CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-834/S020

Trade Name: Plendil

Generic Name: Felodipine

Sponsor: AstraZaeneca LP

Approval Date: August 26, 2002

Indications: The treatment of hypertension.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-834/S020

CONTENTS

Reviews / Information Included in this NDA Review.	
Approval Letter	X
Approvable Letter	
Labeling	
Medical Review(s)	
Chemistry Review(s)	X
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/ Biopharmaceutics Review(s)	X
Administrative/Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-834/S020

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-834/S-020

AstraZeneca LP
Attention: Louis E. Kovach
Associate Director, Regulatory Affairs
1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

Dear Mr. Kovach:

Please refer to your supplemental new drug application dated April 25, 2002, received April 26, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plendil (felodipine) 2.5 mg, 5 mg and 10 mg Extended Release Tablets .

We acknowledge receipt of your submission dated August 16, 2002.

This supplemental new drug application provides for the activation of the Merck, West Point, PA, site as a manufacturer of Plendil 5 mg tablets with changes in batch size, manufacturing equipment and process.

We have completed the review of this supplemental application, and it is approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Denise Hinton, BSN, RN, Regulatory Health Project Manager, at (301) 594-5312.

Sincerely,

{See appended electronic signature page}

Kasturi Srinivasachar, Ph.D.
Chemistry Team Leader, DNDC I for the
Division of Cardio-Renal Drug Products, (HFD-110)
DNDC I, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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

/s/

Kasturi Srinivasachar
8/26/02 05:40:55 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-834/S020

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW	1. ORGANIZATION HFD - 110	2. NDA Number 19-834
3. Name and Address of Applicant (City & State) AstraZeneca 1800 Concord Pike P.O. 8355 Wilmington, Delaware 19803-8355		4. Supplement(s) Number/Date SCM-020 04-25-02
5. Drug Name PLENDIL	6. Nonproprietary Name Felodipine	8. Amendments & Other (reports, etc) - Dates SCM-020(BC) 08-16-02
7. Supplement Provides For: PRIOR APPROVAL SUPPLEMENT activation of the Merck, West Point site as a manufacturer of 5 mg tablets with the following changes: [redacted]		
9. Pharmacological Category Hypertension	10. How Dispensed /x/ RX /__/ OTC	11. Related IND(s)/ NDA(s)/DMF(s)
12. Dosage Form(s) Extended Release Tablets	13. Potency(ies) 2.5 mg, 5 mg and 10 mg	
14. Chemical Name and Structure (±) Ethylmethyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridine-dicarboxylate See structure of Felodipine on next page.		15. Records/Reports Current /x/ Yes /__/ No Reviewed /x/ Yes /__/ No

16. **Comments:**

Manufacturing equipment change is Level 2 change as per SUPAC-MR guidance of September 1997. This change requires PAS and multi-point dissolution profile data in approved and three other media. EER is acceptable and a copy is attached at the end of this review.

17. **Conclusions and Recommendations:**

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) has reviewed this supplement and the amendment and finds the supplement acceptable. See review of Lydia Velazquez dated August 21, 2002. Based on the CMC review and OCPB recommendation this supplement is approved.

18. **REVIEWER Name** Ramsharan D. Mittal **Date** 08-26-02

5 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

26-AUG-2002

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 19834/020**
Priority: **1S**
Org Code: **110**
Stamp: **26-APR-2002** Regulatory Due: **26-AUG-2002**
Action Goal:
District Goal: **22-JUL-2002**
Applicant: **ASTRAZENECA PHARMS**
1800 CONCORD PIKE
WILMINGTON, DE 198038355
Brand Name: **PLENDIL**
Established Name:
Generic Name: **FELODIPINE**
Dosage Form: **EXT (EXTENDED-RELEASE TABLET)**
Strength: **2.5 MG, 5 MG AND 10 MG**

FDA Contacts:
D. HINTON (HFD-110) 301-594-5300 , Project Manager
R. MITTAL (HFD-110) 301-594-5353 , Review Chemist
K. SRINIVASACHAR (HFD-110) 301-594-5376 , Team Leader

Overall Recommendation:

ACCEPTABLE on 15-JUL-2002 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: **2510592**
MERCK AND CO INC
SUMNEYTOWN PIKE BLA20
WEST POINT, PA 19486
DMF No:
AADA No:

Profile: **TCT** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **15-JUL-2002**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **FINISHED DOSAGE MANUFACTURER**

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

/s/

Ramsharan Mittal
8/26/02 02:39:10 PM
CHEMIST

Kasturi Srinivasachar
8/26/02 05:35:47 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-834/S020

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation I

NDA 19-834/SCN020	**SUBMISSION DATE**	April 25, 2002
FAX		August 6, 2002
FAX		August 15, 2002

TYPE:	MANUFACTURING PROCESS CHANGE
BRAND NAME:	Plendil® Tablets
GENERIC NAME:	Felodipine
DOSAGE STRENGTH:	2.5, 5, and 10 mg oral Extended-Release Tablets
SPONSOR:	AstraZeneca, LP
PRIMARY REVIEWER:	Lydia Velazquez, Pharm.D.
TEAM LEADER:	Patrick Marroum, Ph.D.

SUBMISSION:

AstraZeneca LP is activating the Merck & Co., Inc. West Point, PA site as a manufacturer of Plendil® 5 mg tablets. This manufacturing site is currently approved in NDA 19-834; but hasn't been used for production since the original validation. Changes being submitted are intended to accommodate site equipment capacity and to align the facility with the current Wilson, NC facility process. The following changes have been submitted for approval:

[redacted]

The highest level change is a Level 2, Case C equipment change. As a result, AstraZeneca is submitting dissolution data on Plendil® 5 mg tablets film coated with the proposed changes at-West Point compared to dissolution results obtained from the current Wilson process. The sponsor has stated that the proposed manufacturing process has been validated. The dissolution method used was not mentioned in this submission. As a result, a teleconference was held between the Agency and the sponsor on July 15th, 2002. The sponsor stated that the approved dissolution method in the Plendil® NDA license was used in generating the dissolution data. A fax was subsequently sent to us later that day on July 15th, 2002; which is documented in submission 019 dated March 27th, 2002 due to that submission having the same issue. Upon further review of the submitted data, no summary as to how the F_2 similarity factor calculation was performed was provided in order to assess if all calculations were performed correctly. As a result, another

teleconference was held on July 19, 2002; which resulted in further information being faxed to the supplement on August 6th, 2002. Upon review of the mentioned data, some of the dissolution tables faxed were illegible due to font size. This was communicated to the sponsor on August 13th, 2002; which further resulted in a third fax being submitted on August 15th, 2002 with data points that are now legible.

RESULTS:
All dissolution and content uniformity results conformed to the approved specifications and were comparable.

The calculated F_2 values for the batches made at the Wilson facility compared to the proposed changes at the new West Point facility containing multimedia dissolution profiles between ———

The recently faxed dissolution profiles for the proposed updated process validation study compared to the current process validation study had F_2 similarity factor values that ranged from ———

CONCLUSIONS:
Plendil® 5 mg tablets produced utilizing the new manufacturing process are of equivalent quality to the product produced by the current process and the products continue to meet the regulatory specifications registered for the products.

RECOMMENDATION:
The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation I (OCPB/DPEI) has reviewed the information provided in NDA 19-834, Supplement SCS 020 for Plendil® 5 mg tablets and finds the supplement acceptable from the Clinical Pharmacology and Biopharmaceutics perspective.

Please forward the above recommendation to the sponsor.

Lydia Velazquez, Pharm.D.
Division of Pharmaceutical Evaluation I
Primary Reviewer

FT Initialed by Patrick Marroum, Ph.D. _____
CC list: HFD-110: NDA 19-834; HFD-860: (VelazquezL, MehtaM; MarroumP);
CDER Central Document Room (Biopharm)

13 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

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

/s/

Lydia Velazquez
8/21/02 06:16:57 PM
PHARMACOLOGIST

Patrick Marroum
8/22/02 08:27:17 AM
BIOPHARMACEUTICS