding purity was provided, but moisture content was 3.8% w/w. |

#### Key Study Findings

When administered daily for 14 days to rats, the DPI vehicle (93.4% DSPC and 6.6% CaCl) was not associated with any clinical or histopathologic changes compared to the air control. The inhaled dose was approximately 28 mg/kg/day. For rats, the pulmonary deposited dose is assumed to be approximately 10% of the inhaled dose.

## Methods

- Doses: Air Control and Vehicle Control; 25 mg/kg/day target inhaled dose; achieved inhaled dose was calculated to be 28.38 mg/kg/day.
- Frequency of dosing: Daily for 60 minutes
- Route of administration: Inhalation- Nose only
- Formulation/Vehicle: 93.4% DSPC and 6.6% CaCl
- Species/Strain: Sprague-Dawley rats
- Number/Sex/Group: 6
- Age: 9 weeks at initiation of dosing
- Weight: 247-302 g (males), 189-244 g (females) at initiation of dosing
- Satellite groups: 2/sex for vehicle control recovery  
2/sex for TK
- Unique study design: These data were extracted from a 14 day rat study (662487) previously performed by (b) (4) for another inhaled product. The air and vehicle control groups are relevant for TIP. The animals were dosed daily for 14 days. The recovery period was 14 days long. Rats were exposed using nose only inhalation for about 60 minutes each day. Aerosols of the test articles were generated using a rotating brush generator ( (b) (4) ) supplied with filtered fresh air. Chamber air flow rate was about 20 L/min. Sacrifice and necropsy of the main study animals occurred on the day following the last dose of drug. Blood samples for TK were drawn from the vehicle-treated rats on Days 1 and 14 prior to dosing and 2 and 4 hours after exposure. These were analyzed for the presence of the active test article. The active test article was not specifically identified in this summary report since only the data from the air and vehicle controls are presented, but material in the Appendix suggests that it was amphotericin B.
- Deviation from study protocol: Not provided in this study summary.

## Observations and Results

### Test Article Doses/Concentrations in Test Atmospheres

During each exposure period, several samples were taken for gravimetric measurement of aerosol concentration using Durapore filters. These were weighed and some were chemically analyzed for presence of test article (unknown, data not used in this report on vehicle). Aerosol particle size distribution was measured using a (b) (4)

(b) (4) on exposure days 2, 7, and 14.

The mean total mass aerosol concentration of the vehicle in the test atmosphere was 0.90 mg/L.

Particle sizes in the test atmospheres were in the respirable range for rats with mean mass aerodynamic diameter of (b) (4) and (b) (4) of the aerosol particles were below (b) (4).

Inhaled dose was calculated using this equation:

$$\frac{\text{Mean Aerosol concentration of test article (mg/L)} \times \text{Respiratory Minute Volume (L/min)} \times \text{Exposure Duration (min)}}{\text{Body Weight (kg)}}$$

For the respiratory minute volume, the sponsor used Guyton's formula:  
 $2.1 \times \text{Body Weight (g)}^{0.75} / 1000$

For rats, the FDA/CDER generally uses a deposition factor of 0.1 to estimate a pulmonary deposited dose from the inhaled dose.

The achieved inhaled dose of the vehicle was calculated to be 28.38 mg/kg, close to the target inhaled dose.

### **Mortality**

Observed twice daily at the beginning and end of the work day.

There was no mortality.

### **Clinical Signs**

On treatment days, rats were examined prior to exposure, continuously during exposure, and about 2 hours after exposure. They were examined at least once daily on non-dosing days.

No clinical signs of toxicity were observed in the vehicle-treated rats.

### **Body Weights**

Recorded weekly and on the day of necropsy.

Over the 14-day dosing period, body weight gain was reduced slightly in the vehicle group compared to air controls (mean gain of  $51 \pm 7$  g vs.  $44 \pm 9$  g for males and  $23 \pm 9$  vs.  $18 \pm 8$  for females).

**Feed Consumption**

Determined weekly.

There were no significant differences in food consumption between the vehicle and air control groups.

**Ophthalmoscopy**

Performed on all main study and recovery animals prior to dosing, on Day 13 of treatment, and near the end of the recovery period.

No treatment-related changes were observed.

**Hematology**

Blood samples for hematology were drawn from main study animals on Day 14 of treatment and from recovery animals near the end of the recovery period.

There were no treatment-related differences between the groups.

**Clinical Chemistry**

Blood samples for clinical chemistry evaluations were drawn at the same time as those for hematology.

There were no treatment-related differences between the groups.

**Urinalysis**

Urine samples were collected from main study animals on Day 13 in the early morning prior to dosing and from recovery animals near the end of the recovery period.

There were no treatment-related differences between the groups.

**Gross Pathology**

No notable findings in the vehicle control group compared to air controls.

**Organ Weights**

The following were weighed (paired organs weighed together): adrenals, brain, epididymides, heart, kidneys, lungs, liver, ovaries, pituitary, prostate, spleen, salivary glands, testes, thymus, thyroid, uterus.

No treatment-related differences between the groups.

## Histopathology

Adequate Battery- Yes. A standard battery of tissues was collected as well as an expanded panel of respiratory tissues including bronchial and cervical lymph nodes, larynx, lungs (transverse sections of all 5 lobes including major bronchioles), 4 transverse sections of the nasal cavity, pharynx, and trachea (2 anterior transverse sections and 1 longitudinal posterior section including the carina and 1 transverse posterior section at point of transection).

Peer Review- Yes

## Histological Findings

Nothing that appeared related to the vehicle.

## Summary of 14 Day Inhalation Toxicity Study in Dogs of Vehicle Dry Powder Aerosol (DSPC and Calcium Chloride) Compared to Air Control

|                                     |                                                                                                                                                                |
|-------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Study no.:                          | LS-2005-049                                                                                                                                                    |
| Study report location:              | Testing laboratory archives                                                                                                                                    |
| Conducting laboratory and location: |  (b) (4)                                                                    |
| Date of study initiation:           | 1/23/02                                                                                                                                                        |
| GLP compliance:                     | OECD                                                                                                                                                           |
| QA statement:                       | Yes                                                                                                                                                            |
| Drug, lot #, and % purity:          | DPI Vehicle (93.4% DSPC and 6.6% CaCl), Lot Nos. A1289, A1290, and A1291. No information regarding purity was provided, but moisture content was 3.8-4.1% w/w. |

## Key Study Findings

When administered daily for 14 days to dogs, the DPI vehicle (93.4% DSPC and 6.6% CaCl) was not associated with any clinical or histopathologic changes compared to the air control. The inhaled dose was approximately 25 mg/kg/day. For dogs, the pulmonary deposited dose is assumed to be approximately 20% of the inhaled dose.

## Methods

- Doses: Air Control and Vehicle Control; 25 mg/kg/day target inhaled dose; achieved inhaled dose was calculated to be 25.13 mg/kg/day.
- Frequency of dosing: Daily for 17-27 minutes (depending on gravimetric concentration of test article)
- Route of administration: Inhalation- mouth only using face mask
- Formulation/Vehicle: 93.4% DSPC and 6.6% CaCl
- Species/Strain: Beagle dogs
- Number/Sex/Group: 2
- Age: 8 months at initiation of dosing
- Weight: 5.9-7.9 kg (males), 5.0-7.2 kg (females) at initiation of dosing
- Satellite groups: 2/sex for vehicle control recovery
- Unique study design: These data were extracted from a 14 day dog study (662508) previously performed by (b) (4) for another inhaled product. The air and vehicle control groups are relevant for TIP. The animals were dosed daily for 14 days. The recovery period was 14 days long. Dogs were exposed using face masks with mouth tubes for about 17-27 minutes each day (depending on gravimetric concentration of test article). Aerosols of the test articles were generated using a rotating brush generator ( (b) (4) ) supplied with filtered fresh air. Chamber air flow rate was about 12 L/min. Sacrifice and necropsy of the main study animals occurred on Day 15 or 16. Blood samples for TK were drawn on Days 1 and 14 prior to dosing and 2, 4, 8, 12, and 24 hours after exposure, and once daily during recovery. These were analyzed for the presence of the active test article (it was not present above the level of quantification). The active test article was not specifically identified in this summary report since only the data from the air and vehicle controls are presented.
- Deviation from study protocol: Not provided in this study summary.

## Observations and Results

### Test Article Doses/Concentrations in Test Atmospheres

During each exposure period, several samples were taken for gravimetric measurement of aerosol concentration using Durapore filters. These were weighed and some were chemically analyzed for presence of test article (unknown, data not used in this report on vehicle). Aerosol particle size distribution was measured using a (b) (4)

(b) (4) on exposure days 2, 7, and 13.

The mean total mass aerosol concentration of the vehicle in the test atmosphere was 1.52 mg/L.

Particle sizes in the test atmospheres were in the respirable range for rats with mean mass aerodynamic diameter of (b) (4) and (b) (4) of the aerosol particles were below (b) (4).

Inhaled dose was calculated using this equation:

$$\frac{\text{Mean Aerosol concentration of test article (mg/L)} \times \text{Respiratory Minute Volume (L/min)} \times \text{Exposure Duration (min)}}{\text{Body Weight (kg)}}$$

For the respiratory minute volume, the sponsor used 5 L/min.

For dogs, the FDA/CDER generally uses a deposition factor of 0.2 to estimate a pulmonary deposited dose from the inhaled dose.

The achieved inhaled dose of the vehicle was calculated to be 25.13 mg/kg, close to the target inhaled dose.

### **Mortality**

Observed twice daily at the beginning and end of the work day.

There was no mortality.

### **Clinical Signs**

On treatment days, rats were examined prior to exposure, continuously during exposure, and 1-2 hours after exposure.

Slight salivation was observed in the vehicle control dogs. This is not an uncommon finding in dogs when DPIs are administered.

### **Body Weights**

Recorded weekly and on the day of necropsy.

No significant difference between groups.

**Feed Consumption**

Recorded daily.

There were no significant differences in food consumption between the vehicle and air control groups.

**Ophthalmoscopy**

Performed prior to dosing and near the end of the treatment and recovery periods.

No treatment-related changes were observed.

**ECG**

Performed on Days 1 and 14 prior to dosing and 1.5 and 4 hours after exposure.

There were no treatment-related changes.

**Hematology**

Blood samples for hematology were drawn prior to the initiation of dosing, on Day 14 of treatment and on Day 14 of recovery.

There were no treatment-related differences between the groups.

**Clinical Chemistry**

Blood samples for clinical chemistry evaluations were drawn at the same time as those for hematology.

There were no treatment-related differences between the groups.

**Urinalysis**

Urine samples were collected overnight prior to dosing and on Days 13/14 of treatment and Days 13/14 of recovery.

There were no treatment-related differences between the groups.

**Gross Pathology**

No notable findings in the vehicle control group compared to air controls.

## Organ Weights

The following were weighed (paired organs weighed together): adrenals, brain, heart, kidneys, lungs, liver/gallbladder, ovaries, pancreas, pituitary, prostate, spleen, submaxillary salivary glands, testes, thymus, thyroid/parathyroid, uterus.

No treatment-related differences between the groups.

## Histopathology

Adequate Battery- Yes. A standard battery of tissues was collected as well as an expanded panel of respiratory tissues including bronchial and retropharyngeal lymph nodes, larynx, lungs (transverse sections of each midlobe including major bronchioles), anterior and posterior sections of the nasal cavity, pharynx, and trachea (1 longitudinal section including the carina and 1 transverse section at point of transection).

Peer Review- Not noted in summary

## Histological Findings

Nothing that appeared related to the vehicle.

## Summary of Six Month Inhalation Toxicity Study in Dogs of Vehicle Dry powder Aerosol (DSPC and Calcium Chloride) Compared to Air Control

|                                     |                                                                                                                                         |
|-------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| Study no.:                          | LS_2005_021_S                                                                                                                           |
| Study report location:              | Testing laboratory archives                                                                                                             |
| Conducting laboratory and location: | (b) (4)                                                                                                                                 |
| Date of study initiation:           | 8/4/05                                                                                                                                  |
| GLP compliance:                     | No                                                                                                                                      |
| QA statement:                       | No                                                                                                                                      |
| Drug, lot #, and % purity:          | DPI Vehicle (93.4% DSPC and 6.6% CaCl), Lot Nos. 4007T and 4042T were used for the study. No information regarding purity was provided. |

## Key Study Findings

When administered weekly for 6 months to dogs, the DPI vehicle (93.4% DSPC and 6.6% CaCl) was not associated with any clinical or histopathologic changes compared to the air control. On the first day, the inhaled dose was approximately 82 mg/kg and subsequently weekly doses averaged 14 mg/kg. For dogs, the pulmonary deposited dose is assumed to be approximately 20% of the inhaled dose.

## Methods

Doses: Air Control and Vehicle Control; 80 mg/kg target inhaled dose for Day 1 and 16 mg/kg target inhaled dose for Days 8-83; achieved inhaled doses were calculated to be 81.55 mg/kg for Day 1 and an average of 14.00 mg/kg for the rest of the study.

Frequency of dosing: Once weekly for 30 minutes

Route of administration: Inhalation- mouth only using face mask

Formulation/Vehicle: 93.4% DSPC and 6.6% CaCl

Species/Strain: Beagle dog

Number/Sex/Group: 4

Age: Approximately 5 months at arrival (acclimated to lab for 3 weeks prior to study initiation)

Weight: 6.6-8.3 kg (males), 5.1-8.1 kg (females) at arrival

Satellite groups: 3/sex for vehicle control recovery

Unique study design: These data were extracted from a 6 month dog study (664678) previously performed by (b) (4) for another inhaled product (amphotericin B). The air and vehicle control groups are relevant for TIP. The animals were dosed weekly for a total of 27 exposures. The recovery period was 2 months long. The dogs were restrained in slings (with feet on the ground) while wearing closed face masks. Aerosols of the test articles were generated using a rotating brush generator (b) (4) supplied with filtered fresh air. Air flow rate was at least 4 L/min for each exposure line. Sacrifice and necropsy of the main study animals occurred on the day following the last dose of drug.

Deviation from study protocol: Not provided in this study summary.

## Observations and Results

### Test Article Doses/Concentrations in Test Atmospheres

During each exposure period, several samples were taken for gravimetric measurement of aerosol concentration using Durapore (b) (4) filters. These were weighed and some were chemically analyzed for amphotericin B. Aerosol particle size distribution was measured during each exposure session using a (b) (4)

The mean total mass aerosol concentration of the vehicle in the test atmosphere was 4.88 mg/L on Day 1 and 0.97 mg/L for the rest of the study.

Particle sizes in the test atmospheres were in the respirable range for dogs with mean mass aerodynamic diameters of (b) (4) on Day 1 and (b) (4) (b) (4) for the rest of the study. On Day 1, (b) (4) of the aerosol particles were below (b) (4) and on the other dosing days, (b) (4) were below this threshold.

Inhaled dose was calculated using this equation:

$$\frac{\text{Mean Aerosol concentration of test article (mg/L)} \times \text{Respiratory Minute Volume (L/min)} \times \text{Exposure Duration (min)}}{\text{Body Weight (kg)}}$$

For the respiratory minute volume, the sponsor used a value of 4 L/min based on in-house data.

For dogs, the FDA/CDER generally uses a deposition factor of 0.2 to estimate a pulmonary deposited dose from the inhaled dose.

Trace levels of amphotericin B (below level of quantification) were found on some filters from both the vehicle and air control groups.

On Day 1, the achieved inhaled dose of the vehicle was calculated to be 81.55 mg/kg and on Days 8-183 the average achieved inhaled dose of vehicle was 14.00 mg/kg. These are close to the target inhaled doses.

### **Mortality**

Observed twice daily at the beginning and end of the work day.

There was no mortality.

### **Clinical Signs**

On treatment days, dogs were examined prior to exposure, continuously during exposure, and 1-2 hours after exposure. They were examined at least once daily on non-dosing days.

Slight salivation was observed in the vehicle control dogs. This is not an uncommon finding in dogs when DPIs are administered.

### **Body Weights**

Recorded weekly and on the day of necropsy.

There were no significant differences in body weight gain between the vehicle and air control groups.

**Feed Consumption**

Determined daily.

There were no significant differences in food consumption between the vehicle and air control groups.

**Ophthalmoscopy**

Performed on all main study and recovery animals prior to dosing and during Weeks 16 and 26, and near the end of the recovery period.

No treatment-related changes were observed.

**ECG**

Performed prior to the initiation of dosing, during Weeks 8, 16 and 26 after exposure, and around the middle of the recovery period.

There were no treatment-related changes.

**Respiratory Function**

Measured using a pneumotachograph connected to a dose mask and linked to a pressure transducer. Data were collected prior to dosing and about 1 hour after dosing on Days 1, 29, 57, 85, 113, 141, 169, and 183 of treatment, and near the end of the recovery period. Parameters recorded included respiratory rate, tidal volume, and minute volume.

No treatment-related effects were apparent.

**Hematology**

Blood samples for hematology were drawn from fasted animals prior to the initiation of dosing, on Days 2, 30, 58, 86, 114, 142, 170, and 184 (day of necropsy for main study animals), at the mid point of the recovery period, and at the time of necropsy for recovery animals.

There were no treatment-related differences between the groups.

**Clinical Chemistry**

Blood samples for clinical chemistry evaluations were drawn at the same time as those for hematology.

There were no treatment-related differences between the groups.

### **Urinalysis**

Urine samples were collected overnight (over approximately 17 hours) while the animals were being fasted prior to the blood draws for hematology and clinical chemistry testing.

There were no treatment-related differences between the groups.

### **Gross Pathology**

No notable findings in the vehicle control group compared to air controls.

### **Organ Weights**

The following were weighed (paired organs weighed together): adrenals, brain, epididymides, heart, kidneys, lungs, liver, ovaries, pancreas, pituitary, prostate, spleen, submaxillary salivary glands, testes, thymus, thyroid/parathyroid, uterus.

No treatment-related differences between the groups.

### **Histopathology**

Adequate Battery- Yes. A standard battery of tissues was collected as well as an expanded panel of respiratory tissues including bronchial lymph nodes, carina, larynx, left and right anterior, middle, and posterior sections of the lungs, anterior and posterior sections of the nasal cavity, pharynx, retropharyngeal lymph nodes, and trachea.

Peer Review- Not discussed.

#### **Histological Findings**

Nothing that appeared related to the vehicle.

## **7 Genetic Toxicology**

From the TOBI® label: “TOBI® has been evaluated for genotoxicity in a battery of in-vitro and in-vivo tests. The Ames bacterial reversion test, conducted with 5 tester strains, failed to show a significant increase in revertants with or without metabolic activation in all strains. Tobramycin was negative in the mouse lymphoma forward mutation assay, did not induce chromosomal aberrations in Chinese hamster ovary cells, and was negative in the mouse micronucleus test.”

In addition, the following genotoxicity tests conducted with DSPC were negative: Ames assay using *S. typhimurium* (TA98, TA100, TA1635 and TA1537) and *E. coli* (WP2 *uvrA*), chromosome aberration assay in cultured CHO cells, *in vivo* mouse micronucleus assay (IP dosing).

## 8 Carcinogenicity

From the TOBI® label: “A two-year rat inhalation toxicology study to assess carcinogenic potential of TOBI® has been completed. Rats were exposed to TOBI® for up to 1.5 hours per day for 95 weeks. The clinical formulation of the drug was used for this carcinogenicity study. Serum levels of tobramycin of up to 35 mcg/mL were measured in rats, in contrast to the average 1 mcg/mL levels observed in cystic fibrosis patients in clinical trials. There was no drug-related increase in the incidence of any variety of tumor.”

## 9 Reproductive and Developmental Toxicology

Aminoglycoside antimicrobials have been assigned to Pregnancy Category D, based on clinical data. From the TOBI® label: “Subcutaneous administration of up to 100 mg/kg of tobramycin did not affect mating behavior or cause impairment of fertility in male or female rats. Subcutaneous administration of tobramycin at doses of 100 or 20 mg/kg/day during organogenesis was not teratogenic in rats or rabbits, respectively. Doses of tobramycin  $\geq$ 40 mg/kg/day were severely maternally toxic to rabbits and precluded the evaluation of teratogenicity. Aminoglycosides can cause fetal harm (e.g., congenital deafness) when administered to a pregnant woman. Ototoxicity was not evaluated in offspring during nonclinical reproduction toxicity studies with tobramycin.”

## 10 Special Toxicology Studies

None were performed with TIP.

## 11 Integrated Summary and Safety Evaluation

Tobramycin Inhalation Powder (TIP, used in the TOBI® Podhaler™) was well tolerated in rats given daily estimated inhaled free tobramycin doses of up to approximately 38 mg/kg for 6 months and in dogs given estimated daily inhaled free tobramycin doses of up to approximately 28 mg/kg for 28 days. The estimated pulmonary deposited free tobramycin doses for these animals were 3.8 mg/kg for rats and 5.6 mg/kg for dogs. There were no clinical signs of tobramycin toxicity in either species.

In the rats, findings such as minimal squamous hyperplasia in the larynx (often seen with inhalation of particulates), accumulation of alveolar macrophages containing pigment/basophilic debris, hyperplasia at the broncho-alveolar junction, signs of nasal inflammation, degeneration of olfactory epithelium, and minimal respiratory metaplasia of the olfactory mucosa were seen in the respiratory system. Kidney changes identical to those observed in older rats as age-related nephropathy were observed at a greater incidence in TIP-treated rats than controls. These histopathologic findings in the respiratory tissues and kidneys of the rats are similar to those observed following chronic treatment with TOBI® solution given by nebulization.

TIP-related findings in dogs included minimal to moderate inflammation in the mucosa of the nasal turbinates (reversible) and minimal tubular degeneration/regeneration with associated inflammation in the kidneys. TOBI® solution was not studied in dogs.

Toxicokinetic data from both species showed that after repeated dosing with TIP the half life of tobramycin in serum was relatively brief (usually 1-2 hours, but up to 4.4 hours observed); however, it had a long residence time in the lungs (still quantifiable 28 days after the final dose was administered). At the highest dose in rats, C<sub>max</sub> was generally 30-40 µg/ml with AUC<sub>0-24 hr</sub> around 100 µg·hr/ml. At the highest dose in dogs, C<sub>max</sub> was generally 3-7 µg/ml with AUC<sub>0-24 hr</sub> around 13-22 µg·hr/ml.

The clinical dose regimen for the TOBI® Podhaler™ is to inhale the contents of 4 capsules twice daily. Each capsule contains 28 mg of tobramycin base, for a total of 224 mg daily (in divided doses). This is an inhaled dose of 11.2 mg/kg/day in a child weighing 20 kg or an inhaled dose of 3.7 mg/kg/day in a 60 kg adult. The serum C<sub>max</sub> of tobramycin in CF patients who received a single 112 mg dose of TIP using the TOBI® Podhaler™ was approximately 1 µg/ml (inter-subject variability of about 50%), similar to that observed in CF patients who received a single 300 mg dose of the original formulation of TOBI®. The data from the patients, rats, and dogs suggest that the bioavailability of tobramycin from the respiratory tract is likely greater in the healthy animals used in the toxicity studies than it is in patients with CF. The PK study conducted in rats using TOBI® solution submitted with this NDA also supports this conjecture.

The new DPI excipients DSPC and calcium chloride have been adequately characterized and appear reasonably safe for repeated inhalation at the levels used in TIP (see Section 2.4 for a detailed discussion). Repeat dose inhalation toxicity studies in rats and dogs did not show any signs of toxicity. Both excipients have been used previously in products given by other routes of administration.

The data from the nonclinical studies show that repeated dosing with TIP using the TOBI® Podhaler™ is unlikely to cause greater systemic or pulmonary toxicity related to tobramycin than the currently marketed drug TOBI® (solution for nebulization) when used as directed.

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/s/  
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AMY L ELLIS  
07/27/2012

WENDELYN J SCHMIDT  
07/30/2012

I concur with Dr. Ellis' evaluation of the completeness and interpretation of the data provided for this NDA.

## PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA Number: 201,688**

**Applicant: Novartis**

**Receipt Date: 12/21/11**

**Drug Name: TOBI Podhaler NDA/BLA Type: S**

On **initial** overview of the NDA/BLA application for filing:

|   | <b>Content Parameter</b>                                                                                                                                                                                                                                                                                                         | <b>Yes</b> | <b>No</b> | <b>Comment</b> |
|---|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|-----------|----------------|
| 1 | Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?                                                                                                                                                      | X          |           |                |
| 2 | Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?                                                                                                                                                                                                                   | X          |           |                |
| 3 | Is the pharmacology/toxicology section legible so that substantive review can begin?                                                                                                                                                                                                                                             | X          |           |                |
| 4 | Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?        | X          |           |                |
| 5 | If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA). | X          |           |                |
| 6 | Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?                                                                                                                 | X          |           |                |
| 7 | Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?                                                                                                      | X          |           |                |
| 8 | Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?                                                                                                                                                                                                                | X          |           |                |

File name: 5\_Pharmacology\_Toxicology Filing Checklist for NDA\_BLA or Supplement  
010908

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR  
NDA/BLA or Supplement**

|    | <b>Content Parameter</b>                                                                                                                                                                                        | <b>Yes</b> | <b>No</b> | <b>Comment</b>                                                                                                                                    |
|----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| 9  | Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57? | X          |           | Nonclinical sections of label based on TOBI; appears appropriate. May need to consider whether excipient genotoxicity data needs to be mentioned. |
| 10 | Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)                                                                                                                       | X          |           |                                                                                                                                                   |
| 11 | Has the applicant addressed any abuse potential issues in the submission?                                                                                                                                       |            |           | Not applicable for this product.                                                                                                                  |
| 12 | If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?                                                                                                                     |            |           | Not applicable for this product.                                                                                                                  |

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE?** Yes

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

N/A

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Nothing to relay to sponsor.

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Reviewing Pharmacologist Date

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Team Leader/Supervisor Date

File name: 5\_Pharmacology\_Toxicology Filing Checklist for NDA\_BLA or Supplement  
010908

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/s/  
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AMY L ELLIS  
01/25/2012

WENDELYN J SCHMIDT  
01/25/2012