DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201688/S-008

SUPPLEMENT APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Bijal Pandhi, PharmD
Global Program Regulatory Manager
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Pandhi:

Please refer to your Supplemental New Drug Application (sNDA) dated August 31, 2015, received August 31, 2015, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for TOBI Podhaler (tobramycin inhalation powder) oral inhalation, 28 mg.

This "Prior Approval" supplemental new drug application provides for changes to the Instructions for Use (IFU) based on the completion of Post Marketing Requirement (PMR 1928-3) Study TBM100C2412, entitled, *"A multi-center, human factors engineering (HFE) usability study in cystic fibrosis patients to validate the approved instructions for use (IFU) of TOBI Podhaler (tobramycin inhalation powder) using placebo capsules."*

APPROVAL

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 agreed-upon labeling text.

LABELING

Submit the final IFU as soon as it is available, but no more than 30 days after it is printed. The final IFU must be identical to the enclosed IFU, submitted on December 14, 2016.

The final IFU should be submitted 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 IFU for approved NDA 201688/S-008**." Approval of this submission by FDA is not required before the IFU is used.

POSTMARKETING REQUIREMENTS UNDER SECTION 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.

Since TOBI Podhaler (tobramycin inhalation powder) was approved on March 22, 2013, we have become aware of the results of the study you conducted to fulfill postmarketing requirement (PMR) 1928-3, "An actual use human factors study to validate the approved Instructions for Use (IFU)."

(b) (4)

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 serious risk of resistance development for *Pseudomonas aeruginosa* due to inappropriate use of the product with subsequent administration of a subtherapeutic dose of TOBI Podhaler (tobramycin inhalation powder).

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:

- **1928-5:** Conduct a human factors validation study to demonstrate that the user interface of the product can support safe and effective use for the intended users. The human factors validation study should be conducted in patients aged 6 years and older under simulated yet representative of realistic use conditions and include all the critical tasks identified from your updated use-related risk analysis.

  The timetable you submitted on December 14, 2016, states that you will conduct this study according to the following schedule:

  Draft Protocol Submission: January 2017
  Final Protocol Submission: May 2017
  Study/Trial Completion: November 2018
  Final Report Submission: May 2019

Submit clinical protocols to your IND 64,409, with a cross-reference to this NDA. Submit all final report(s) 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.

REPORTING REQUIREMENTS

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

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

Sincerely,

{See appended electronic signature page}

Joseph Toerner, MD, MPH
Deputy Director for Safety
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE: Approved IFU

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

/s/

JOSEPH G TOERNER
12/16/2016