CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-863

CORRESPONDENCE

Tanveer Ahmad, Ph.D.
Otsuka America Pharmaceutical, Inc.
2440 Research Blvd.
Rockville, MD. 20850

Date: July 2, 1998

Re: NDA 20863
Cilostazol (OPC-13013)

Dear Dr. Ahmad:

Please provide information about the metabolic profile of cilostazol for mice and female rabbits. Please incorporate this information into Table 5.3-12: "Interspecies Comparisons...." on page 57 of the Comprehensive Review of the Non-Clinical Pharmacology of Cilostazol (OPC 13013).

Please provide plasma levels and AUCs for cilostazol and its metabolites (particularly OPC 13015 and OPC 13213) for female rabbits at doses utilized in the rabbit developmental toxicity study.

Please provide plasma protein binding for cilostazol and metabolites (particularly OPC 13015 and OPC 13213) for female rabbits at concentrations encountered under conditions in the rabbit developmental toxicity study, and in mice at concentrations encountered under the conditions of the mouse carcinogenicity study.

Please provide electronic copies of the Tables of Contents for the Comprehensive Review of the Non-Clinical Pharmacology of Cilostazol (OPC 13013), and the Comprehensive Review of Absorption, Distribution, Metabolism and Excretion (ADME) of Cilostazol.

John E. Koerner, Ph.D.

CC:
Original NDA
HFD-110
HFD-110/GBuehler
HFD-110/JKoerner

DEPARTMENT OF HEALTH & HUMAN SERVICES

G. Buehler

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAY 22 1998

Tanveer Ahmad, Ph.D.
Otsuka America Pharmaceutical, Inc.
2440 Research Blvd.
Rockville, MD. 20850

Date: May 21, 1998

Re: NDA 20863
Cilostazol (OPC-13013)

Dear Dr. Ahmad:

In our telephone conversation of May 20, 1998, you had requested that I fax to you my request for information. This fax serves as my written request for information.

Please submit electronic versions of the following documents:

Section 5.1
Comprehensive Review of Non-Clinical Pharmacology of Cilostazol (OPC-13013)
Volume 8, pgs 001-160
Section 5.3
Comprehensive Review of Absorption, Distribution, Metabolism, and Excretion (ADME) of Cilostazol
Volume 34, pgs 001-066

Please also provide information and literature references that support involvement of platelet aggregation in intermittent claudication.

Please indicate when this information will be provided, as this information will facilitate review of your NDA. It is fine with me if the electronic versions of the non-clinical pharmacology and pharmacokinetics summaries are provided prior to information on the role of platelet aggregation in intermittent claudication. Please call me if you have any questions.

John Koerner

John Koerner, Ph.D.

cc:
Original NDA
HFD-110
HFD-110/GBuehler
HFD-110/JKoerner

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

BUEHLER

NDA 20-863

Otsuka America Pharmaceutical, Inc.
Attention: Tanveer Ahmad, Ph.D.
2440 Research Boulevard
Rockville, MD 20878

Dear Dr. Ahmad:

Please refer to your pending September 18, 1997 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Pletal (cilostazol) Tablets.

We also refer to your amendment dated October 15, 1997.

We have completed our review of the manufacturing and controls section of your submission and have identified the following deficiencies:

1. Please consider using the following storage statement in the package insert:

[see USP Controlled Room Temperature]

2. Please consider using one of the following abbreviated labeling statements if space on the immediate container is limited. In this case, the full statement (# 1 above) must appear on the outer carton and in the package insert.

3. Inactive ingredients should be listed in alphabetical order on page 1 of the package insert.

4. Please refer to the "Guidance for Industry, Implementation of Section 126, Elimination of Certain Labeling Requirements, of the FDA Modernization Act of 1997" that is available on the Internet at www.fda.gov/cder/guidance/index.htm. Please replace the proposed "Caution: Federal law prohibits dispensing without a prescription" legend with "Rx only" in your labeling.

5. Please refer to NDA volume 1.3, page 293 (section 3.2.6.2.1)

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact:

Mr. Gary Buehler
Regulatory Health Project Manager
(301) 594-5332

Sincerely yours,

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA
HFD-110
HFD-810/ONDC Division Director (only for CMC related issues)
HFD-110/GBuehler/4/13/98;4/15/98
sb/4/14/98;4/21/98
R/D: FZielinski/4/15/98
JShort4/15/98
NMorgenstern/4/16/98

INFORMATION REQUEST (IR)

Buehler

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NDA 20-863

Food and Drug Administration
Rockville MD 20857

SEP 30 1997

Otsuka America Pharmaceutical, Inc.
Attention: David H. Warnock, Ph.D.
2440 Research Boulevard
Rockville, MD 20850

Dear Dr. Warnock:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Pletal (cilostazol) Tablets

Therapeutic Classification: 1S

Date of Application: September 18, 1997

Date of Receipt: September 19, 1997

Our Reference Number: NDA 20-863

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on November 18, 1997 in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102(c) of the new drug regulations and in accordance with the policy described in the Center for Drug Evaluation and Research Staff Manual Guide CDER 4820.6, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Please request the meeting at least 15 days in advance. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA, please contact:

Mr. Gary Buehler
Regulatory Health Project Manager
(301) 594-5332

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc
Orig. NDA
HFD-110
DISTRICT OFFICE
HFD-110/GBuehler/9/23/97
sb/9/23/97;9/29/97
R/D: NMorgenstern/9/25/97

ACKNOWLEDGEMENT - AC