



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201688

NDA APPROVAL

Novartis Pharmaceuticals Corporation
Attn: John Noh, Pharm.D.
Global Program Regulatory Manager
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Noh:

Please refer to your New Drug Application (NDA) dated December 21, 2011, received December 21, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TOBI Podhaler (tobramycin inhalation powder) for Oral Inhalation, 28 mg.

We acknowledge receipt of your amendments dated November 27, 2012, February 20, March 18 and 21, 2013.

The November 27, 2012, submission constituted a complete response to our October 19, 2012, action letter.

This new drug application provides for the use of the TOBI Podhaler (tobramycin inhalation powder) for Oral Inhalation for the management of cystic fibrosis patients with *Pseudomonas aeruginosa*.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient information, and text for the patient instructions for use). Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE-CONTAINER LABELS

Submit final printed carton and immediate-container labels that are identical to the enclosed carton and immediate-container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).” Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission **“Final Printed Carton and Container Labels for approved NDA 201688.”** Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

MARKET PACKAGE

Please submit one market package of the drug product when it is available to the following address:

J. Christopher Davi, MS, Senior Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 6121
10903 New Hampshire Avenue
Silver Spring, Maryland
Use zip code 20903 if shipping via United States Postal Service (USPS).
Use zip code 20993 if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify the unexpected serious risk of resistance development in *Pseudomonas aeruginosa* in patients with cystic fibrosis.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 1928-1** 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.

The timetable you submitted on March 21, 2013, states that you will conduct this study according to the following schedule:

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** 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 FEV₁% 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.

The timetable you submitted on March 21, 2013, states that you will conduct this study according to the following schedule:

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

- 1928-3** 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.

The timetable you submitted on March 21, 2013, states that you will conduct this study according to the following schedule:

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

Submit the protocols to your IND 64,409, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

“Required Postmarketing Protocol Under 505(o)”, “Required Postmarketing Final Report Under 505(o)”, “Required Postmarketing Correspondence Under 505(o)”.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your 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.

The timetable you submitted on March 21, 2013, states that you will conduct this study according to the following schedule:

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

Submit clinical protocols to your IND 64,409 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial.

All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol**,” “**Postmarketing Commitment Final Report**,” or “**Postmarketing Commitment Correspondence**.”

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call J. Christopher Davi, MS, Senior Regulatory Project Manager, at (301) 796-0702.

Sincerely,

(See appended electronic signature page)

John Farley, MD, MPH
Acting Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURES: Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHN J FARLEY
03/22/2013