CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201688s000

SUMMARY REVIEW

Division Director Summary Review

Date	(electronic stamp)
From	John Farley, M.D.,M.P.H.
Subject	Acting Division Director Summary Review
NDA #	201,688
Applicant Name	Novartis Pharmaceuticals Corporation
Date of Submission	11/27/12
PDUFA Goal Date	5/27/13
Proprietary Name / Established (USAN) Name	TOBI Podhaler / tobramycin inhalation powder
Dosage Forms / Strength	Inhalation powder hard capsules / 28 mg
Proposed Indication	TOBI Podhaler is indicated for the management of cystic fibrosis patients with *Pseudomonas aeruginosa.*
Action:	Approval

Introduction

The applicant has resubmitted this New Drug Application (NDA) for Tobramycin Inhalation Powder, referred to by the approved proprietary name, TOBI Podhaler, in this review. The TOBI Podhaler is a powder formulation of tobramycin with the proposed indication, "the management of cystic fibrosis patients with *Pseudomonas aeruginosa"*. The active ingredient, tobramycin, is identical to the active ingredient in the intravenous formulation of tobramycin (approved since 1976 for the treatment of *Pseudomonas aeruginosa* in patients with CF) and the inhaled tobramycin solution TOBI® (approved since 1997 for the same indication proposed for TOBI Podhaler) and also owned by the applicant.

TOBI Podhaler 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. The T-326 dry powder inhaler, intended for replacement every 7 days, is not an FDA-cleared device. TOBI Podhaler 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.

Background/Regulatory

The NDA was originally submitted by the applicant on Dec. 21, 2011. Following review, a Complete Response letter was issued on Oct. 19, 2012. There was a single Chemistry Manufacturing and Controls / Device deficiency cited in the Complete Response letter:

> During a recent inspection of the (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility.

Satisfactory resolution of these deficiencies is required before this application may be approved.

I have previously concluded that there were no Product Quality Microbiology, Human Factors, Non-Clinical Pharmacology Toxicology, Clinical Pharmacology, Clinical Microbiology, Clinical/Statistical Efficacy, or Safety issues which would preclude approval. The reader is referred to my Division Director Summary Review of October 19, 2012 for a detailed discussion. In this October 19, 2012 Summary Review, I also summarized the September 5, 2012 meeting of the Anti-Infective Drugs Advisory Committee discussion of this NDA, PREA exemption, and the Office of Scientific Investigations recommendation that the clinical data is reliable based upon clinical site inspections.

Chemistry Manufacturing and Controls / Device

During the initial review of this NDA, deficiencies at (b) (4) manufacturing facility, (b) (4) were noted. In the resubmission of this NDA, the applicant stated that they believed (b) (4) submission dated (b) (4) fully addressed the deficiencies noted at (b) (4) manufacturing facility. The CDRH Office of Compliance determined the response from (b) (4) was adequate and re-inspection of (b) (4) was not necessary.

In an amendment to the resubmitted NDA, the applicant withdrew (b) (4) as a tobramycin drug substance manufacturer and chose to rely on (b) (4) as the sole source of tobramycin for Tobi Podhaler. This was acceptable to the CMC Reviewer, Dr. Mark Seggel, who stated that drug substances manufactured at the two facilities were, for all practical purposes, indistinguishable. In addition, drug substances from both facilities were used in the manufacture of clinical trial batches, and drug substance from (b) (4) was used in the manufacture of two of three primary stability batches.

The CDER Office of Compliance issued an overall recommendation of Acceptable for manufacturing facilities. The CMC Reviewer concluded that there were no CMC issues precluding approval, and that the deficiency listed in the Complete Response letter of Oct. 19, 2012 had been adequately addressed. I concur with this assessment.

Safety

The applicant provided a safety update in the resubmission of the NDA and this was reviewed by the Clinical Reviewer, Dr. Shrimant Mishra. The Reviewer concluded that the data included in the safety update was consistent with data previously reviewed in the original submission. Noted in the safety update were several reports of cough associated with drug discontinuation and several reports of possible incorrect use of the device among patients older than 10 years of age. The reviewer recommended that language concerning cough and patient monitoring to promote correct use in the Prescribing

Information be edited to reflect this new data. I concur with the Reviewer's recommendations and conclusions.

Labeling

The Prescribing Information was discussed with the applicant and updated in the review of this resubmission to reflect data in the safety update.

In discussions with the applicant during the first review cycle, the Patient Information / Instructions for Use were extensively revised with input from Agency Human Factors and Labeling reviewers. The Instructions for Use were rewritten for clarity and an illustration was added to each step required to administer the dose and insure that the capsule is properly punctured and empty. The revised Instructions for Use will be formally evaluated as a Post-Marketing Requirement.

The carton labeling was revised to remove (b) (4) as a country of origin of the drug substance to reflect the CMC amendment discussed above: text change from "(b) (4) to "*Product of Hungary*".

During review of the resubmission, the proposed proprietary name TOBI Podhaler was re-reviewed by Dr. Aleksander Winiarski and deemed acceptable.

Decision/Action/Risk Benefit Assessment

Regulatory Action
Approval

Risk Benefit Assessment
In my October 19, 2012 Summary Review, I describe and discuss the evidence of safety and efficacy provided by the applicant in this NDA, including summarizing Studies C2301, C2302, and C2303. As discussed above, the deficiency described in the Complete Response letter issued on Oct. 19, 2012 has been satisfactorily addressed.

TOBI Podhaler is a new mechanism of delivery of a drug which has been previously demonstrated to be efficacious for the proposed indication. Cystic fibrosis is an orphan disease and the application highlights some of the challenges conducting clinical trials in this population. For example, the infeasibility of adequate accrual of patients in Study C2303 illustrates that a placebo-controlled trial in cystic fibrosis patients chronically colonized with *P. aeruginosa* is no longer considered acceptable to patients or physicians. Alternatives to reduce the burden of treatment in this population are needed. TOBI Podhaler would offer an important alternative to patients that may improve compliance as the time to administer treatment is considerably shorter than TOBI® by nebulizer.

The applicant has provided substantial evidence of efficacy consisting of a robust demonstration of superiority over placebo in Study C2301 and supportive data from Study C2302 and Study C2303. The safety findings in Study C2302 suggest that some

patients may elect to discontinue TOBI Podhaler due to adverse effects such as cough. Patients would need to be monitored carefully as they initiate therapy and be switched to TOBI® by nebulizer if necessary. The increase in MIC and clinical implications of this finding will be evaluated in a post-marketing requirement. The Instructions for Use have been extensively revised, and will be evaluated in a post-marketing requirement.

I conclude that the risk benefit is favorable and the new drug product should be approved.

Post-marketing Risk Evaluation and Mitigation Strategies
None

Postmarketing Requirements

1928-1 Conduct a prospective, observational study in the United States, which includes a five year period of time after introduction of the TOBI Podhaler to the market to determine if decreased susceptibility to tobramycin is increasing in *Pseudomonas aeruginosa* from cystic fibrosis (CF) patients. The study will enroll 500 patients. This study should also monitor resistance to these additional antibacterial drugs: meropenem, imipenem, ceftazidime, aztreonam and ciprofloxacin. Within the study, the following treatment emergent pathogens should be evaluated: *Staphylococcus aureus, Stenotrophomonas maltophilia, Achromobacter xylosoxidans,* and *Burkholderia* spp. Provide a detailed protocol to the Agency for review and comment prior to commencing the study. Interim reports of changes in *P. aeruginosa* susceptibility and treatment-emergent pathogens from CF patients should be submitted annually for the duration of the study period. After the first year, the report should be cumulative. The Agency may consider this postmarketing requirement fulfilled after three years if the data do not warrant a longer surveillance period.

Agreed upon timetable:

Final protocol submission:	December 2013
First interim report:	May 2016
Second interim report:	May 2017
Third interim report:	May 2018
Fourth interim report:	May 2019
Fifth interim report:	May 2020
Study completion date:	February 2021
Final report submission:	July 2021

1928-2 Conduct a one year, prospective observational cohort study in the United States of CF patients chronically colonized with *P. aeruginosa* who use TOBI Podhaler as part of their regular care compared to patients using other FDA approved inhaled antipseudomonal antibacterial drugs to assess clinical outcomes, including patients with increased *P. aeruginosa*

minimum inhibitory concentrations to tobramycin at baseline. The study will enroll 500 patients. The clinical outcomes should include use of other antipseudomonal antibacterial drugs, non-respiratory and respiratory-related hospitalizations, mortality, and changes in FEV_1% predicted from baseline. This study should also include sputum pharmacokinetics and assess changes in *P. aeruginosa* sputum log10 CFU/g. Within the study, the following treatment emergent pathogens should be evaluated: *Staphylococcus aureus, Stenotrophomonas maltophilia, Achromobacter xylosoxidans,* and *Burkholderia spp.* This study should utilize appropriate approaches to the design and statistical analysis (e.g., baseline covariates, propensity scores) to account for potential differences between the treatment cohorts.

Agreed upon timetable:

Final protocol submission:	December 2013
Study completion date:	February 2017
Final report submission:	July 2017

1928-3 Conduct an actual use human factors study to validate the approved Instructions for Use (IFU). The study will enroll 45 patients in total with three age groups of 15 patients each: 6-10 years, 11-17 years, and > 18 years. Only CF patients naïve to use of the Podhaler device will be enrolled. These patients will not be trained prior to reading the IFU and will be observed during the study.

Agreed upon timetable:

Draft protocol submission	August 2013
Final protocol submission	February 2014
Study completion date	May 2015
Final report submission	August 2015

Postmarketing Commitment

1928-4 Create adjunct instructions for use using alternative media and validate these instructions for use to ensure the patient can safely and effectively perform the critical tasks for the intended use of this product.

Agreed upon timetable:

Draft protocol submission	September 2013
Final protocol submission	May 2014
Study completion date	August 2015
Final report submission	November 2015

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/s/

JOHN J FARLEY
03/22/2013