DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020863/S-024

SUPPLEMENT APPROVAL

Otsuka Pharmaceutical Development & Commercialization, Inc.
Attention: Mariana Tran, PhD, RAC
Associate Director, Global Regulatory Affairs
2440 Research Boulevard
Rockville, Maryland 20850

Dear Dr. Tran:

Please refer to your Supplemental New Drug Application (sNDA) dated and, received November 10, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Pletal (cilostazol) 50 mg and 100 mg Tablets.

This Prior Approval supplemental new drug application provides for revisions to the approved labeling as follows (additions are shown as underlined text and deletions are shown as strikethrough text):

1. Under **WARNINGS AND PRECAUTIONS**, the following section as added:

> **5.2 Left Ventricular Outflow Tract Obstruction**
>
> Left ventricular outflow tract obstruction has been reported in patients with sigmoid shaped interventricular septum. Monitor patients for the development of a new systolic murmur or cardiac symptoms after starting cilostazol.

2. Under **ADVERSE REACTIONS** the following text was added to the list under section 6:

> The following adverse reactions are discussed in greater detail in other sections of the labeling:
> - Patients with Heart Failure *[see Boxed Warning]*
> - Tachycardia *[see Warnings and Precautions (5.1)]*
> - Left Ventricular Outflow Tract Obstruction *[see Warnings and Precautions (5.2)]*
> - Hematologic Adverse Reactions *[see Warnings and Precautions (~~5.2~~5.3)]*
> - Hemostatic Disorders or Active Pathologic Bleeding *[see Warnings and Precautions (~~5.3~~5.4)]*

3. Under **NON CLINICAL TOXICOLOGY**, the following text was added:

   13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
   Dietary administration of cilostazol to male and female rats and mice for up to 104 weeks, at doses up to 500 mg/kg/day in rats and 1000 mg/kg/day in mice, revealed no evidence of carcinogenic potential. The maximum doses administered in both rat and mouse studies were, on a systemic exposure basis, less than the human exposure at the MRHD of the drug. Cilostazol tested negative in bacterial gene mutation, bacterial DNA repair, mammalian cell gene mutation, and mouse in vivo bone marrow chromosomal aberration assays. It was, however, associated with a significant increase in chromosomal aberrations in the in vitro Chinese Hamster Ovary Cell assay.

   In female mice, cilostazol caused a reversible contraceptive effect at a dose (300 mg/kg) that was approximately 7.4-fold greater than the Maximum Recommended Human Dose (MRHD) on a body surface area basis. These findings have not been demonstrated in other animal species.

4. The **HIGHLIGHTS** section was updated to reflect the change to **WARNINGS AND PRECAUTIONS.**

5. The **TABLE OF CONTENTS** was updated to reflect the addition of a new section to **WARNINGS AND PRECAUTIONS.**

6. The **WARNINGS AND PRECAUTIONS** section as renumbered.

7. The revision date was updated.

No revisions were made to the Patient Package Insert. There are no other changes from the last approved package insert.

APPROVAL & LABELING

We have completed our review of this supplemental application and 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 package insert, 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 include 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).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. 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.

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, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

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, please call:

Lori Anne Wachter, RN, BSN, RAC
Regulatory Project Manager for Safety
(301) 796-3975

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, PharmD.
Deputy Director for Safety
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
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/

MARY R SOUTHWORTH
05/17/2017