DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 18533/S-040

SUPPLEMENT APPROVAL

Janssen Research & Development, LLC
Attention: Melissa L. Gannon
Director, Global Regulatory Affairs
920 U.S. Highway 202
P.O. Box 300
Raritan, NJ 08869

Dear Ms. Gannon:

Please refer to your Supplemental New Drug Application (sNDA) dated March 4, 2003, received March 5, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Nizoral (ketoconazole) Tablets, 200 mg.

We acknowledge receipt of your amendments dated October 19, 2012, and February 28, May 28, June 25, July 8, 16, and 25, 2013.

The July 25, 2013, submission constituted a complete response to our June 19, 2006, action letter.

This supplemental new drug application provides for the following revisions to the package insert:

1. **BOXED WARNING:**
   a. To include a statement that Nizoral Tablets should be used only when other effective antifungal therapy is not available or tolerated and the potential benefits are considered to outweigh the potential risks.
   b. Updated information regarding Hepatotoxicity.
   c. Updated information regarding QT Prolongation and Drug Interactions Leading to QT Prolongation.

2. **INDICATIONS AND USAGE** [redacted] (b) (4)

3. **CONTRAINDICATIONS** Section: Addition of a new subsection on liver disease and updated information on drug interactions.

4. **WARNINGS** Section:
    a. Revisions to the Hepatotoxicity and QT Prolongation and Drug Interactions Leading to QT Prolongation subsections.
    b. Addition of the following new subsections: Adrenal Insufficiency, Adverse Reactions Associated with Unapproved Uses, Hypersensitivity, Enhanced Sedation, and Myopathy.

5. **PRECAUTIONS** Section:
    a. Revisions to the following subsections: General, Drug Interactions, Carcinogenesis, Mutagenesis, Impairment of Fertility, Pregnancy, Nonteratogenic Effects, and Nursing Mothers.

6. **ADVERSE REACTIONS** Section:
   Revised information in the Clinical Trials and Post-Marketing Experience subsections.

7. Revisions to the **MICROBIOLOGY, OVERDOSAGE**, and **DOSAGE AND ADMINISTRATION** Sections.

A new Medication Guide has also been added to the product labeling.

In addition, we have made the following revisions to the product labeling. These revisions are reflected in the attached package insert:

- In the **ADVERSE REACTIONS** Section, the first sentence should read as follows: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

- In the **ADVERSE REACTIONS** Section, **Post-Marketing Experience** subsection, the first sentence should read as follows: The following adverse reactions have been identified during postapproval use of Nizoral tablets. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- (b) (4)

- Editorial revisions.

We have completed our review of this supplemental 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 and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

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 none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to (301) 847-8444.

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 Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, M.D., M.P.H.
Deputy Director for Safety
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

SUMATHI NAMBIAR
07/25/2013