CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-863

CHEMISTRY REVIEW(S)

G. Buehler

SEP 2 - 1998

DIVISION OF CARDIO-RENAL DRUGS
Review of Chemistry, Manufacturing and Controls

NDA 20-863 Review # **4** Complete August 26, 1998

Submission Type	Document Date	CDER Date	Topics
NDA Orig. Amend SN 072	Aug 17, 1998	Aug 18, 1998	(a) Dissolution spec, (b) NMT (c) Revised stability protocol (d) Corrected carton labels

Name and Address of Applicant

Otsuka America Pharm. Inc.
2440 Research Blvd.
Rockville, Maryland 20878

Tanveer Ahmad, Ph.D., Sr. Director, Reg. Affairs
Phone (301) 527-4674

Ms. Brenda Wolling (Alternative Contact)
Phone (301) 527-4887

Drug Product Name

Proprietary: **Pletal**
Nonproprietary: cilostazol
Code Name: OPC-13013, also known as Pletaal in Japan
Chemical type/Therapeutic Class: **1 S**

Patent Status: US Patent # 4,277,479 issued to Otsuka 7/7/81 expires 8/29/99

Pharmacological Category / Indication: Cilostazol is a 3,4-dihydro quinolinone derivative that is intended for the treatment of intermittent claudication. It is a vasodilator and antiplatelet - antithrombotic.

Dosage Form: Conventional immediate release tablet for oral administration

Strengths: 50 mg Triangular Tablets and 100 mg Round Tablets

Dispensed: Rx only

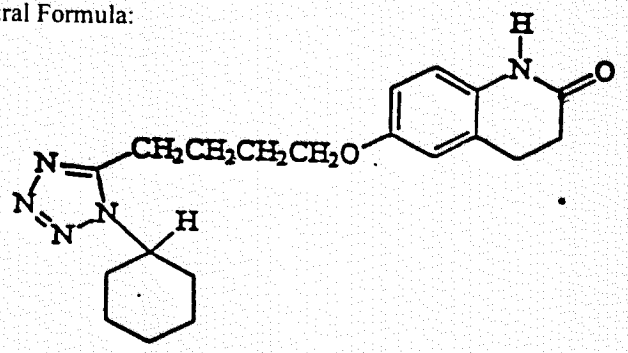
Chemical name, molecular and structural formula, molecular weight:

Chemical name: 6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydro-2(1H)-Quinolinone

Generic Name: cilostazol CAS # 73963-72-1

Molecular formula: $C_{20}H_{27}N_5O_2$ Molecular Weight: 369.52

Structural Formula:



Remarks and Comments:

(1) Dissolution specification: Otsuka America selected the specification recommended by Dr Patrick Marroum

(2) Drug product water specification: Otsuka agreed to the regulatory specification

(3) The long term stability protocol for "annual batches" is revised to include water content testing
(4) The storage statement in the carton label is in agreement with Draft FDA Guidance.
(5) Otsuka provided a Record of Telephone Conversations that occurred on August 10, 11, 12 and 13. It is a complete and accurate summary of discussions between FDA and Otsuka staff.
(6) Analytical methods validation by Philadelphia District Laboratory and St. Louis Laboratory was requested on March 20, 1998. -- Philadelphia Lab received samples on April 8, 1998. The analyst completed validation and the Laboratory Director is reviewing the entire package. The validation report is expected by September 1, 1998. -- St. Louis Lab received samples on April 13, 1998. Validation work is expected to begin in FY 99.
(7) **All CMC topics required for approval are complete and acceptable. I recommend approval.**

Florian Zielinski 8/26/98

Florian Zielinski, Ph.D. Review Chemist, New Drug Chemistry I

Distribution:

Original NDA 20-863
HFD 110 Division File
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HFD 110 Gary Buehler
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Initialed by Kasturi Srinivasachar K. Srinivasachar 9-2-98

File name fwz: NDA 20863 Cilostazol Review #4

DIVISION OF CARDIO-RENAL DRUGS
Review of Chemistry, Manufacturing and Controls

NDA 20-863 Review # 3 Complete August 13, 1998

Submission Type	Document Date	CDER Date	Topic
NDA Orig. Amend SN 052	June 26, 1998	June 30, 1998	Response to 483 Observation
NDA Orig. Amend SN 059	July 21, 1998	July 22, 1998	1-Year stability data for 50 mg triangular Pletal Tablets
NDA Orig. Amend SN 060	July 24, 1998	July 24, 1998	Updated Package Insert
NDA Orig. Amend SN 070	August 11, 1998	August 11, 1998	Revised Package Insert and container & carton labels

Name and Address of Applicant
Otsuka America Pharm. Inc.
2440 Research Blvd.
Rockville, Maryland 20878

Tanveer Ahmad, Ph.D., Sr. Director, Reg. Affairs
Phone (301) 527-4674

Ms. Brenda Wolling (Alternative Contact)
Phone (301) 527-4887

Drug Product Name
Proprietary: **Pletal**
Nonproprietary: cilostazol
Code Name: OPC-13013, also known as Pletaal in Japan
Chemical type/Therapeutic Class: **1 S**

Patent Status: US Patent # 4,277,479 issued to Otsuka 7/7/81 expires 8/29/99

Pharmacological Category / Indication: Cilostazol is a 3,4-dihydro quinolinone derivative that is intended for the treatment of intermittent claudication. It is a vasodilator and antiplatelet - antithrombotic.

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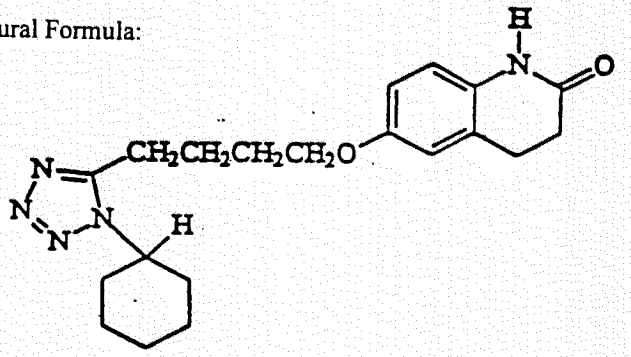
Generic Name: cilostazol CAS # 73963-72-1

Molecular formula: $C_{20}H_{27}N_5O_2$ Molecular Weight: 369.52

Structural Formula:



Florian Zielinski, Ph.D. Review Chemist, New Drug Chemistry I

Florian Zielinski Aug 13, 98

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File name fwz: NDA 20863 Cilostazol Review #3

G. Buehler

JUN 15 1998

DIVISION OF CARDIO-RENAL DRUGS
Review of Chemistry, Manufacturing and Controls

NDA 20-863 Review # 2 Assigned 5/15/98 Complete 5/18/98

Submission Type	Document Date	CDER Date	Topic
NDA Original Amendment SN 030	~~April~~ May 8, 1998	May 11, 1998	Reply to FDA Request for CMC Information Letter dated 4/24/98

Name and Address of Applicant

Otsuka America Pharm. Inc.
2440 Research Blvd.
Rockville, Maryland 20878

Matthew J O'Brien, Ph.D., Director, Reg. Affairs
Phone (301) 527-4701
FAX (301) 721-7527

Drug Product Name

Proprietary: **Pletal**
Nonproprietary: cilostazol
Code Name: OPC-13013, also known as Pletaal in Japan
Chemical type/Therapeutic Class: 1 S

Patent Status: US Patent # 4,277,479 issued to Otsuka 7/7/81, expires 8/29/99

Pharmacological Category / Indication: Cilostazol is a 3,4-dihydro quinolinone derivative that is intended for the treatment of intermittent claudication. It is a vasodilator and antiplatelet - antithrombotic.

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Chemical name:
6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydro-2(1H)-Quinolinone

Generic Name: cilostazol CAS # 73963-72-1

Molecular formula: $C_{20}H_{27}N_5O_2$ Molecular Weight: 369.52

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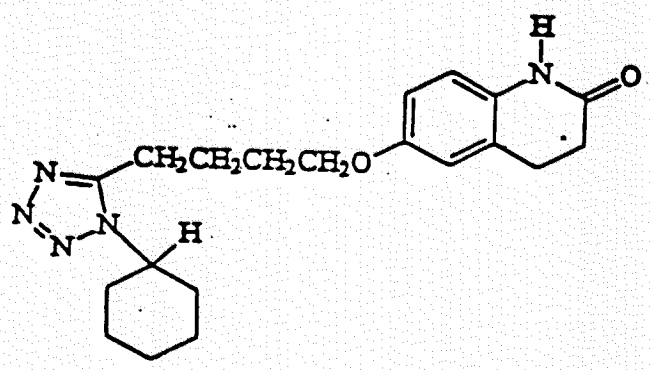

Remarks and Comments:

(1) Establishment Evaluation Request submitted electronically on November 3, 1997. PAI of Otsuka Pharm Co, Second Tokushima Factory, Japan (profile: tablet, prompt release) will be conducted June 2 to 5, 1998. All other establishments are acceptable as of April 3, 1998.

(2) Analytical methods validation (requested on March 20, 1998) by Philadelphia District Laboratory and St. Louis Laboratory is in progress.

(3) **The deficiencies noted in CMC Review # 1, Section H, List Of Chemistry Deficiencies and Comments conveyed to the applicant are addressed in an acceptable manner.**

Florian Zielinski 5/18/98

Florian Zielinski, Ph.D.
Review Chemist,
New Drug Chemistry I

File name fwz: NDA 20863 Cilostazol Review #2

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Initialed by Kasturi Srinivasachar K. Srinivasachar 6-1-98

APR - 9 1998

DIVISION OF CARDIO-RENAL DRUGS
Review of Chemistry, Manufacturing and Controls

NDA 20-863 Review # 1 Assigned 9/23/97 Complete April 3, 1998

Submission Type	Document Date	CDER Date	Topic
Original NDA SN 000	Sept 18, 1997	Sept 22, 1997	Pletal Tablets (cilostazol) for intermittent claudication
NDA Amendment	Oct 15, 1997	Oct 20, 1997	Categorical Excl for EA Req.

Name and Address of Applicant

Otsuka America Pharm. Inc.
2440 Research Blvd.
Rockville, Maryland 20878

David Warnock, Ph.D., Director, Reg. Affairs
Phone (301) 527-4927
FAX (301) 721-7527

Drug Product Name

Proprietary: **Pletal**
Nonproprietary: cilostazol
Code Name: OPC-13013, also known as Pletaal in Japan
Chemical type/Therapeutic Class: **1 S**

Patent Status: US Patent # 4,277,479 issued to Otsuka 7/7/81, expires 8/29/99

Pharmacological Category / Indication: Cilostazol is a 3,4-dihydro quinolinone derivative that is intended for the treatment of intermittent claudication. It is a vasodilator and antiplatelet - antithrombotic.

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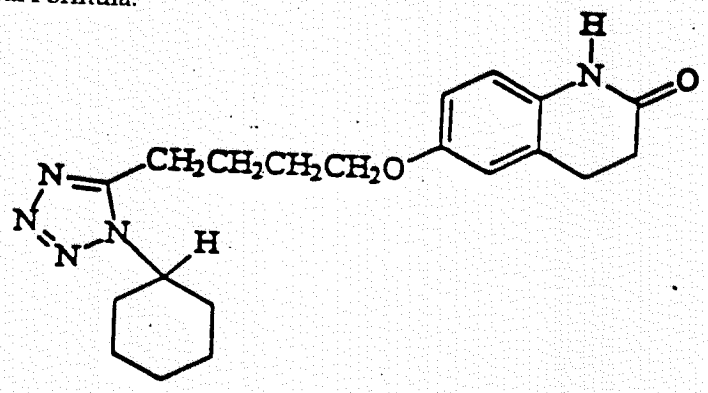

Supporting Documents :

Related Documents:
(1) Minutes from pre-NDA meeting held December 4, 1996
(2) Minutes from Filing Meeting, Oct 22, 1997: The NDA, as submitted, met Chemistry, Manufacturing and Control filing requirements of 314.101 (a)(1) because it contains sufficient CMC information to permit a substantive review.

Consults: None

Remarks and Comments:
(1) Establishment Evaluation Request submitted electronically on November 3, 1997. PAI of Otsuka Pharm Co, Second Tokushima Factory, Japan (profile: tablet, prompt release) was assigned on February 4, 1998. All other establishments are acceptable as of March 17, 1998.
(2) Analytical methods validation by Philadelphia District Laboratory and St. Louis Laboratory was requested on March 20, 1998.
(3) The trade name, Pletal, was accepted by CDER-LAN Committee on May 22, 1997.
(4) Categorically excluded from the requirement to prepare an Environmental Assessment because the expected introduction concentration (EIC) into the aquatic environment is less than 1 part per billion.
(5) **The deficiencies noted in Section H, List Of Chemistry Deficiencies and Comments, are not of such a nature to impede approval of this application. They will be conveyed to the applicant.**

Florian Zielinski April 3, 1998

Florian Zielinski, Ph.D.,
Review Chemist,
New Drug Chemistry I

File name fwz: NDA 20863 Cilostazol Review #1

Distribution:
Original NDA 20-863
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HFD-810 Charles Hoiberg
Initialed by James Short

JS 4/9/98