CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-834/S019

Trade Name: Plendil

Generic Name: Felodipine

Sponsor: AstraZeneca LP

Approval Date: August 26, 2002

Indications: The treatment of hypertension.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-834/S019

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Reviews / Information Included in this NDA Review.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-834/S019

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-834 / S-019

AstraZeneca LP
Attention: Cindy M. Lancaster
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Ms. Lancaster:

Please refer to your supplemental new drug application dated March 27, 2002, received March 29, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plendil (felodipine) Extended Release Tablets 2.5mg, 5 mg and 10 mg.

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

This "Changes Being Effected in 30 Days" supplemental new drug application provides for optimization of the film coating process for Plendil 2.5 mg and 10 mg Tablets, involving a new film coating ——— and new coating pans. In addition, changes to the ——— solids content for the 2.5 mg strength and a ——— the film coated tablets are proposed.

We have completed the review of this supplement 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, 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

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/s/

Kasturi Srinivasachar
9/26/02 03:53:26 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-834/S019

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 SCS-019 03-27-02
5. Drug Name PLENDIL	6. Nonproprietary Name Felodipine	8. Amendments & Other (reports, etc) - Dates SCS-019(BB) 08-16-02
7. Supplement Provides For: CBE-30 SUPPLEMENT the approval of optimization of the film coating process for Plendil 2.5 mg and 10 mg tablets, minor changes to the [redacted] contents for the 2.5 mg strength, and a reduction in the [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 after the table.		15. Records/Reports Current /x/ Yes /__/ No Reviewed /x/ Yes /__/ No

16. **Comments:**
Manufacturing process changes for mixing the [redacted] come under Level 2 and require CBE Supplement. This requires one batch with three months' stability data in a CBE and-long term stability data of first batch reported in Annual Report. Changes in [redacted] that are not control releasing come under level 1 changes. This requires first production batch on long-term stability data reported in Annual Reports. Change to alternate equipment (coating pan) of the same design and operating principal of the same or of a different capacity is Level 1 Change. This requires dissolution documentation none beyond application requirements. 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 amendment and finds the supplement acceptable. See review of Lydia Velazquez dated August 14, 2002. Based on the CMC review and OCPB recommendation this supplement is approved.

18. **REVIEWER Name** Ramsharan D. Mittal **Date** 09-24-02

3 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

15-JUL-2002

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 19834/019**
Priority: **1S**
Org Code: **110**
Stamp: **29-MAR-2002** Regulatory Due: **29-SEP-2002**
Action Goal:
District Goal: **25-AUG-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**

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/s/

Ramsharan Mittal
9/25/02 03:14:09 PM
CHEMIST

Kasturi Srinivasachar
9/25/02 06:44:41 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-834/S019

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation I

NDA 19-834/SCN019	**SUBMISSION DATE:**	Mar 27, 2002
FAX		July 15, 2002
FAX		July 30, 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 seeking approval of a proposed film coating process for Plendil® 2.5 and 10 mg tablets which includes a new film coating ——— and new coating pans. Other changes being submitted include: 1) changes to the ——— 2) ——— and 3) a level 1 site change within the same building as confirmed by the sponsor via telecon on July 15th, 2002. As a result, AstraZeneca is submitting dissolution data on three batches of Plendil® 2.5 and 10 mg tablets film coated using the proposed level 1 process compared to dissolution results obtained from previous validation studies representing the current process and the revised manufacturing process for the mentioned strengths with f_2 similarity factor calculations. The sponsor has stated that the equipment being used in the current film coating process and the proposed process are of the same design and operating principal. Plendil® tablets are coated with excipients that are not release controlling. Therefore, release of active ingredient is not expected to occur by the film coating changes proposed. The sponsor has stated that the revised 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 attached in Appendix II. However, no raw data was submitted at that time for the individual dissolution batches of the current and proposed processes in order to appropriately assess all dissolution profiles. Individual raw data was not provided for the F_2 similarity factor calculation either in order to assess if all calculations were performed correctly. As a result, another telecon was conducted with the sponsor on July 17, 2002 which resulted in additional information being faxed on July 30, 2002 containing all data necessary for the assessment of all issues just mentioned.

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 019 for Plendil® tablets and finds the supplement acceptable from a 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)

Appendix I
Results of Data Submitted

Table 1

PLENDIL® 2.5 mg Extended Release Tablets – Batch Analysis Data

		Current Process			Proposed Updated Process		
Test	Specification	Batch 2086572	Batch 2086573	Batch 2086574	Batch 2086592	Batch 2086594	Batch 2086595
Appearance	A sage-green, film coated, round, biconvex tablet with code number 450 on one side and PLENDIL on the other	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
Assay							
Degradate							
Dose Uniformity	Conforms to USP requirements	Avg. 98.6% (97.1 –100.1) RSD 1.0%	Avg. 97.9% (92.9 –100.6%) RSD 2.5%	Avg. 99.4% (97.3 –102.0%) RSD 1.5%	Avg. 94.5% (93.4 – 95.6%) RSD 0.8%	Avg. 96.1% (94.7 – 97.0%) RSD 0.8%	Avg. 96.2% (94.1 – 97.6%) RSD 1.1%
Identity	HPLC- the retention times of felodipine peak in the sample and the standard chromatograms are essentially the same (within ± 2.5%)	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
Drug Release[1]	Conforms to USP[2] After 2 hrs – 10 to 30% After 6 hrs – 42 to 68% After 10 hrs - ≥ 75%	18% (16–19%) 59% (53–64%) 90% (84–95%)	16% (15–17%) 52% (51–55%) 84 % (81–88%)	17% (15– 20%) 56% (51–65%) 87% (82–96%)	16% (14–18%) 53% (49–60%) 84% (76–91%)	16% (14–18%) 53% (49–56%) 84% (76–90%)	16% (14–18%) 54% (51–61%) 85% (81–93%)

1 n = 6 for the pre-change batches, n = 24 for the post change validation batches.
2 USP General Drug Release Standard -Extended Release Articles

NDA 19-834
PLENDIL® (felodopine) Extended Release Tablets
CBE 30 Supplement

Table 2

PLENDIL® 10 mg Extended Release Tablets – Batch Analysis Data

		Current Process			Proposed Updated Process		
Test	Specification	Batch 2088574	Batch 2088934	Batch 2088935	Batch 2086916	Batch 2086917	Batch 2088471
Appearance	A red-brown, film coated, round, biconvex tablet with code number 452 on one side and PLENDIL on the other	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
Assay							
Degradate							
Dose Uniformity	Conforms to USP requirements	Avg. 102.0% (100.9-104.7) RSD 1.1%	Avg. 99.7% (98.8–100.8%) RSD 0.7%	Avg. 99.3% (98.9–99.7%) RSD 0.3%	Avg. 102.2% (100.6– 103.6%) RSD 0.9%	Avg. 101.9% (99.9–103.0%) RSD 0.9%	Avg. 101.6% (100.2– 102.7%) RSD 0.8%
Identity	HPLC- the retention times of felodipine peak in the sample and the standard chromatograms are essentially the same (within ± 2.5%)	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
Drug Release[1]	Conforms to USP[2] After 2 hrs – 10 to 30% After 6 hrs – 42 to 68 After 10 hrs - ≥ 75%	16% (15–17%) 56% (53–59%) 92% (87–97%)	17% (16–17%) 55 (53–57%) 85 % (80–87%)	16% (14–17%) 53% (51–55%) 81% (79–85%)	16% (14–20%) 55% (51–67%) 86% (81– 101%)	17% (15–21%) 58% (53–67%) 90% (84– 103%)	16% (14–20%) 55% (50–66%) 88% (82– 102%)

1. n = 6 for the pre-change batches, n = 24 for the post change validation batches.
2. USP General Drug Release Standard -Extended Release Articles

Table 3
PLENDIL® 2.5 mg Extended Release Tablets – Dissolution Profile Comparison

	Average Drug Release Results			
	Current Process, Validation Study NSV 96-037	Proposed Updated Process Validation Study		
Time	Avg. Drug Release Result for the Batches	Batch 2086592	Batch 2086594	Batch 2086595
After 2 hrs	19%	16%	16%	16%
After 6 hrs	59%	53%	53%	54%
After 10 hrs	90%	84%	84%	85%
F_2 similarity factor vs. avg. of batches from NSV 96-037		64	64	67

Table 4
PLENDIL® 10 mg Extended Release Tablets – Dissolution Profile Comparison

	Average Drug Release Results				
	Current Process Validation Study NSV 97-060	Current Process Validation Study NSV 2001-010	Proposed Updated Process Validation Study		
Time	Average Drug Release Result for the Batches	Average Drug Release Result for the Batch	Batch 2086916	Batch 2086917	Batch 2088471
After 2 hrs	19%	17%	16%	17%	16%
After 6 hrs	60%	54%	55%	58%	55%
After 10 hrs	91%	84%	86%	90%	88%
F_2 similarity factor-vs. avg. of batches from NSV 97-060			67	85	70
F_2 similarity factor – vs. avg. of batch from NSV 2001-010			88	68	79

RESULTS:

Three validation batches, each of 2.5 mg and 10 mg tablets were coated using the proposed changes. Batch analysis data for both 2.5mg and 10mg tablets just mentioned was compared to three lots manufactured by the current process are included in tables 1 and 2 below. All dissolution and content uniformity results conformed to the approved specifications and were comparable.

The average dissolution results for each of the new batches was compared to the average dissolution results from previous validation studies and is illustrated in tables 3 and 4. The calculated F_2 values for the validation batches made with the proposed changes using the average results from the previous studies as reference data were between 50 and 100 and are illustrated in a tabulated format in tables 3 and 4.

CONCLUSIONS:

Plendil® 2.5 and 10 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.

Appendix II
July 15th 2002 FAX

AstraZeneca

Fax

To Lydia Velazquez, Ph.D. Fax number 301-4[illegible]-32[illegible]

Company FDA

From [illegible] Fax number (610) 655 [illegible]

Date 7/[illegible]/02 Total pages 3

Subject Plendil NDA 19-834

CONFIDENTIAL

Attached please find Dissolution Information for Plendil NDA 19-834

Thank you,

[signature]

AstraZeneca
725 Chesterbrook Blvd
Wayne, PA 19087

Tel +1 610 695 1000

AstraZeneca

Date: July 15, 2002

Lydia Velazquez, Ph.D
Division of Cardio-Renal Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room, HFD-110
1451 Rockville Pike
Rockville, MD 20857

Re: NDA 19-834
PLENDIL® (felodipine) Extended Release Tablets
Dissolution Information

Dear Dr. Velazquez:

The purpose of this supplement is to provide the requested dissolution information regarding Plendil Extended Release Tablets.

The currently approved NDA dissolution method uses the following parameters:

- Paddle method
- 50 RPM
- Release medium: 500 ml of pH 6.5 phosphate buffer with 1% sodium lauryl sulfate

The currently approved NDA dissolution specifications are as follows:

After 2 hours – 10 to 30 %
After 6 hours – 42 to 68 %
After 10 hours - ≥ 75 %

US Regulatory Affairs
AstraZeneca LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

AZ0010 (8/06)

NDA 19-834 PLENDIL® (felodipine) Extended Release Tablets

Please direct any questions or requests for additional information to me, or in my absence, to Patricia Patterson, Associate Director, at (610) 695-1539.

Sincerely,

Thomas A. Santilli for

Louis E. Kovach, Associate Director
Regulatory Affairs
Telephone: (302) 885-4501
Fax: (302) 886-2822

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/s/

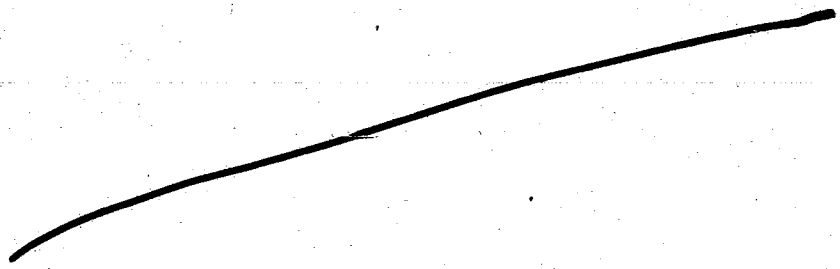
Lydia Velazquez
8/14/02 03:04:49 PM
PHARMACOLOGIST

Patrick Marroum
8/15/02 08:46:04 AM
BIOPHARMACEUTICS

Responses to FDA Conversation with the Agency on November 9, 1999

On July 23, 1999, a prior approval supplement was submitted to NDA 19-834 for the use of an alternate blister packaging for PLENDIL® Extended Release Tablets. In S-016, data are provided to show that the new alternate ——— blister" packaging meets USP XXIII <671> criteria for moisture vapor transmission and these results (MVTR) are provided in the supplement. In a phone conversation between Mr. Alansky and Dr. Mittal of the Agency on November 9, 1999, Dr. Mittal requested that moisture vapor transmission results be provided for the current blister used for PLENDIL® Tablets. In response to Dr. Mittal's request, Table 1 provides MVTR data for the current blister used to package PLENDIL® Tablets.

Table 1 – Moisture Vapor Transmission Results (MVTR) for the Current Blister



AstraZeneca

Fax

To	Dr. Ramsharan Mittal	**Fax number**	301-594-5494
Company	FDA		
From	Len Alansky	**Fax number**	610-695-4031
Date	12 November, 1999; 10:33	**Total pages**	1(2)
Subject	Reference NDA 19-834 Supplement S-016 Dated July 23, 1999 Moisture Permeation Data for Current Plendil® Blister Package		

CONFIDENTIAL

Dear Dr. Mittal,

As requested in your telephone message left November 9, 1999 please find the moisture vapor transmission results for the current blister package of Plendil Tablets.

Let me know if you have additional questions.

Sincerely,

Len Alansky
CMC Manager

cc: Emery Gigger (AZLP)

AstraZeneca L.P.
725 Chesterbrook Blvd
Wayne, PA 19087

Tel +1 610 695 1000