**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

# 201820Orig1s000

***Trade Name:*** Bethkis

***Generic Name:*** tobramycin 300 mg/4mL inhalation solution

***Sponsor:*** Chiesi Pharmaceuticals, Inc.

***Approval Date:*** October 12, 2012

***Indications:*** For the use of Bethkis (tobramycin 300 mg/4mL inhalation solution) for the management of cystic fibrosis patients with *P. aeruginosa*.

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# 201820Orig1s000

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***APPLICATION NUMBER:***

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# APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201820

**NDA APPROVAL**

Chiesi Pharmaceuticals, Inc.
Attention: Erika Panico, RAC
Vice President and Managing Director
9605 Medical Center Drive, Suite 380
Rockville, MD 20850

Dear Ms. Panico:

Please refer to your New Drug Application (NDA) dated October 22, 2010, received October 25, 2010, submitted under 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Bethkis (tobramycin 300 mg/4mL inhalation solution).

We acknowledge receipt of your amendments dated January 6, April 12, May 7, June 15, July 20, September 19 and October 4, 9, (3) and 11 (2), 2012.

The April 12, 2012, submission constituted a complete response to our August 25, 2011, action letter.

This new drug application provides for the use of Bethkis (tobramycin 300 mg/4mL inhalation solution) for the management of cystic fibrosis patients with *P. 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.

We note that your October 11, 2012, submission includes final printed labeling (FPL) for your package insert and information for patient insert. We have not reviewed this FPL. You are responsible for assuring that the wording in this printed labeling is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

## 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 for your package insert and information for patient insert. 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

We acknowledge your October 12, 2012, submission containing final printed carton and container labels.

## CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on October 11, 2012 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 201820**." 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.

## 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 a serious risk of upper airway and bronchial hypersensitivity/irritation (including the risk for acute decreases in $FEV_1$, bronchospasm, wheezing, dyspnea, cough, etc.) that could result from the high osmolality of Bethkis (tobramycin 300 mg/4mL inhalation solution) in patients with low $FEV_1$.

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:

**1931:** A long term ( 24 week, 3on/off cycle) postmarketing observational study in 50 patients describing the safety and tolerability of Bethkis® in patients with a stable $FEV_1 \geq 25$ to <40% predicted. The following efficacy outcomes should also be collected: sustained FEV improvement, number of exacerbations, anti-pseudomonal use, and planned and unplanned hospitalization and death. Provide a detailed protocol to the Agency for review and comment prior to commencing the study.

Final Protocol Submission: June 30, 2013
First Interim Report: March 31, 2015
Study Completion Date: September 30, 2015
Final Report Submission: December 31, 2015

Submit clinical protocols to your IND 72,068 for this product. Submit nonclinical and chemistry, manufacturing, and control protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(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 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/trial, 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 Carmen DeBellas, Regulatory Project Manager, at (301) 796-1203.

Sincerely,

*{See appended electronic signature page}*

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

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling

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

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/s/

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JOHN J FARLEY
10/12/2012