CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 75-896

***Name*:** Felodipine Extended-release Tablets USP, 2.5 mg, 5 mg, and 10 mg

***Sponsor*:** Mutual Pharmaceutical Company, Inc.

***Approval Date*:** November 2, 2004

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APPLICATION NUMBER:

ANDA 75-896

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-896

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

ANDA 75-896

Food and Drug Administration
Rockville MD 20857

NOV 2 2004

Mutual Pharmaceutical Company, Inc.
Attention: Robert Dettery
1100 Orthodox Street
Philadelphia, PA 19124

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated June 6, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Felodipine Extended-release Tablets USP, 2.5 mg, 5 mg and 10 mg.

Reference is also made to the Tentative Approval letter issued by this office on February 6, 2004, and to your amendments dated April 30, and June 25, 2001; and October 1, October 4, October 5, and October 19, 2004. We acknowledge receipt of your correspondence dated October 1, and October 29, 2004, addressing the courts findings of non-infringement by Mutual of the '081 patent.

As noted in our tentative approval letter dated February 6, 2004, the listed drug product referenced in your application, Plendil Extended-release Tablets of AstraZeneca, is subject to a period of patent protection that is scheduled to expire on October 3, 2007, (U.S. Patent No. 4,803,081), the '081 patent. In response to your paragraph IV certification to this patent, you informed the agency that AstraZeneca Pharmaceuticals LP initiated a patent infringement action against you in the United States District Court for the Eastern District of Pennsylvania (AstraZeneca AB, Aktiebolaget Hassle, KBI-E Inc., KBI Inc. and AstraZeneca LP v. Mutual Pharmaceutical Company, Inc. (Mutual), Civil Action No. 00-CV-4731). Subsequently, you notified the Agency that on November 12, 2003, the District Court ruled in favor of AstraZeneca and concluded that Mutual did infringe upon the '081 patent. Mutual appealed the District Court's decision to the U.S. Court of Appeals for the Federal Circuit. On September 30, 2004, the U.S. Court of Appeals overturned the District Court's decision by ruling that Mutual did not infringe the '081 patent. On October 29, 2004, the District Court

officially vacated its earlier ruling and stated that Mutual did not infringe the '081 patent under this ANDA.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Felodipine Extended-release Tablets USP, 2.5 mg, 5 mg, and 10 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Plendil Extended-release Tablets USP, 2.5 mg, 5 mg and 10 mg, respectively, of AstraZeneca Pharmaceuticals LP.

Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application. The "interim" dissolution specifications are as follows:

Dissolution Testing should be conducted in [redacted] The test product should meet the following "interim" specifications:

Sampling Time (hours)	% Dissolved
1	[redacted]
4	
8	

The "interim" dissolution test(s) and tolerances should be finalized by submitting dissolution data for the first three production size batches. These data should be submitted as a "Special Supplement - Changes Being Effected" when there are no revisions to be made to the "interim" specifications or when the final specifications are tighter than the "interim" specifications. In all other instances, the information should be submitted in the form of a Prior Approval Supplement.

With this approval, Mutual is eligible for 180-day generic drug exclusivity for Felodipine Extended-release Tablets USP, 2.5 mg, 5 mg, and 10 mg as provided for under the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments) in Section 505(j)(5)(B)(iv) of the Act. This is because the Agency has determined that Mutual was the first ANDA applicant to submit a substantially complete ANDA for this drug product containing a paragraph IV certification to the '081 patent. This exclusivity began on October 29, 2004, the date

the District Court entered its judgment concluding that Mutual did not infringe the '081 patent.

If you have any questions concerning the effective date of approval of an abbreviated new drug application and the Agency's elimination of the requirement that an ANDA applicant successfully defend a patent infringement suit to be eligible for 180-days of marketing exclusivity, please refer to the interim rule published in the November 5, 1998 Federal Register (Volume 63, No. 214, 59710).

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications, HFD-42
5600 Fishers Lane
Rockville, MD 20857

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications (HFD-42) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Robert L. Lest / for 11/2/2004

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-896
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-610/Orange Book Staff
HFD-600/C. Parise
HFD-604/D. Hare

HFD-646/B.Mirzai-Azarm/ B. M. Azam 10/29/04.
HFD-647/U.Venkataram/ U.V. Venkataram 10/29/04
HFD-617/S.Shepperson/ SShepperson 10-29-04
see email { HFD-613/A.Vezza/
HFD-613/L.Golson/

11/1/04

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F/T by sms 10-21-04

APPROVAL

Robert West
11/2/2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-896

TENTATIVE APPROVAL LETTER

ANDA 75-896

FEB 6 2004

Mutual Pharmaceutical Company, Inc.
Attention: Robert Dettery
1100 Orthodox St.
Philadelphia, PA 19124

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated June 6, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Felodipine Extended-Release Tablets 2.5 mg, 5 mg, and 10 mg.

Reference is also made to your amendments dated April 11, May 13, and September 10, 2003. We also acknowledge receipt of your correspondence dated July 21, August 29, September 12, and November 17, 2000; and November 26, 2003, addressing the patent issues noted below.

We have completed the review of this abbreviated application, and based upon the information you have presented to date we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. However, we are unable to grant final approval to your application at this time because of ongoing litigation over the listed patent as explained below. Therefore, the application is **tentatively approved**. This determination is based upon information available to the agency at this time (i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product). The determination is subject to change on the basis of new information that may come to our attention. This letter does not address notice issues related to the 180-day exclusivity provisions under Section 505(j)(5)(B)(iv) of the Act.

The listed drug product (RLD) referenced in your application, Plendil Tablets 2.5 mg, 5 mg, and 10 mg, of AstraZeneca Pharmaceuticals LP, is subject to a period of patent protection. As noted in the agency's publication entitled Approved Drug

Products with Therapeutic Equivalence Evaluations, the "Orange Book", U.S. Patent No. 4,803,081 (the '081 patent) is due to expire on October 3, 2007. Your ANDA contains a patent certification under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, or sale of Felodipine Extended-release Tablets 2.5 mg, 5 mg, and 10 mg under this ANDA will not infringe the '081 patent. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately unless an action is brought against Mutual Pharmaceutical Company Inc. (Mutual) for infringement of the '081 patent that was the subject of the paragraph IV certification. This action must be brought against Mutual prior to the expiration of forty-five (45) days from the date the notice you provided under Section 505(j)(2)(i) was received by the NDA/patent holder. You have notified the agency that Mutual complied with the requirements of Section 505(j)(2)(B) of the Act. As a result, litigation was brought against Mutual in the United States District Court for the Eastern District of Pennsylvania involving a challenge to the '081 patent (AstraZeneca AB, Aktiebolaget Hassle, KBI-E Inc., KBI Inc., and AstraZeneca LP v. Mutual Pharmaceutical Company, Inc., Civil Action No. 00-CV-4731). You have also notified the agency that on November 12, 2003, U.S. District Judge Michael M. Baylson entered a Final Judgement in favor of AstraZeneca and against Mutual. In addition, the Court ordered that this ANDA should not be approved until the '081 patent expires (currently October 3, 2007). Furthermore, you have informed the agency that Mutual has appealed the district court decision. Therefore, final approval cannot be granted until:

1. a. the date of the appellate court decision, or in the absence of a favorable appellate court decision,

   b. the '081 patent has expired, and

2. The agency is assured there is no new information that would affect whether final approval should be granted.

In order to reactivate your application prior to final approval, please submit a MINOR AMENDMENT - FINAL APPROVAL REQUESTED 90 days prior to the date you believe that your ANDA will be eligible for final approval. This amendment should include an explanation of why you believe that the ANDA is eligible for final approval, and it should also identify changes, if any, in the conditions under which the ANDA was tentatively approved, i.e., updated information such as final-printed labeling,

chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made, and it should be designated clearly in your cover letter as a MINOR AMENDMENT - FINAL APPROVAL REQUESTED.

In addition to the amendment requested above, the agency may request at any time prior to the date of final approval that you submit an additional amendment containing the requested information. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your application, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this abbreviated application as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (cGMPs) are subject to agency review before final approval of the application will be made. Such changes should be categorized as representing either "major" or "minor" changes, and they will be reviewed according to OGD policy in effect at the time of receipt. The submission of multiple amendments prior to final approval may also result in a delay in the issuance of the final approval letter.

This drug product may not be marketed without final agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under section 501 of the Act and 21 U.S.C. 331(d). Also, until the agency issues the final approval letter, this drug product will not be deemed to be approved for marketing under 21 U.S.C. 355, and will not be listed in the "Orange Book".

For further information on the status of this application, or prior to submitting additional amendments, please contact Stanely Shepperson, Project Manager, at 301-827-5849.

Sincerely yours,

Gary Buehler 2/6/04
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-896
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-610/Orange Book Staff

Endorsements:
HFD-647/B.M. Azarm/ B.M. Azarm 12/18/03
HFD-647/U.Venkataram/ U.V. Venkataram 12/18/03.
HFD-617/S.Shepperson/ S. Shepperson 12/18/03
HFD-613/A.Vezza/ A. Vezza 12/18/03
HFD-613/L.Golson/ L. Golson 12/18/03

AM Mutual 75896

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F/T by rad12/17/03

TENTATIVE APPROVAL

Robert Lost
2/3/2004

Comc satisfactory
Lloyd Sayre
1/9/04.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-896

LABELING

N 53489-368-99

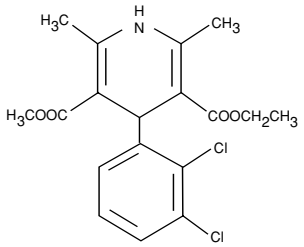
617

℞ only

FELODIPINE EXTENDED-RELEASE TABLETS

DESCRIPTION

Felodipine is a calcium antagonist (calcium channel blocker). Felodipine is a dihydropyridine derivative that is chemically described as ± ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate. Its molecular formula is $C_{18}H_{19}Cl_2NO_4$ and its structural formula is:



Felodipine is a slightly yellowish, crystalline powder with a molecular weight of 384.26. It is insoluble in water and is freely soluble in dichloromethane and ethanol. Felodipine is a racemic mixture.

Felodipine tablets provide extended release of felodipine. They are available as tablets containing 2.5 mg, 5 mg, or 10 mg of felodipine for oral administration. In addition to the active ingredient felodipine, the tablets contain the following inactive ingredients: felodipine tablets 2.5 mg — carnauba wax, hypromellose, hydroxypropyl cellulose, microcrystalline cellulose, polyethylene glycol, povidone, silicon dioxide, titanium dioxide, D&C Yellow #10 Lake, FD&C Red No. 40 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake. Felodipine tablets 5 mg — carnauba wax, hypromellose, microcrystalline cellulose, polyethylene glycol, polysorbate 80, povidone, silicon dioxide, titanium dioxide, FD&C Red No. 40 Aluminum Lake, D&C Yellow No. 10 Aluminum Lake. Felodipine tablets 10 mg — carnauba wax, hypromellose, hydroxypropyl cellulose, microcrystalline cellulose, polyethylene glycol, povidone, silicon dioxide, titanium dioxide, D&C Yellow #10 Lake, FD&C Red No. 40 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake.

CLINICAL PHARMACOLOGY

Mechanism of Action

Felodipine is a member of the dihydropyridine class of calcium channel antagonists (calcium channel blockers). It reversibly competes with nitrendipine and/or other calcium channel blockers for dihydropyridine binding sites, blocks voltage-dependent Ca^{++} currents in vascular smooth muscle and cultured rabbit atrial cells, and blocks potassium-induced contracture of the rat portal vein.

In vitro studies show that the effects of felodipine on contractile processes are selective, with greater effects on vascular smooth muscle than cardiac muscle. Negative inotropic effects can be detected *in vitro,* but such effects have not been seen in intact animals.

The effect of felodipine on blood pressure is principally a consequence of a dose-related decrease of peripheral vascular resistance in man, with a modest reflex increase in heart rate (see **Cardiovascular Effects**). With the exception of a mild diuretic effect seen in several animal species and man, the effects of felodipine are accounted for by its effects on peripheral vascular resistance.

Pharmacokinetics and Metabolism

Following oral administration, felodipine is almost completely absorbed and undergoes extensive first-pass metabolism. The systemic bioavailability of felodipine is approximately 20%. Mean peak concentrations following the administration of felodipine are reached in 2.5 to 5 hours. Both peak plasma concentration and the area under the plasma concentration time curve (AUC) increase linearly with doses up to 20 mg. Felodipine is greater than 99% bound to plasma proteins.

Following intravenous administration, the plasma concentration of felodipine declined triexponentially with mean disposition half-lives of 4.8 minutes, 1.5 hours, and 9.1 hours. The mean contributions of the three individual phases to the overall AUC were 15, 40, and 45%, respectively, in the order of increasing $t_{1/2}$.

Following oral administration of the immediate-release formulation, the plasma level of felodipine also declined polyexponentially with a mean terminal $t_{1/2}$ of 11 to 16 hours. The mean peak and trough steady-state plasma concentrations achieved after 10 mg of the immediate-release formulation given once a day to normal volunteers, were 20 and 0.5 nmol/L, respectively. The trough plasma concentration of felodipine in most individuals was substantially below the concentration needed to effect a half-maximal decline in blood pressure (EC_{50}) [4-6 nmol/L for felodipine], thus precluding once-a-day dosing with the immediate-release formulation.

Following administration of a 10-mg dose of felodipine, the extended-release formulation, to young, healthy volunteers, mean peak and trough steady-state plasma concentrations of felodipine were 7 and 2 nmol/L, respectively. Corresponding values in hypertensive patients (mean age 64) after a 20-mg dose of felodipine were 23 and 7 nmol/L. Since the EC_{50} for felodipine is 4 to 6 nmol/L, a 5- to 10-mg dose of felodipine in some patients, and a 20-mg dose in others, would be expected to provide an antihypertensive effect that persists for 24 hours (see **Cardiovascular Effects** below and **DOSAGE AND ADMINISTRATION**).

The systemic plasma clearance of felodipine in young healthy subjects is about 0.8 L/min, and the apparent volume of distribution is about 10 L/kg.

Following an oral or intravenous dose of ^{14}C-labeled felodipine in man, about 70% of the dose of radioactivity was recovered in urine and 10% in the feces. A negligible amount of intact felodipine is recovered in the urine and feces (< 0.5%). Six metabolites, which account for 23% of the oral dose, have been identified; none has significant vasodilating activity.

Following administration of felodipine to hypertensive patients, mean peak plasma concentrations at steady state are about 20% higher than after a single dose. Blood pressure response is correlated with plasma concentrations of felodipine.

The bioavailability of felodipine is influenced by the presence of food. When administered either with a high fat or carbohydrate diet, C_{max} is increased by approximately 60%; AUC is unchanged. When felodipine was administered after a light meal (orange juice, toast, and cereal), however, there is no effect on felodipine's pharmacokinetics. The bioavailability of felodipine was increased approximately two-fold when taken with grapefruit juice. Orange juice does not appear to modify the kinetics of felodipine. A similar finding has been seen with other dihydropyridine calcium antagonists, but to a lesser extent than that seen with felodipine.

Geriatric Use— Plasma concentrations of felodipine, after a single dose and at steady state, increase with age. Mean clearance of felodipine in elderly hypertensives (mean age 74) was only 45% of that of young volunteers (mean age 26). At steady state mean AUC for young patients was 39% of that for the elderly. Data for intermediate age ranges suggest that the AUCs fall between the extremes of the young and the elderly.

Hepatic Dysfunction— In patients with hepatic disease, the clearance of felodipine was reduced to about 60% of that seen in normal young volunteers.

Renal impairment does not alter the plasma concentration profile of felodipine; although higher concentrations of the metabolites are present in the plasma due to decreased urinary excretion, these are inactive.

Animal studies have demonstrated that felodipine crosses the blood-brain barrier and the placenta.

Cardiovascular Effects

Following administration of felodipine, a reduction in blood pressure generally occurs within 2 to 5 hours. During chronic administration, substantial blood pressure control lasts for 24 hours, with trough reductions in diastolic blood pressure approximately 40-50% of peak reductions. The antihypertensive effect is dose dependent and correlates with the plasma concentration of felodipine.

A reflex increase in heart rate frequently occurs during the first week of therapy; this increase attenuates over time. Heart rate increases of 5-10 beats per minute may be seen during chronic dosing. The increase is inhibited by beta-blocking agents.

The P-R interval of the ECG is not affected by felodipine when administered alone or in combination with a beta-blocking agent. Felodipine alone or in combination with a beta-blocking agent has been shown, in clinical and electrophysiologic studies, to have no significant effect on cardiac conduction (P-R, P-Q, and H-V intervals).

In clinical trials in hypertensive patients without clinical evidence of left ventricular dysfunction, no symptoms suggestive of a negative inotropic effect were noted; however, none would be expected in this population (see **PRECAUTIONS**).

Renal/Endocrine Effects

Renal vascular resistance is decreased by felodipine while glomerular filtration rate remains unchanged. Mild diuresis, natriuresis, and kaliuresis have been observed during the first week of therapy. No significant effects on serum electrolytes were observed during short- and long-term therapy.

In clinical trials in patients with hypertension, increases in plasma noradrenaline levels have been observed.

Clinical Studies

Felodipine produces dose-related decreases in systolic and diastolic blood pressure as demonstrated in six placebo-controlled, dose response studies using either immediate-release or extended-release dosage forms. These studies enrolled over 800 patients on active treatment, at total daily doses ranging from 2.5 to 20 mg. In those studies felodipine was administered either as monotherapy or was added to beta blockers. The results of the 2 studies with felodipine given once daily as monotherapy are shown in the table below:

MEAN REDUCTIONS IN BLOOD PRESSURE (mmHg)*

Dose	N	Systolic/Diastolic Mean Peak Response	Mean Trough Response	Trough/Peak Ratios (%s)
		Study 1 (8 weeks)		
2.5 mg	68	9.4/4.7	2.7/2.5	29/53
5 mg	69	9.5/6.3	2.4/3.7	25/59
10 mg	67	18.0/10.8	10.0/6.0	56/56
		Study 2 (4 weeks)		
10 mg	50	5.3/7.2	1.5/3.2	33/40 **
20 mg	50	11.3/10.2	4.5/3.2	43/34 **

* Placebo response subtracted

** Different number of patients available for peak and trough measurements

INDICATIONS AND USAGE

Felodipine is indicated for the treatment of hypertension.

Felodipine may be used alone or concomitantly with other antihypertensive agents.

CONTRAINDICATIONS

Felodipine is contraindicated in patients who are hypersensitive to this product.

PRECAUTIONS

General

Hypotension — Felodipine, like other calcium antagonists, may occasionally precipitate significant hypotension and, rarely, syncope. It may lead to reflex tachycardia which in susceptible individuals may precipitate angina pectoris. (See **ADVERSE REACTIONS.**)

Heart Failure — Although acute hemodynamic studies in a small number of patients with NYHA Class II or III heart failure treated with felodipine have not demonstrated negative inotropic effects, safety in patients with heart failure has not been established. Caution, therefore, should be exercised when using felodipine in patients with heart failure or compromised ventricular function, particularly in combination with a beta blocker.

Patients with Impaired Liver Function — Patients with impaired liver function may have elevated plasma concentrations of felodipine and may respond to lower doses of felodipine; therefore, a starting dose of 2.5 mg once a day is recommended. These patients should have their blood pressure monitored closely during dosage adjustment of felodipine. (See **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION.**)

Peripheral Edema — Peripheral edema, generally mild and not associated with generalized fluid retention, was the most common adverse event in the clinical trials. The incidence of peripheral edema was both dose and age dependent. Frequency of peripheral edema ranged from about 10% in patients under 50 years of age taking 5 mg daily to about 30% in those over 60 years of age taking 20 mg daily. This adverse effect generally occurs within 2-3 weeks of the initiation of treatment.

Information for Patients

Patients should be instructed to take felodipine whole and not to crush or chew the tablets. They should be told that mild gingival hyperplasia (gum swelling) has been reported. Good dental hygiene decreases its incidence and severity.

NOTE: As with many other drugs, certain advice to patients being treated with felodipine is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions

CYP3A4 Inhibitors — Felodipine is metabolized by CYP3A4. Coadministration of CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, erythromycin, grapefruit juice, cimetidine) with felodipine may lead to several-fold increases in the plasma levels of felodipine, either due to an increase in bioavailability or due to a decrease in metabolism. These increases in concentration may lead to increased effects, (lower blood pressure and increased heart rate). These effects have been observed with coadministration of itraconazole (a potent CYP3A4 inhibitor). Caution should be used when CYP3A4 inhibitors are coadministered with felodipine. A conservative approach to dosing felodipine should be taken. The following specific interactions have been reported:

Itraconazole — Coadministration of another extended release formulation of felodipine with itraconazole resulted in approximately 8-fold increase in the AUC, more than 6-fold increase in the C_{max}, and 2-fold prolongation in the half-life of felodipine.

Erythromycin — Coadministration of felodipine with erythromycin resulted in approximately 2.5-fold increase in the AUC and C_{max}, and about 2-fold prolongation in the half-life of felodipine.

Grapefruit juice — Coadministration of felodipine with grapefruit juice resulted in more than 2-fold increase in the AUC and C_{max}, but no prolongation in the half-life of felodipine.

Cimetidine — Coadministration of felodipine with cimetidine (a non-specific CYP-450 inhibitor) resulted in an increase of approximately 50% in the AUC and the C_{max}, of felodipine.

Beta-Blocking Agents — A pharmacokinetic study of felodipine in conjunction with metoprolol demonstrated no significant effects on the pharmacokinetics of felodipine. The AUC and C_{max} of metoprolol, however, were increased approximately 31 and 38%, respectively. In controlled clinical trials, however, beta blockers including metoprolol were concurrently administered with felodipine and were well tolerated.

Digoxin — When given concomitantly with felodipine the pharmacokinetics of digoxin in patients with heart failure were not significantly altered.

Anticonvulsants — In a pharmacokinetic study, maximum plasma concentrations of felodipine were considerably lower in epileptic patients on long-term anticonvulsant therapy (e.g., phenytoin. carbamazepine, or phenobarbital) than in healthy volunteers. In such patients, the mean area under the felodipine plasma concentration-time curve was also reduced to approximately 6% of that observed in healthy volunteers. Since a clinically significant interaction may be anticipated, alternative antihypertensive therapy should be considered in these patients.

Tacrolimus — Felodipine may increase the blood concentration of tacrolimus. When given concomitantly with felodipine, the tacrolimus blood concentration should be followed and the tacrolimus dose may need to be adjusted.

Other Concomitant Therapy — In healthy subjects there were no clinically significant interactions when felodipine was given concomitantly with indomethacin or spironolactone.

Interaction with Food — See **CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism.**

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study in rats fed felodipine at doses of 7.7, 23.1 or 69.3 mg/kg/day (up to 61 times** the maximum recommended human dose on a mg/m² basis), a dose-related increase in the incidence of benign interstitial cell tumors of the testes (Leydig cell tumors) was observed in treated male rats. These tumors were not observed in a similar study in mice at doses up to 138.6 mg/kg/day (61 times** the maximum recommended human dose on a mg/m² basis). Felodipine, at the doses employed in the 2-year rat study, has been shown to lower testicular testosterone and to produce a corresponding increase in serum luteinizing hormone in rats. The Leydig cell tumor development is possibly secondary to these hormonal effects which have not been observed in man.

In this same rat study a dose-related increase in the incidence of focal squamous cell hyperplasia compared to control was observed in the esophageal groove of male and female rats in all dose groups. No other drug-related esophageal or gastric pathology was observed in the rats or with chronic administration in mice and dogs. The latter species, like man, has no anatomical structure comparable to the esophageal groove.

Felodipine was not carcinogenic when fed to mice at doses up to 138.6 mg/kg/day (61 times** the maximum recommended human dose on a mg/m² basis) for periods of up to 80 weeks in males and 99 weeks in females.

Felodipine did not display any mutagenic activity *in vitro* in the Ames microbial mutagenicity test or in the mouse lymphoma forward mutation assay. No clastogenic potential was seen *in vivo* in the mouse micronucleus test at oral doses up to 2500 mg/kg (1,100 times** the maximum recommended human dose on a mg/m² basis) or *in vitro* in a human lymphocyte chromosome aberration assay.

A fertility study in which male and female rats were administered doses of 3.8, 9.6 or 26.9 mg/kg/day (up to 24 times** the maximum recommended human dose on a mg/m² basis) showed no significant effect of felodipine on reproductive performance.

**Based on patient weight of 50 kg

Pregnancy:

Pregnancy Category C.

Teratogenic Effects: — Studies in pregnant rabbits administered doses of 0.46, 1.2, 2.3, and 4.6 mg/kg/day (from 0.8 to 8 times** the maximum recommended human dose on a mg/m² basis) showed digital anomalies consisting of reduction in size and degree of ossification of the terminal phalanges in the fetuses. The frequency and severity of the changes appeared dose related and were noted even at the lowest dose. These changes have been shown to occur with other members of the dihydropyridine class and are possibly a result of compromised uterine blood flow. Similar fetal anomalies were not observed in rats given felodipine.

In a teratology study in cynomolgus monkeys, no reduction in the size of the terminal phalanges was observed, but an abnormal position of the distal phalanges was noted in about 40% of the fetuses.

Nonteratogenic Effects — A prolongation of parturition with difficult labor and an increased frequency of fetal and early postnatal deaths were observed in rats administered doses of 9.6 mg/kg/day (8 times** the maximum human dose on a mg/m² basis) and above.

Significant enlargement of the mammary glands, in excess of the normal enlargement for pregnant rabbits, was found with doses greater than or equal to 1.2 mg/kg/day (2.1 times the maximum human dose on a mg/m² basis). This effect occurred only in pregnant rabbits and regressed during lactation.

Similar changes in the mammary glands were not observed in rats or monkeys.

There are no adequate and well-controlled studies in pregnant women. If felodipine is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus, possible digital anomalies of the infant, and the potential effects of felodipine on labor and delivery and on the mammary glands of pregnant females.

**Based on patient weight of 50 kg

Nursing Mothers

It is not known whether this drug is secreted in human milk and because of the potential for serious adverse reactions from felodipine in the infant, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use:

Clinical studies of felodipine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Pharmacokinetics, however, indicate that the availability of felodipine is increased in older patients (see **CLINICAL PHARMACOLOGY, Geriatric Use**). In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

In controlled studies in the United States and overseas, approximately 3,000 patients were treated with felodipine as either the extended-release or the immediate-release formulation.

The most common clinical adverse events reported with felodipine administered as monotherapy at the recommended dosage range of 2.5 mg to 10 mg once a day were peripheral edema and headache. Peripheral edema was generally mild, but it was age and dose related and resulted in discontinuation of therapy in about 3% of the enrolled patients. Discontinuation of therapy due to any clinical adverse event occurred in about 6% of the patients receiving felodipine, principally for peripheral edema, headache, or flushing.

Adverse events that occurred with an incidence of 1.5% or greater at any of the recommended doses of 2.5 mg to 10 mg once a day (felodipine, N = 861; Placebo, N = 334), without regard to causality, are compared to placebo and are listed by dose in the table below. These events are reported from controlled clinical trials with patients who were randomized to a fixed dose of felodipine or titrated from an initial dose of 2.5 mg or 5 mg once a day. A dose of 20 mg once a day has been evaluated in some clinical studies. Although the antihypertensive effect of felodipine is increased at 20 mg once a day, there is a disproportionate increase in adverse events, especially those associated with vasodilatory effects (see **DOSAGE AND ADMINISTRATION**).

Percent of Patients with Adverse Events in Controlled Trials * of felodipine (N=861) as Monotherapy without Regard to Causality (Incidence of discontinuations shown in parentheses)

Body System Adverse Events	Placebo N=334	2.5 mg N=255	5 mg N=581	10 mg N=408
Body as a Whole				
Peripheral Edema	3.3 (0.0)	2.0 (0.0)	8.8 (2.2)	17.4 (2.5)
Asthenia	3.3 (0.0)	3.9 (0.0)	3.3 (0.0)	2.2 (0.0)
Warm Sensation	0.0 (0.0)	0.0 (0.0)	0.9 (0.2)	1.5 (0.0)
Cardiovascular				
Palpitation	2.4 (0.0)	0.4 (0.0)	1.4 (0.3)	2.5 (0.5)
Digestive				
Nausea	1.5 (0.9)	1.2 (0.0)	1.7 (0.3)	1.0 (0.7)
Dyspepsia	1.2 (0.0)	3.9 (0.0)	0.7 (0.0)	0.5 (0.0)
Constipation	0.9 (0.0)	1.2 (0.0)	0.3 (0.0)	1.5 (0.2)
Nervous				
Headache	10.2 (0.9)	10.6 (0.4)	11.0 (1.7)	14.7 (2.0)
Dizziness	2.7 (0.3)	2.7 (0.0)	3.6 (0.5)	3.7 (0.5)
Paresthesia	1.5 (0.3)	1.6 (0.0)	1.2 (0.0)	1.2 (0.2)
Respiratory				
Upper Respiratory Infection	1.8 (0.0)	3.9 (0.0)	1.9 (0.0)	0.7 (0.0)
Cough	0.3 (0.0)	0.8 (0.0)	1.2 (0.0)	1.7 (0.0)
Rhinorrhea	0.0 (0.0)	1.6 (0.0)	0.2 (0.0)	0.2 (0.0)
Sneezing	0.0 (0.0)	1.6 (0.0)	0.0 (0.0)	0.0 (0.0)
Skin				
Rash	0.9 (0.0)	2.0 (0.0)	0.2 (0.0)	0.2 (0.0)
Flushing	0.9 (0.3)	3.9 (0.0)	5.3 (0.7)	6.9 (1.2)

* Patients in titration studies may have been exposed to more than one dose level of felodipine.

Adverse events that occurred in 0.5 up to 1.5% of patients who received felodipine in all controlled clinical trials at the recommended dosage range of 2.5 mg to 10 mg once a day, and serious adverse events that occurred at a lower rate, or events reported during marketing experience (those lower rate events are in italics) are listed below. These events are listed in order of decreasing severity within each category, and the relationship of these events to administration of felodipine is uncertain: ***Body as a Whole:*** Chest pain, facial edema, flu-like illness; ***Cardiovascular:*** *Myocardial infarction, hypotension, syncope, angina pectoris, arrhythmia,* tachycardia, premature beats; ***Digestive:*** Abdominal pain, diarrhea, vomiting, dry mouth, flatulence, acid regurgitation; ***Endocrine:*** Gynecomastia; ***Hematologic:*** *Anemia;* ***Metabolic:*** ALT (SGPT) increased; ***Musculoskeletal:*** Arthralgia, back pain, leg pain, foot pain, muscle cramps, myalgia, arm pain, knee pain, hip pain; ***Nervous/Psychiatric:*** Insomnia, depression, anxiety disorders, irritability, nervousness, somnolence, decreased libido; ***Respiratory:*** Dyspnea, pharyngitis, bronchitis, influenza, sinusitis, epistaxis, respiratory infection; ***Skin:*** Angioedema, contusion, erythema, urticaria, *leukocytoclastic vasculitis;* ***Special Senses:*** Visual disturbances; ***Urogenital:*** Impotence, urinary frequency, urinary urgency, dysuria, polyuria.

Gingival Hyperplasia — Gingival hyperplasia, usually mild, occurred in < 0.5% of patients in controlled studies. This condition may be avoided or may regress with improved dental hygiene. (See **PRECAUTIONS, Information for Patients.**)

Clinical Laboratory Test Findings

Serum Electrolytes — No significant effects on serum electrolytes were observed during short- and long-term therapy (see **CLINICAL PHARMACOLOGY, Renal/Endocrine Effects**).

Serum Glucose — No significant effects on fasting serum glucose were observed in patients treated with felodipine in the U.S. controlled study.

Liver Enzymes — 1 of 2 episodes of elevated serum transaminases decreased once drug was discontinued in clinical studies; no follow-up was available for the other patient.

OVERDOSAGE

Oral doses of 240 mg/kg and 264 mg/kg in male and female mice, respectively, and 2390 mg/kg and 2250 mg/kg in male and female rats, respectively, caused significant lethality.

In a suicide attempt, one patient took 150 mg felodipine together with 15 tablets each of atenolol and spironolactone and 20 tablets of nitrazepam. The patient's blood pressure and heart rate were normal on admission to hospital; he subsequently recovered without significant sequelae.

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly bradycardia.

If severe hypotension occurs, symptomatic treatment should be instituted. The patient should be placed supine with the legs elevated. The administration of intravenous fluids may be useful to treat hypotension due to overdosage with calcium antagonists. In case of accompanying bradycardia, atropine (0.5-1 mg) should be administered intravenously. Sympathomimetic drugs may also be given if the physician feels they are warranted.

It has not been established whether felodipine can be removed from the circulation by hemodialysis.

To obtain up-to-date information about the treatment of overdose, consult your Regional Poison-Control Center. Telephone numbers of certified poison-control centers are listed in the *Physicians' Desk Reference (PDR).* In managing overdose, consider the possibilities of multiple-drug overdoses, drug-drug interactions, and unusual drug kinetics in your patient.

DOSAGE AND ADMINISTRATION

The recommended starting dose is 5 mg once a day. Depending on the patient's response, the dosage can be decreased to 2.5 mg or increased to 10 mg once a day. These adjustments should occur generally at intervals of not less than 2 weeks. The recommended dosage range is 2.5 to 10 mg once daily. In clinical trials, doses above 10 mg daily showed an increased blood pressure response but a large increase in the rate of peripheral edema and other vasodilatory adverse events (see **ADVERSE REACTIONS**). Modification of the recommended dosage is usually not required in patients with renal impairment.

Felodipine should regularly be taken either without food or with a light meal (see **CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism**). Felodipine should be swallowed whole and not crushed or chewed.

Geriatric Use — Patients over 65 years of age are likely to develop higher plasma concentrations of felodipine (see **CLINICAL PHARMACOLOGY**). In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range (2.5 mg daily). Elderly patients should have their blood pressure closely monitored during any dosage adjustment.

Patients with Impaired Liver Function — Patients with impaired liver function may have elevated plasma concentrations of felodipine and may respond to lower doses of felodipine extended-release tablets; therefore, patients should have their blood pressure monitored closely during dosage adjustment of felodipine extended-release tablets (see **CLINICAL PHARMACOLOGY**).

HOW SUPPLIED

FELODIPINE EXTENDED-RELEASE TABLETS are supplied as follows:

Felodipine extended-release tablets, 2.5 mg, round, light green, film-coated, unscored, debossed MP 771	
Bottles of 30 unit of use	NDC 53489-368-07
Bottles of 100	NDC 53489-368-01
Bottles of 250	NDC 53489-368-03
Bottles of 500	NDC 53489-368-05
Bottles of 1000	NDC 53489-368-10
Felodipine extended-release tablets, 5 mg, round, light orange, film-coated, unscored, debossed MP 772	
Bottles of 30 unit of use	NDC 53489-369-07
Bottles of 100	NDC 53489-369-01
Bottles of 250	NDC 53489-369-03
Bottles of 500	NDC 53489-369-05
Bottles of 1000	NDC 53489-369-10
Felodipine extended-release tablets, 10 mg, round, brown, film-coated, unscored, debossed MP 773	
Bottles of 30 unit of use	NDC 53489-370-07
Bottles of 100	NDC 53489-370-01
Bottles of 250	NDC 53489-370-03
Bottles of 500	NDC 53489-370-05
Bottles of 1000	NDC 53489-370-10

Store at 20º to 25ºC (68º to 77ºF). [See USP Controlled Room Temperature]

PROTECT FROM LIGHT

DISPENSE IN TIGHT, LIGHT-RESISTANT CONTAINER

Manufactured by:
MUTUAL PHARMACEUTICAL COMPANY, INC.
Philadelphia, PA 19124 USA

Revised: August 2004NP

Each Extended-Release tablet contains:
Felodipine, USP . . . . . 2.5 mg

Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room Temperature]
Protect from light.

DISPENSE IN TIGHT, LIGHT-RESISTANT CONTAINER

Tablets should be swallowed whole, not crushed or chewed.

Tablet debossed: MP 771

8/04CP

NDC 53489-368-07

FELODIPINE
EXTENDED-RELEASE TABLETS

2.5 mg

30 TABLETS

℞ only

MUTUAL PHARMACEUTICAL CO., INC.
PHILADELPHIA, PA 19124 USA

See package insert for full prescribing information.

Lot No.: Exp. Date:

N 53489-368-07

NDC 53489-368-01

FELODIPINE
EXTENDED-RELEASE TABLETS
2.5 mg

100 TABLETS

℞ only

MUTUAL PHARMACEUTICAL CO., INC.
PHILADELPHIA, PA 19124 USA

Each Extended-Release tablet contains: Felodipine, USP . . . 2.5 mg

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature]

Protect from light.

DISPENSE IN TIGHT, LIGHT-RESISTANT CONTAINER

Tablets should be swallowed whole, not crushed or chewed.

Tablet debossed: MP 771

8/04CP

See package insert for full prescribing information.

Lot No.: Exp. Date:

3 53489-368-01 8

Each Extended-Release tablet contains:
Felodipine, USP . . . . . 2.5 mg

Store at 20° to 25°C (68° to 77°F),
[See USP Controlled Room Temperature]
Protect from light.

DISPENSE IN TIGHT, LIGHT-RESISTANT CONTAINER

Tablets should be swallowed whole, not crushed or chewed.

Tablet debossed: MP 771

8/04CP

NDC 53489-368-03

FELODIPINE
EXTENDED-RELEASE TABLETS
2.5 mg

250 TABLETS

℞ only

MUTUAL PHARMACEUTICAL CO., INC.
PHILADELPHIA, PA 19124 USA

See package insert for full prescribing information.

Lot No.: Exp. Date:

N 53489-368-03 2

Each Extended-Release tablet contains:
Felodipine, USP . . . . . 2.5 mg

Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room Temperature]

Protect from light.

DISPENSE IN TIGHT, LIGHT-RESISTANT CONTAINER

Tablets should be swallowed whole, not crushed or chewed.

Tablet debossed: MP 771

8/04CP

NDC 53489-368-05

FELODIPINE
EXTENDED-RELEASE TABLETS

2.5 mg

500 TABLETS

℞ only

MUTUAL PHARMACEUTICAL CO., INC.
PHILADELPHIA, PA 19124 USA

See package insert for full prescribing information.

Lot No.: Exp. Date:

1/2" x 1-3/4" unvarnished Area

N 3 53489-368-05 9


3 53489-368-10 0
1/2" x 1-3/4"
unvarnished
Area
Lot No.: Exp. Date:
See package insert for full
prescribing information.
NDC 53489-368-10
FELODIPINE
EXTENDED-RELEASE
TABLETS
2.5 mg
1000 TABLETS
℞ only
MUTUAL PHARMACEUTICAL CO., INC.
PHILADELPHIA, PA 19124 USA
Each Extended-Release tablet contains:
Felodipine, USP . . . . . 2.5 mg
Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room Temperature]
Protect from light.
DISPENSE IN TIGHT, LIGHT-
RESISTANT CONTAINER.
Tablets should be swallowed whole,
not crushed or chewed.
Tablet debossed: MP 771
8/04CP

Each Extended-Release tablet contains:
Felodipine, USP . . . . . 5 mg

Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room Temperature]
Protect from light.

DISPENSE IN TIGHT, LIGHT-RESISTANT CONTAINER.

Tablets should be swallowed whole, not crushed or chewed.

Tablet debossed: MP 772 804CP

NDC 53489-369-07

FELODIPINE
EXTENDED-RELEASE TABLETS

5 mg

30 TABLETS ℞ only

MUTUAL PHARMACEUTICAL CO., INC.
PHILADELPHIA, PA 19124 USA

See package insert for full prescribing information.

Lot No.: Exp. Date:

3 53489-369-07

NDC 53489-369-01

FELODIPINE
EXTENDED-RELEASE TABLETS
5 mg

100 TABLETS

℞ only

MUTUAL PHARMACEUTICAL CO., INC.
PHILADELPHIA, PA 19124 USA

Each Extended-Release tablet contains:
Felodipine, USP . . . . . 5 mg

Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room Temperature]
Protect from light.

DISPENSE IN TIGHT, LIGHT-RESISTANT CONTAINER.

Tablets should be swallowed whole, not crushed or chewed.

Tablet debossed: MP 772

8/04CP

See package insert for full prescribing information.

Lot No.: Exp. Date:

N3 53489-369-01 5

Each Extended-Release tablet contains:
Felodipine, USP . . . . . 5 mg

Store at 20° to 25°C (68° to 77°F),
[See USP Controlled Room Temperature]
Protect from light.

DISPENSE IN TIGHT, LIGHT-RESISTANT CONTAINER.

Tablets should be swallowed whole, not crushed or chewed.

Tablet debossed: MP 772

8/04CP

NDC 53489-369-03

FELODIPINE
EXTENDED-RELEASE TABLETS
5 mg

250 TABLETS

℞ only

MUTUAL PHARMACEUTICAL CO., INC.
PHILADELPHIA, PA 19124 USA

See package insert for full prescribing information.

Lot No.: Exp. Date:

N 53489-369-03 6

Each Extended-Release tablet contains:
Felodipine, USP . . . . . 5 mg

Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room Temperature]

Protect from light.

DISPENSE IN TIGHT, LIGHT-RESISTANT CONTAINER.

Tablets should be swallowed whole, not crushed or chewed.

Tablet debossed: MP 772

8/04CP

NDC 53489-369-05

FELODIPINE
EXTENDED-RELEASE TABLETS

5 mg

500 TABLETS

℞ only

MUTUAL PHARMACEUTICAL CO., INC.
PHILADELPHIA, PA 19124 USA

See package insert for full prescribing information.

Lot No.: Exp. Date:

1/2" x 1-3/4" unvarnished Area

N 53489-369-05 3

Each Extended-Release tablet contains:
Felodipine, USP . . . . . 5 mg

Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room Temperature]

Protect from light.

DISPENSE IN TIGHT, LIGHT-RESISTANT CONTAINER.

Tablets should be swallowed whole, not crushed or chewed.

Tablet debossed: MP 772

8/04CP

NDC 53489-369-10

FELODIPINE
EXTENDED-RELEASE TABLETS

5 mg

1000 TABLETS

℞ only

MUTUAL PHARMACEUTICAL CO., INC.
PHILADELPHIA, PA 19124 USA

See package insert for full prescribing information.

Lot No.: Exp. Date:

1/2" x 1-3/4" unvarnished Area

3 53489-369-10 7

Each Extended-Release tablet contains:
Felodipine, USP . . . . . 10 mg

Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room Temperature]
Protect from light.

DISPENSE IN TIGHT, LIGHT-RESISTANT CONTAINER

Tablets should be swallowed whole, not crushed or chewed.

Tablet debossed: MP 773

8/04CP

NDC 53489-370-07

FELODIPINE
EXTENDED-RELEASE TABLETS

10 mg

30 TABLETS

℞ only

MUTUAL PHARMACEUTICAL CO., INC.
PHILADELPHIA, PA 19124 USA

See package insert for full prescribing information.

Lot No.: Exp. Date:

N 53489-370-07 3

NDC 53489-370-01

FELODIPINE
EXTENDED-RELEASE TABLETS
10 mg

100 TABLETS

℞ only

MUTUAL PHARMACEUTICAL CO., INC.
PHILADELPHIA, PA 19124 USA

Each Extended-Release tablet contains:
Felodipine, USP . . . . . 10 mg

Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room Temperature]

Protect from light.

DISPENSE IN TIGHT, LIGHT-RESISTANT CONTAINER.

Tablets should be swallowed whole, not crushed or chewed.

Tablet debossed: MP 773

8/04CP

See package insert for full prescribing information.

Lot No.: Exp. Date:

N 53489-370-01 1

Each Extended-Release tablet contains:
Felodipine, USP . . . . . 10 mg

Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room Temperature]
Protect from light.

DISPENSE IN TIGHT, LIGHT-RESISTANT CONTAINER.

Tablets should be swallowed whole, not crushed or chewed.

Tablet debossed: MP 773

8/04CP

NDC 53489-370-03

FELODIPINE
EXTENDED-RELEASE TABLETS
10 mg

250 TABLETS

℞ only

MUTUAL PHARMACEUTICAL CO., INC.
PHILADELPHIA, PA 19124 USA

See package insert for full prescribing information.

Lot No.: Exp. Date:

N 53489-370-03 5

Each Extended-Release tablet contains:
Felodipine, USP . . . . . 10 mg

Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room Temperature]

Protect from light.

DISPENSE IN TIGHT, LIGHT-RESISTANT CONTAINER.

Tablets should be swallowed whole, not crushed or chewed.

Tablet debossed: MP 773

8/04CP

NDC 53489-370-05

FELODIPINE
EXTENDED-RELEASE TABLETS

10 mg

500 TABLETS

℞ only

MUTUAL PHARMACEUTICAL CO., INC.
PHILADELPHIA, PA 19124 USA

See package insert for full prescribing information.

Lot No.: Exp. Date:

1/2" x 1-3/4" unvarnished Area

N 53489-370-05 9

Each Extended-Release tablet contains:
Felodipine, USP . . . . . 10 mg

Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room Temperature]

Protect from light.

DISPENSE IN TIGHT, LIGHT-RESISTANT CONTAINER.

Tablets should be swallowed whole, not crushed or chewed.

Tablet debossed: MP 773

8/04CP

NDC 53489-370-10

FELODIPINE
EXTENDED-RELEASE TABLETS

10 mg

1000 TABLETS

℞ only

MUTUAL PHARMACEUTICAL CO., INC.
PHILADELPHIA, PA 19124 USA

See package insert for full prescribing information.

Lot No.: Exp. Date:

1/2" x 1-3/4" unvarnished Area

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-896

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

See updated labeling comments 9/7/00

ANDA Number: **75-896** Date of Submission: **June 6, 2000**

Applicant's Name: **Mutual Pharmaceutical Company, Inc.**

Established Name: **Felodipine Extended-release Tablets, 10 mg**

Labeling Deficiencies:

1. CONTAINER 30s, 100s, 250s, 500s and 1000s

   We encourage you to differentiate your product strengths by boxing, contrasting colors, or some other means.

2. INSERT

   a. GENERAL COMMENT

      Because you have elected to have a shared insert with the 2.5 mg and the 5 mg strength tablets, these ANDAs will have to be approved together or further revisions to your insert will be needed.

   b. DESCRIPTION

      Third sentence - "molecular" rather than ———

   c. CLINICAL PHARMACOLOGY

      Pharmacokinetics and Metabolism

      i. Fourth paragraph - Delete the hyphen between the quantity and the units when expressing a dose (e.g., "10 mg" rather than "10-mg").

      ii. Last paragraph, second sentence - ... 60%; AUC is ... (add semicolon)

   d. PRECAUTIONS

      Drug Interactions - Add the following text to the beginning of this subsection:

      CYP3A4 Inhibitors - Felodipine is metabolized by CYP3A4. Coadministration of CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, erythromycin, grapefruit juice, cimetidine) with felodipine may lead to several-fold increases in the plasma levels of felodipine, either due to an increase in bioavailability or due to a decrease in metabolism. These increases in concentration may lead to increased effects, (lower blood pressure and increased heart rate). These effects have been observed with coadministration of itraconazole (a potent CYP3A4 inhibitor). Caution should be used when CYP3A4 inhibitors are coadministered with felodipine. A conservation approach to dosing felodipine should be taken. The following specific interactions have been reported:

      Itraconazole - Coadministration of another extended-release formulation of felodipine with itraconazole resulted in approximately 8-fold increase in the AUC, more than 6-fold increase in the C_{max} and 2-fold prolongation in the half-life of felodipine.

Erythromycin - Coadministration of felodipine with erythromycin resulted in approximately 2.5-fold increase in the AUC and C_{max} and about 2-fold prolongation in the half-life of felodipine.

Grapefruit juice - Coadministration of felodipine with grapefruit juice resulted in more than 2-fold increase in the AUC and C_{max}, but no prolongation in the half-life of felodipine.

Cimetidine - Coadministration of felodipine with cimetidine (a non-specific CYP-450 inhibitor) resulted in an increase of approximately 50% in the AUC and C_{max} of felodipine.

Beta-Blocking Agents - A pharmacokinetic ... well tolerated.

Digoxin - When given ... altered.

e. ADVERSE REACTIONS

Paragraph beginning "Adverse events that occurred in ..."

i. Cardiovascular - "*arrhythmia*" (spelling)

ii. Respiratory - "... sinusitis, epistaxis ..." (comma rather than period)

f. HOW SUPPLIED

We encourage you to indicate the scoring configuration of your tablets in this section.

Please revise your container labels and insert labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes -

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes No
If no, list why:

Container Labels: 30s, 100s, 250s, 500s, and 1000s

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Plendil®

NDA Number: 19-834

NDA Drug Name: Plendil® (felodipine) Extended-release Tablets

NDA Firm: Astra Zeneca

Date of Approval of NDA Insert and supplement #: 2-8-00 (S-014)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: side-by-sides

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 24		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? NO.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	

Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?	X		
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?	X		
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. The most recent approved labeling of the reference listed drug is Plendil®, Astra Zeneca - NDA 19-834/S-014; approved 2-8-00; revised 10-99.

2. The inactive ingredients are accurately listed in the DESCRIPTION section (p 8538 v 1.17).

3. Mutual is the manufacturer (p 8936 v 1.17).

4. This is the first generic application for this drug product.

5. There are two patents for this drug product:

   4,803,081 (paragraph 4) - new pharmaceutical preparations with extended-release (4-3-07) - The firm has certified that this patent will not be infringed upon by the manufacture, use, or sale of their drug product.
   4,264,611 (paragraph 3) U-3 - treatment of hypertension (6-19-01)

6. Both fasting and fed/fasting studies were done.

7. The tablet description is accurate as seen in the HOW SUPPLIED section (p 9467 v B 1.3).

8. There is no USP monograph for this drug product nor is it in the PF. However, the drug substance, felodipine, does have a drug monograph in the USP.

9. Storage temperature/dispensing recommendations:

   RLD - Store below 30°C (86°F). Keep container tightly closed. Protect from light.

   ANDA - Same as RLD.

   USP - (drug substance) - Preserve in tight, light-resistant containers.

10. Container sizes:

    RLD - 30s, 100s, UD 100s
    ANDA - 30s (CRC), 100s, 250s, 500s, 1000s (all containers are made of HDPE)

11. The RLD is not scored per picture in the PDR while the ANDA does not indicate the scoring configuration in the HOW SUPPLIED section nor in the tablet description found in the Finished Dose Form section of the submission. I am guessing that the tablet is unscored since it is an extended-release preparation.

12. The firm has submitted ANDA 75-931 for the 5 mg strength tablet and have stated that they will be submitting an ANDA shortly for the 2.5 mg strength tablet. All three strengths are extended-release and they will all share an insert

Date of Review: 7-27-00 **Date of Submission:** 6-6-00

Primary Reviewer: Adolph Vezza **Date:** 8/2/00

A. Vezza

Team Leader: Charlie Hoppes **Date:** 8/7/00

Charlie Hoppes

(this review supersedes the review dated 8-3-00)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-896** Date of Submission: **June 6, August 14 and 29, 2000**

Applicant's Name: **Mutual Pharmaceutical Company, Inc.**

Established Name: **Felodipine Extended-release Tablets, 2.5 mg, 5 mg, and 10 mg**

Labeling Deficiencies:

1. CONTAINER 30s, 100s, 250s, 500s and 1000s

   We encourage you to differentiate your product strengths by boxing, contrasting colors, or some other means.

2. INSERT

   a. GENERAL COMMENT

      Please note that the labeling comments listed below are directed to your draft insert labeling submitted on August 29, 2000. Please note that there have been recent and significant changes in the package insert labeling approved for the referenced listed drug, Plendil®, AstraZeneca; approved August 28, 2000; revised May 2000.

   b. DESCRIPTION

      Third sentence - "molecular" rather than "———"

   c. CLINICAL PHARMACOLOGY

      i. Pharmacokinetics and Metabolism, fourth paragraph - Delete the hyphen between the quantity and the units when expressing a dose (e.g., "10 mg" rather than "10-mg").

      ii. ——— - Revise this subsection title to read "*Geriatric Use*".

   d. PRECAUTIONS

      i. Drug Interactions - "coadministered" and "coadministration" (delete hyphens)

      ii. Carcinogenesis, Mutagenesis, Impairment of Fertility

         A). First paragraph - "61 times**" rather than " ——— " (two instances)

         B). Third paragraph - "61 times**" rather than " ——— "

         C). Fourth paragraph - "1,100 times**" rather than " ——— "

         D). Last paragraph - "... 26.9 mg/kg/day (up to 24 times** the maximum recommended human dose on a mg/m^2 basis.) showed ..."

      iii. Pregnancy

         A). Teratogenic Effects, first sentence - "... 0.8 to 8 times** ..." rather than "... ——— ..."

B). Nonteratogenic Effects

1). First paragraph - "... (8 times** ..." rather than "... (——— ..."

2). Second paragraph - "... (2.1 times the maximum ..." rather than "... ——————————..."

iv. Add the following subsection with associated text as the last subsection of this section:

Geriatric Use

Clinical studies of felodipine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Pharmacokinetics, however, indicate that the availability of felodipine is increased in older patients (see **CLINICAL PHARMACOLOGY, Geriatric Use**). In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

e. ADVERSE REACTIONS

i. First sentence - "3,000" (add comma)

ii. Third paragraph - "ADMINISTRATION" (spelling)

iii. Paragraph beginning "Adverse events that occurred in ..."

A). Cardiovascular - "*arrhythmia*" (spelling)

B). Respiratory - "... sinusitis, epistaxis ..." (comma rather than period)

f. OVERDOSAGE

First sentence - "2,390" and "2,250" (add commas)

g. DOSAGE AND ADMINISTRATION

i. Fourth sentence - "2.5 to 10 mg" rather than "2.5-10 mg"

ii. Use in the Elderly or Patients with Impaired Liver Function

Revise this subsection to be two different subsections as seen below:

Geriatric Use - Patients over 65 years of age are likely to develop higher plasma concentrations of felodipine (see **CLINICAL PHARMACOLOGY**). In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range (2.5 mg daily). Elderly patients should have their blood pressure closely monitored during any dosage adjustment.

Patients with Impaired Liver Function - Patients with impaired liver function may have elevated plasma concentrations of felodipine and may respond to lower doses of felodipine extended-release tablets; therefore, patients should have their blood pressure monitored closely during dosage adjustment of felodipine extended-release tablets (see **CLINICAL PHARMACOLOGY**).

h. HOW SUPPLIED

We encourage you to indicate the scoring configuration of your tablets in this section. Do you propose an unscored tablet to match the referenced listed drug?

Please revise your container labels and insert labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes -

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes No
If no, list why:

Container Labels: 30s, 100s, 250s, 500s, and 1000s

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Plendil®

NDA Number: 19-834

NDA Drug Name: Plendil® (felodipine) Extended-release Tablets

NDA Firm: Astra Zeneca

Date of Approval of NDA Insert and supplement #: 8-28-00 (S-015)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: side-by-sides

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 24		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? NO.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	

Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?	X		
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?	X		
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. The most recent approved labeling of the reference listed drug is Plendil®, Astra Zeneca - NDA 19-834/S-015; approved 8-28-00; revised 5-00. There were some revisions asked for in the approval letter for S-015 which I have asked the generic to put into their insert. This was a result of the NDA letter not asking AstraZeneca to submit the changes as a supplement (they didn't specify how to submit the changes so they may end up in an annual report) and my speaking to Natalia Morgenstern - a supervisory PM - She indicated that New Drugs sometimes doesn't specify how the innovator is to submit the asked for revisions and that if they had other changes they wished to submit as a supplement they would add these revisions on - if not, they would probably submit them in an annual report. She was not too concerned.

2. The inactive ingredients are accurately listed in the DESCRIPTION section (p 8538 v 1.17).

3. Mutual is the manufacturer (p 8936 v 1.17).

4. This is the first generic application for this drug product.

5. There are two pending patents for this drug product:

   4,803,081 (paragraph 4) - new pharmaceutical preparations with extended-release (4-3-07) - The firm has certified that this patent will not be infringed upon by the manufacture, use, or sale of their drug product.
   4,264,611 (paragraph 3) U-3 - treatment of hypertension (6-19-01)

6. Both fasting and fed/fasting studies were done.

7. The tablet descriptions are accurate as seen in the HOW SUPPLIED section.

8. There is no USP monograph for this drug product nor is it in the PF. However, the drug substance, felodipine, does have a drug monograph in the USP.

9. Storage temperature/dispensing recommendations:

   RLD - Store below 30°C (86°F). Keep container tightly closed. Protect from light.

   ANDA - Same as RLD.

   USP - (drug substance) - Preserve in tight, light-resistant containers.

10. Container sizes:

    RLD - 30s, 100s, UD 100s
    ANDA - 30s (CRC), 100s, 250s, 500s, 1000s (all containers are made of HDPE)

11. The RLD is not scored per picture in the PDR while the ANDA does not indicate the scoring configuration in the HOW SUPPLIED section nor in the tablet description found in the Finished Dose Form section of the submission. I am guessing that the tablet is unscored since it is an extended-release preparation.

12. The firm had submitted ANDA 75-931 for the 5 mg strength. However, they have requested withdrawal of that ANDA and submitted the info for the 5 mg strength as an amendment to this application. The 8/29/00 amendment to this ANDA adds the 2.5 mg strength tablet. All three strengths are extended-release and they will all share an insert

Date of Review: 9-7-00 **Date of Submission:** 6-6-00, 8-14 and 8-29-00

Primary Reviewer: Adolph Vezza **Date:** 9/14/00

A. Vezza

Team Leader: Charlie Hoppes **Date:** 9/15/00

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cc:

ANDA: 75-896
DUP/DIVISION FILE
HFD-613/AVezza/CHoppes (no cc)
aev/9/7/00|V:\FIRMSAM\MUTUAL\LTRS&REV\75896NA2.L
Review

APPEARS THIS WAY
ON ORIGINAL

TENTATIVE APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-896** Date of Submission: **March 7, 2001**

Applicant's Name: **Mutual Pharmaceutical Company, Inc.**

Established Name: **Felodipine Extended-release Tablets, 2.5 mg, 5 mg, and 10 mg**

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: 30s, 100s, 250s, 500s, and 1000s
Satisfactory in FPL as of March 7, 2001 submission

Professional Package Insert Labeling:
Satisfactory in FPL as of March 7, 2001 submission.

Revisions needed post-approval: PI – PRECAUTIONS, change third subsection heading to "Patients with Impaired Liver Function", Delete "[redacted]" from the first sentence of this subsection.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Plendil®

NDA Number: 19-834

NDA Drug Name: Plendil® (felodipine) Extended-release Tablets

NDA Firm: Astra Zeneca

Date of Approval of NDA Insert and supplement #: 8-28-00 (S-015)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: side-by-sides

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 24		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	

Error Prevention Analysis			
Has the firm proposed a proprietary name? NO.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	

Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. The most recent approved labeling of the reference listed drug is Plendil®, Astra Zeneca - NDA 19-834/S-015; approved 8-28-00; revised 5-00. There were some revisions asked for in the approval letter for S-015 which I have asked the generic to put into their insert. This was a result of the NDA letter not asking AstraZeneca to submit the changes as a supplement (they didn't specify how to submit the changes so they may end up in an annual report) and my speaking to Natalia Morgenstern - a supervisory PM - She indicated that New Drugs sometimes doesn't specify how the innovator is to submit the asked for revisions and that if they had other changes they wished to submit as a supplement they would add these revisions on - if not, they would probably submit them in an annual report. She was not too concerned.

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   4,803,081 (paragraph 4) - new pharmaceutical preparations with extended-release (4-3-07) - The firm has certified that this patent will not be infringed upon by the manufacture, use, or sale of their drug product.
   4,264,611 (paragraph 3) U-3 - treatment of hypertension (6-19-01)

6. Both fasting and fed/fasting studies were done.

7. The tablet descriptions are accurate as seen in the HOW SUPPLIED section.

8. There is no USP monograph for this drug product nor is it in the PF. However, the drug substance, felodipine, does have a drug monograph in the USP.

9. Storage temperature/dispensing recommendations:

   RLD - Store below 30°C (86°F). Keep container tightly closed. Protect from light.

   ANDA - Same as RLD.

   USP - (drug substance) - Preserve in tight, light-resistant containers.

10. Container sizes:

    RLD - 30s, 100s, UD 100s
    ANDA - 30s (CRC), 100s, 250s, 500s, 1000s (all containers are made of HDPE)

11. The RLD is not scored per picture in the PDR and neither is the ANDA (all 3 strengths).

12. The firm had submitted ANDA 75-931 for the 5 mg strength. However, they have requested withdrawal of that ANDA and submitted the info for the 5 mg strength as an amendment to this application. The 8/29/00 amendment to this ANDA adds the 2.5 mg strength tablet. All three strengths are extended-release and they will all share an insert

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Date of Review: **3-15-01** **Date of Submission:** **3-7-01**

Primary Reviewer: **Adolph Vezza** **Date:** 3/22/01

A. Vezza

Team Leader: **Charlie Hoppes** **Date:** 3/22/01

cc:

ANDA: 75-896
DUP/DIVISION FILE
HFD-613/AVezza/CHoppes (no cc)
aev/3/15/01|V:\FIRMSAM\MUTUAL\LTRS&REV\75896TAP.L
Review

APPEARS THIS WAY
ON ORIGINAL

acky 12/18/03 (Superseded by Approval Summary on 10-5-04 Submission
AVgr 10/18/04

~~TENTATIVE~~ APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-896** Date of Submission: **April 11, 2003**

Applicant's Name: **Mutual Pharmaceutical Company, Inc.**

Established Name: **Felodipine Extended-release Tablets, 2.5 mg, 5 mg, and 10 mg**

5/12

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? Yes
Container Labels: 30s, 100s, 250s, 500s, and 1000s
Satisfactory in FPL as of March 7, 2001 submission [Vol 8.2].
Professional Package Insert Labeling:
Satisfactory in FPL as of April 11, 2003 submission [Vol 10.1 - rev May 2002NP].
Revisions needed post-approval: Firm to submit commitment that they will not distribute this drug product before changing the storage temperature recommendations to "Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Plendil®
NDA Number: 19-834
NDA Drug Name: Plendil® (felodipine) Extended-release Tablets
NDA Firm: Astra Zeneca
Date of Approval of NDA Insert and supplement #: 5-22-02 (S-017)
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: side-by-sides
Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 24		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? NO.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	

Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date			

for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. The most recent approved labeling of the reference listed drug is Plendil®, Astra Zeneca - NDA 19-834/S-017; approved 5-22-02; revised 9-00 (in draft).

2. The inactive ingredients are accurately listed in the DESCRIPTION section (p 8538 v 1.17).

3. Mutual is the manufacturer (p 8936 v 1.17).

4. This is the first generic application for this drug product.

5. There is one pending patent for this drug product:

   4,803,081 (paragraph 4) - new pharmaceutical preparations with extended-release (~~4-3-07~~ 10/3/07) - The firm has certified that this patent will not be infringed upon by the manufacture, use, or sale of their drug product.

6. Both fasting and fed/fasting studies were done.

7. The tablet descriptions are accurate as seen in the HOW SUPPLIED section.

8. There is no USP monograph for this drug product nor is it in the PF. However, the drug substance, felodipine, does have a drug monograph in the USP.

9. Storage temperature/dispensing recommendations:

   RLD - Store below 30°C (86°F). Keep container tightly closed. Protect from light.
   ANDA - Same as RLD.
   USP - (drug substance) - Preserve in tight, light-resistant containers.

10. Container sizes:

    RLD - 30s, 100s, UD 100s
    ANDA - 30s (CRC), 100s, 250s, 500s, 1000s (all containers are made of HDPE)

11. The RLD is not scored per picture in the PDR and neither is the ANDA (all 3 strengths).

12. The firm had submitted ANDA 75-931 for the 5 mg strength. However, they have requested withdrawal of that ANDA and submitted the info for the 5 mg strength as an amendment to this application. The 8/29/00 amendment to this ANDA adds the 2.5 mg strength tablet. All three strengths are extended-release and they will all share an insert

Date of Review: 5-7-03 **Date of Submission:** 4-11-03

Primary Reviewer: Adolph Vezza A. Vezza **Date:** 5/12/03

Team Leader: Lillie Golson LG Golson **Date:** 5/12/03

cc:

ANDA: 75-896
DUP/DIVISION FILE
HFD-613/AVezza/CHoppes (no cc)
aev/3/15/01|V:\FIRMSAM\MUTUAL\LTRS&REV\75896TAP.L
Review

(supersedes Approval Summary dated 5-12-04)
APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-896** Date of Submission: **October 5, 2004**

Applicant's Name: **Mutual Pharmaceutical Company, Inc.**

Established Name: **Felodipine Extended-release Tablets USP, 2.5 mg, 5 mg, and 10 mg**

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? Yes
Container Labels: 30s, 100s, 250s, 500s, and 1000s
Satisfactory in FPL as of October 5, 2004 submission [Vol 13.1].
Professional Package Insert Labeling:
Satisfactory in electronic format as of October 5, 2004 submission.
FILE PATH: \\CDSESUBOGD1\N75896\N_000\2004-10-5\Felodipine.10-4.pdf
Revisions needed post-approval: Container Labels - Not all of the container labels have a period at the end of the "DISPENSE IN TIGHT, LIGHT RESISTANT CONTAINER." statement. Encourage firm to use "USP" in association with the established in on container labels and appropriate places in the insert. Place the statement "The USP drug release test # is pending." as the last paragraph in the DESCRIPTION section.

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Plendil®
NDA Number: 19-834
NDA Drug Name: Plendil® (felodipine) Extended-release Tablets
NDA Firm: Astra Zeneca
Date of Approval of NDA Insert and supplement #: 6-7-04 (S-022)
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: side-by-sides
Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 27	X		
Is this name different than that used in the Orange Book?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? NO.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	

Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	

Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD: (portions taken from previous review)

1. The most recent approved labeling of the reference listed drug is Plendil®, Astra Zeneca - NDA 19-834/S-022; approved 6-7-04; revised 11-03.

2. The inactive ingredients are accurately listed in the DESCRIPTION section (p 8538 v 1.17).

3. Mutual is the manufacturer (p 8936 v 1.17).

4. This is the first generic application for this drug product.

5. There is one pending patent for this drug product:

   4,803,081 (paragraph 4) - new pharmaceutical preparations with extended-release (4-3-07) - The firm has certified that this patent will not be infringed upon by the manufacture, use, or sale of their drug product. The firm's claim was upheld by the court system.

6. Both fasting and fed/fasting studies were done.

7. The tablet descriptions are accurate as seen in the HOW SUPPLIED section.

8. There is a USP monograph for this drug product [USP 27].

9. Storage temperature/dispensing recommendations:

   RLD - Store below 30°C (86°F). Keep container tightly closed. Protect from light.
   ANDA - Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature] Protect from light. DISPENSE IN TIGHT, LIGHT-RESISTANT CONTAINER.
   USP - Preserve in tight, light-resistant containers.

10. Container sizes:
    RLD - 30s, 100s, UD 100s
    ANDA - 30s (CRC), 100s, 250s, 500s, 1000s (all containers are made of HDPE)

11. The RLD is not scored per picture in the PDR and neither is the ANDA (all 3 strengths).

12. The firm had submitted ANDA 75-931 for the 5 mg strength. However, they have requested withdrawal of that ANDA and submitted the info for the 5 mg strength as an amendment to this application. The 8/29/00 amendment to this ANDA adds the 2.5 mg strength tablet. All three strengths are extended-release and they will all share an insert

13. I spoke to Sherry Schultz of the firm on 10-19-04 - She faxed me a copy of a letter the firm is submitting stating the commitment to incorporate the statement "The USP drug release test # is pending." as the last paragraph in the DESCRIPTION section at the time of next printing. The USP has one dissolution test for this drug product - Mutual has submitted a different dissolution test.

Date of Review: 10-18-04 **Date of Submission:** 10-5-04

Primary Reviewer: Adolph Vezza **Date:** 10/20/04

Team Leader: Lillie Golson **Date:**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-896

CHEMISTRY REVIEWS

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 75-896

3. NAME AND ADDRESS OF APPLICANT
Mutual Pharmaceutical Company, Inc.
Attention: Robert Dettery
1100 Orthodox Street
Philadelphia, PA 19124

4. LEGAL BASIS FOR SUBMISSION
Innovator Product: Plendil® ER Tablets (NDA #19-834)
Innovator Company: AstraZeneca

On pages 7 - 11 the applicant includes Patent Certification and Exclusivity Statement.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Felodipine ER Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
Original Submission: 06/06/00

FDA:
Acceptance for Filing: 06/06/00

10. PHARMACOLOGICAL CATEGORY
Anti-hypertensive

11. Rx or OTC
RX

12. RELATED IND/NDA/DMF(s)
See review element #37

13. DOSAGE FORM
Tablets/Oral

14. POTENCIES
10 mg

15. CHEMICAL NAME AND STRUCTURE

Chemical name:
(±)-Ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate

Chemical Formula: $C_{18}H_{19}Cl_2NO_4$

Molecular Weight: 384.26

Cas Number: [72509-76-3; 86189-69-7]

16. RECORDS AND REPORTS

17. COMMENTS

CMC - Not Satisfactory
Bio - Pending
MV - DS is compendial, DP is not compendial
EER - Pending
Labeling - Not Satisfactory (08/02/00)

18. CONCLUSIONS AND RECOMMENDATIONS

This application is not approvable at this time - Major

19. REVIEWER: Bita Mirzai-Azarm

DATE COMPLETED: 10/13/00

APPEARS THIS WAY
ON ORIGINAL

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CHEMISTRY REVIEW #1

5. Additionally, please note that chemistry, manufacturing and controls information regarding the 2.5 and 5 mg products (amendments dated August 14 and 29, 2000) have not been reviewed. Please review the deficiencies identified in section A for relevance to these products. Revise any pertinent documentation and resubmit.

Sincerely yours,

for Margaret A. Sayre 11/16/00

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 75-896
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-647/B.M.Azarm/10/13/00, 10/26/00 (revised) Bita M. Azarm 11/08/00.

HFD-647/U.Venkataram/10/27/00 for cl V 11-08-2000

HFD-617/BmcNeal/11/6/00 B. McNeal 11/14/00

F/T by pah/11/7/00
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CHEMISTRY REVIEW - NOT APPROVABLE - MAJOR

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 75-896

3. NAME AND ADDRESS OF APPLICANT
Mutual Pharmaceutical Company, Inc.
Attention: Robert Susan B. Wilson
1100 Orthodox Street
Philadelphia, PA 19124

4. LEGAL BASIS FOR SUBMISSION
Innovator Product: Plendil® ER Tablets (NDA #19-834)
Innovator Company: AstraZeneca

The applicant includes Patent Certification and Exclusivity Statement.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Felodipine ER Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
Original Submission: 06/06/00
Major Amendment: 08/14/00 (addition of 5 mg strength)
Major Amendment: 08/29/00 (addition of 2.5 mg strength)
Original Amendment: 11/15/00
Major Amendment: 03/07/01

FDA:
Acceptance for Filing: 06/06/00
Deficiency Letter: 11/16/00

10. PHARMACOLOGICAL CATEGORY
Anti-hypertensive

11. Rx or OTC
RX

12. RELATED IND/NDA/DMF(s)
See review element #37

13. DOSAGE FORM
Tablets/Oral

14. POTENCIES
2.5 mg, 5 mg, and 10 mg

15. CHEMICAL NAME AND STRUCTURE

Chemical name:
(±)-Ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate

Chemical Formula: $C_{18}H_{19}Cl_2NO_4$

Molecular Weight: 384.26

Cas Number: [72509-76-3; 86189-69-7]

16. RECORDS AND REPORTS

17. COMMENTS

CMC - Not Satisfactory
Bio - Pending
MV - DS is compendial, DP is not compendial
EER - Withhold
Labeling - Satisfactory (03/22/01)

18. CONCLUSIONS AND RECOMMENDATIONS

This application is not approvable at this time.

19. REVIEWER: Bita Mirzai-Azarm

DATE COMPLETED: 07/16/01

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CHEMISTRY REVIEW #2

cc: ANDA 75-896
ANDA DUP
Field Copy

Endorsements:

HFD-647/B.M.Azarm/07/16/01, 07/20/01 (revised) Rita M. Azarm 08/13/01.

HFD-647/U.Venkataram/7/23/01 U.V. Venkataram

HFD-617/BmcNeal/8/7/01 B. McNeal 8/13/01 8/13/01

F/T by rad8/7/01

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CHEMISTRY REVIEW - NOT APPROVABLE - MINOR

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 75-896

3. NAME AND ADDRESS OF APPLICANT
Mutual Pharmaceutical Company, Inc.
Attention: Sherry Schultz
1100 Orthodox Street
Philadelphia, PA 19124

4. LEGAL BASIS FOR SUBMISSION
Innovator Product: Plendil® ER Tablets (NDA #19-834)
Innovator Company: AstraZeneca

The applicant includes Patent Certification and Exclusivity Statement.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Felodipine ER Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
Original Submission: 06/06/00
Major Amendment: 08/14/00 (addition of 5 mg strength)
Major Amendment: 08/29/00 (addition of 2.5 mg strength)
Original Amendment: 11/15/00
Major Amendment: 03/07/01
Minor Amendment: 09/24/01

FDA:
Acceptance for Filing: 06/06/00
Deficiency Letter: 11/16/00
Deficiency Letter: 08/15/01

10. PHARMACOLOGICAL CATEGORY
Anti-hypertensive

11. Rx or OTC
RX

12. RELATED IND/NDA/DMF(s)
See review element #37

13. DOSAGE FORM
Tablets/Oral

14. POTENCIES
2.5 mg, 5 mg, and 10 mg

15. CHEMICAL NAME AND STRUCTURE
Chemical name:
(±)-Ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate

Chemical Formula: $C_{18}H_{19}Cl_2NO_4$

Molecular Weight: 384.26

Cas Number: [72509-76-3; 86189-69-7]

16. RECORDS AND REPORTS

17. COMMENTS
CMC - Not Satisfactory
Bio - Acceptable (08/01/01)
MV - DS is compendial, DP is not compendial
EER - Withhold
Labeling - Satisfactory (03/22/01)

18. CONCLUSIONS AND RECOMMENDATIONS
This application is not approvable at this time.

19. REVIEWER: Bita Mirzai-Azarm
DATE COMPLETED: 10/25/01

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CHEMISTRY REVIEW #3

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

Please provide available room temperature data that includes dissolution data determined in accordance with the Division of Bioequivalence recommendations.

Sincerely yours,

11/8/01

for Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 75-896
ANDA DUP
Field Copy

Endorsements:

HFD-647/B.M.Azarm/10/25/01 Bita M. Azarm 11/07/01

HFD-647/U.Venkataram/10/31/01 for U.V. S. Bajaram 11/7/01

HFD-617/S.Shepperson/11/05/01 S. Shepp 11-7-01

F/T by: alm/11/06/01

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CHEMISTRY REVIEW - NOT APPROVABLE - FAX

APPEARS THIS WAY
ON ORIGINAL

1. CHEMISTRY REVIEW NO. 4

2. ANDA # 75-896

3. NAME AND ADDRESS OF APPLICANT
Mutual Pharmaceutical Company, Inc.
Attention: Robert Dettery
1100 Orthodox Street
Philadelphia, PA 19124

4. LEGAL BASIS FOR SUBMISSION
Innovator Product: Plendil® ER Tablets (NDA #19-834)
Innovator Company: AstraZeneca

The applicant includes Patent Certification and Exclusivity Statement.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Felodipine ER Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
Original Submission: 06/06/00
Major Amendment: 08/14/00 (addition of 5 mg strength)
Major Amendment: 08/29/00 (addition of 2.5 mg strength)
Original Amendment: 11/15/00
Major Amendment: 03/07/01
Amendment: 08/15/01
Minor Amendment: 09/24/01
Fax Amendment: 11/28/01
Telephone Amendment: 02/05/02

FDA:
Acceptance for Filing: 06/06/00
Deficiency Letter: 11/16/00
Deficiency Letter: 08/15/01
Deficiency Letter: 11/13/01
Telephone Conversation: 02/01/02

10. PHARMACOLOGICAL CATEGORY
Anti-hypertensive

11. Rx or OTC
RX

12. RELATED IND/NDA/DMF(s)
See review element #37

13. DOSAGE FORM
Tablets/Oral

14. POTENCIES
2.5 mg, 5 mg, and 10 mg

15. CHEMICAL NAME AND STRUCTURE
Chemical name:
(+)-Ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate

Chemical Formula: $C_{18}H_{19}Cl_2NO_4$

Molecular Weight: 384.26

Cas Number: [72509-76-3; 86189-69-7]

16. RECORDS AND REPORTS

17. COMMENTS
CMC - ~~Satisfactory~~ Not BM
Bio - Acceptable (01/28/02)
MV - DS is compendial, DP is not compendial
EER - Acceptable on 11/28/01
Labeling - Satisfactory (03/22/01)

18. CONCLUSIONS AND RECOMMENDATIONS
This application is not approvable.

19. REVIEWER: Bita Mirzai-Azarm
DATE COMPLETED: 01/30/02

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confidential commercial

information from

CHEMISTRY REVIEW #4

cc: ANDA 75-896
ANDA DUP
Field Copy
HFD-92

Endorsements:

HFD-647/B.M.Azarm/01/30/02, 02/11/02 (review of Telephone Amendment), 03/15/02 (revised) Bita M. Azarm 03/22/02.

HFD-647/U.Venkataram/3/15/02 U.V. Venkataram 3/22/02

HFD-617/S.Shepperson/3/18/02 S. Shepperson 3/22/02

F/T by: dss/3/19/02

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CHEMISTRY REVIEW - NOT APPROVABLE

APPEARS THIS WAY
ON ORIGINAL

1. CHEMISTRY REVIEW NO. 5

2. ANDA # 75-896

3. NAME AND ADDRESS OF APPLICANT
Mutual Pharmaceutical Company, Inc.
Attention: Robert Dettery
1100 Orthodox Street
Philadelphia, PA 19124

4. LEGAL BASIS FOR SUBMISSION
Innovator Product: Plendil® ER Tablets (NDA #19-834)
Innovator Company: AstraZeneca

The applicant includes Patent Certification and Exclusivity Statement.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Felodipine ER Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
Original Submission: 06/06/00
Major Amendment: 08/14/00 (addition of 5 mg strength)
Major Amendment: 08/29/00 (addition of 2.5 mg strength)
Patent Correspondecne: 08/29/2000
Patent Corresponcence: 09/12/2000
Original Amendment: 11/15/2000
Patent Amendment: 11/17/2000
Major Amendment: 03/07/01
Bioequivalence Amendment: 4/30/2001
Bioequivalence Amendment: 6/25/2001
Amendment: 08/15/01
Minor Amendment: 09/24/01
Fax Amendment: 11/28/01
Telephone Amendment: 02/05/02
Labeling Amendment: 04/11/2003
Labeling Telephone Amendment: 05/13/2003
Minor Amendment: 09/10/03
Patent Correspondence: November 26, 2003

FDA:
Acceptance for Filing: 06/06/00
Deficiency Letter: 11/16/00
Deficiency Letter: 08/15/01
Deficiency Letter: 11/13/01
Telephone Conversation: 02/01/02
Deficiency Letter: 03/27/03

10. PHARMACOLOGICAL CATEGORY
Anti-hypertensive

11. Rx or OTC
RX

12. RELATED IND/NDA/DMF(s)
See review element #37

13. DOSAGE FORM
ER Tablets/Oral

14. POTENCIES
2.5 mg, 5 mg, and 10 mg

15. CHEMICAL NAME AND STRUCTURE
Chemical name:
(±)-Ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate

Chemical Formula: $C_{18}H_{19}Cl_2NO_4$

Molecular Weight: 384.26

Cas Number: [72509-76-3; 86189-69-7]

16. RECORDS AND REPORTS

17. COMMENTS
CMC - Satisfactory
Bio - Acceptable (01/28/02)
MV - DS is compendial, DP is not compendial. MV acceptable 5/29/2002. MV not required per OGD policy.
EER - Acceptable on 11/28/01 and 12/1/03.
Labeling - Satisfactory (03/22/01) and 05/12/03.

18. CONCLUSIONS AND RECOMMENDATIONS
This application may be tentatively approved.

19. REVIEWER:
Bita Mirzai-Azarm

DATE COMPLETED:
11/04/03, 11/17/03 (revised)

Redacted 30 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #5

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS
DS - USP
DP - non-USP
Request for Lab assignment for ANDA MV was sent on 01/30/02. Request was withdrawn per OGD's new policy.

32. LABELING
Satisfactory per A. Vezza on 03/22/01 and on 05/12/03.

33. ESTABLISHMENT INSPECTION
Acceptable on 11/28/01 and 12/1/03.

34. BIOEQUIVALENCY/MICROBIOLOGY STATUS
Acceptable per P. Nwakama on 01/28/02.

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:
Request for exclusion from requirements for environmental impact analysis statement is enclosed.

36. ORDER OF REVIEW:
The application submission(s) covered by this review was taken in the date order of receipt

Yes ___ No X

If no, explain reason(s) below:

Minor Amendment.

SPOT? Yes _____ No ___X

If yes, complete a SPOT form.

37. **DMF CHECKLIST FOR ANDA #75-896 REVIEW # 5**

DMF #	DMF TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT OF REVIEW	DATE REVIEW COMPLETED
[redacted]	II/ [redacted]	1	Adequate	Jan 13, 2003
	Comments:			
[redacted]	III/ [redacted]	4		
	Comments:			
[redacted]	III/ [redacted]	4		
	Comments:			
[redacted]	III/ [redacted]	4		
	Comments:			
[redacted]	III/ [redacted]	4		
	Comments:			
[redacted]	III/ [redacted]	4		
	Comments:			

ACTION CODES: (1) DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows:

(2) Type 1 DMF;
(3) Reviewed previously and no revision since last review;
(4) Sufficient information in application;
(5) Authority to reference not granted;
(6) DMF not available;
(7) Other (explain under "Comments").

Bita Mirzai-Azarm
Reviewer Signature

Bita M. Azarm

12/18/03
Date

cc: ANDA 75-896
ANDA DUP
Field Copy
HFD-92

Endorsements:

HFD-647/B.M.Azarm/11/04/03, 11/17/03 (revised) B.M.Azarm 12/18/03

HFD-647/U.Venkataram/11.20.03 U.V.Venkataram 12/18/03

HFD-617/S.Shepperson/12.12.03 S.Shepperson 12/18/03

F/T by: rad12/17/03

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CHEMISTRY REVIEW - APPROVABLE

APPEARS THIS WAY
ON ORIGINAL

1. CHEMISTRY REVIEW NO. 6

2. ANDA # 75-896

3. NAME AND ADDRESS OF APPLICANT
Mutual Pharmaceutical Company, Inc.
Attention: Sherry Schultz
1100 Orthodox Street
Philadelphia, PA 19124

4. LEGAL BASIS FOR SUBMISSION
Innovator Product: Plendil® ER Tablets (NDA #19-834)
Innovator Company: AstraZeneca

The applicant includes Patent Certification and Exclusivity Statement.

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME: Felodipine ER Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
Original Submission: 06/06/2000
Major Amendment: 08/14/2000 (addition of 5 mg strength)
Major Amendment: 08/29/2000 (addition of 2.5 mg strength)
Patent Correspondence: 08/29/2000
Patent Correspondence: 09/12/2000
Original Amendment: 11/15/2000
Patent Amendment: 11/17/2000
Major Amendment: 03/07/2001
Bioequivalence Amendment: 4/30/2001
Bioequivalence Amendment: 6/25/2001
Amendment: 08/15/2001
Minor Amendment: 09/24/2001
Fax Amendment: 11/28/2001
Telephone Amendment: 02/05/2002
New Correspondence: 9/24/2002
New Chemisty Correspondence: 1/14/2003
Labeling Amendment: 04/11/2003
Labeling Telephone Amendment: 05/13/2003
Minor Amendment: 09/10/2003
Patent Correspondence: 11/26/2003

Minor Amendment: 10/1/2004 **(Request for Final Approval)**
Patent Correspondence: 10/1/2004
New Correspondence 10/4/2004
Labeling Amendment 10/5/2004
Patent Correspondence 10/29/2004
FDA:
Acceptance for Filing: 06/06/2000
Deficiency Letter: 11/16/2000
Deficiency Letter: 08/15/2001
Deficiency Letter: 11/13/2001
Telephone Conversation: 02/01/2002
Deficiency Letter: 03/27/2003
Tentative Approval Letter: 2/6/2004

10. PHARMACOLOGICAL CATEGORY
Anti-hypertensive

11. Rx or OTC
RX

12. RELATED IND/NDA/DMF(s)
See review element #37

13. DOSAGE FORM
ER Tablets/Oral

14. POTENCIES
2.5 mg, 5 mg, and 10 mg

15. CHEMICAL NAME AND STRUCTURE
Chemical name:
(±)-Ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate

Chemical Formula: $C_{18}H_{19}Cl_2NO_4$

Molecular Weight: 384.26

CAS Number: [72509-76-3; 86189-69-7]

16. RECORDS AND REPORTS

17. COMMENTS
CMC – Satisfactory
Bio – Acceptable (01/28/02)
MV – DS is compendial, DP is compendial.
EER – Acceptable on 11/28/01 and 12/1/03.
Labeling – Satisfactory (03/22/01); 05/12/03 and 10/20/04.

18. CONCLUSIONS AND RECOMMENDATIONS
No CMC changes. The request for Final Approval may be granted.

19. REVIEWER:
Bita Mirzai-Azarm

DATE COMPLETED:
10/12/04

cc: ANDA 75-896
ANDA DUP
Field Copy
HFD-92

Endorsements:

HFD-647/B.M.Azarm/10/12/04 Bita M. Azarm 10/29/04.

HFD-647/U.Venkataram/10.13.04 U.V. Venkataram 10/29/2004.

HFD-617/S.Shepperson/10-20-04 10/29/04

F/T by: sms 10-20-04

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CHEMISTRY REVIEW – APPROVABLE

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-896

BIOEQUIVALENCE REVIEWS

FELODIPINE EXTENDED-RELEASE
2.5 mg, 5 mg and 10 mg Tablets
ANDA 75-896
Reviewer: Patrick Nwakama
File Name: 75-896S.600

Mutual Pharmaceutical Company, Inc.
1100 Orthodox Street
Philadelphia, PA 19124
Submission Date: 06/06/00 (10 mg)
~~07/21/00 (5 mg)~~ (KS) 3/27/01
08/14/00 (Orig. Amendment)
08/29/00 (2.5 mg)
03/07/01 (Orig. Amendment)

Review of Bioequivalence Studies, Dissolution Data and Waiver Requests (Electronic Submission)

Introduction

Indication:	Anti-hypertensive Agent
Type of Submission:	Original Submission
First Generic:	Yes
Contents of Submission:	*in vivo* Bioequivalence Fasting, Non-fasting and Steady State Studies
RLD:	Plendil® Extended-Release Tablets (Merck)
Recommended Dose:	2.5 - 10 mg once daily

Background

Felodipine is an oral calcium-channel blocker used in the treatment of hypertension. It belongs to the dihydropyridine class as nifedipine, isradipine and amlodipine. It is a potent peripheral vasodilator that has greater selectivity for vascular smooth muscle relative to cardiac muscle than does nifedipine. Felodipine causes vasodilation in coronary, skeletal, and cerebral vasculature by inhibiting both influx of extracellular calcium and the contractile processes of the smooth muscle cells. It has no effect on atrioventricular (AV) or sinoatrial (SA) nodal conduction. Negative inotropic effects are rarely observed clinically because of felodipine's tendency to produce reflex tachycardia in response to its vasodilatory activity.

Felodipine is rapidly absorbed when given orally but its bioavailability is about 13-16% because of extensive first-pass metabolism. Peak serum concentrations are attained in 2.5 - 5 hours. Bioavailability is enhanced by food. The Cmax is increased by about 60% with high fat or carbohydrate diet while the AUC remained unchanged. Grapefruit juice appears to double the bioavailability of felodipine. It is about 99% protein bound and completely metabolized to inactive compounds in the liver before excretion through the kidney and feces. The elimination half-life is about 11 - 16 hours. Felodipine elimination is significantly altered by liver dysfunction and aging. Felodipine's plasma levels, after a single dose and at steady state, increase with age. Renal impairment does not change felodipine concentrations.

Financial Disclosure

Form FDA 3454 was submitted. The firm has no conflict of interest with the investigators.

Protocol No.: 991004, Comparative, Randomized, Single-Dose, 2-Way Crossover Bioavailability Study of Mutual and Astra Merck (Plendil®) 10 mg Felodipine Extended-Release Tablets in Healthy Adult Males Under Fasting Conditions

Study Information

STUDY FACILITY INFORMATION

Clinical Facility:	[redacted]
Medical Director:	[redacted], M.D.
Scientific Director:	[redacted] Pharm.D.
Clinical Study Dates:	01/18/00 to 02/04/00
Analytical Facility	[redacted]
Principal Investigator:	[redacted] Ph.D.
Analytical Study Dates:	03/05/00 to 03/24/00
Storage Period:	66 days (Long-term stability: 51 days)

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Felodipine Extended-Release	Plendil®)
Manufacturer:	Mutual Pharmaceutical Co., Inc.	Astra Merck
Manufacture Date:	01/06/2000	N/A
Expiration Date:	N/A	09/01
ANDA Batch Size:	[redacted]	N/A
Batch/Lot Number:	BB7730042	H4386
Potency:	98.7	99.7
Content Uniformity:	99.3	100.5
Strength:	10 mg	10 mg
Dosage Form:	Tablet	Tablet
Dose Administered:	10 mg	10 mg
Study Condition:	Fasting	Fasting
Length of Fasting:	10 hours	10 hours

RANDOMIZATION		DESIGN	
Randomized:	Y	**Design Type:**	Crossover
No. of Sequences:	2	**Replicated Treatment Design:**	N
No. of Periods:	2	**Balanced:**	Y
No. of Treatments:	2	**Washout Period:**	14 days

Randomization Scheme:

AB: 1,4,5,9,10,12,13,15,17,19,20,22,25,28,29,31,34,36,37,40,41,43,44,47,49,51

BA: 2,3,6,7,8,11,14,16,18,21,23,24,26,27,30,32,33,35,38,39,42,45,46,48,50,52

**Subjects # 33, 38, 42-44 did not complete study and Subjects # 5 and 51 were excluded from analyses.

DOSING		SUBJECTS	
Single or Multiple Dose:	Single	**IRB Approval:**	Y
Steady State:	N	**Informed Consent Obtained:**	Y
Volume of Liquid Intake:	360 mL	**No. of Subjects Enrolled:**	52
Route of Administration:	Oral	**No. of Subjects Completing:**	47
Dosing Interval:	N/A	**No. of Subjects Plasma Analyzed:**	45
Number of Doses:	N/A	**No. of Dropouts:**	5
Loading Dose:	N/A	**Sex(es) Included:**	Male (18 - 40 years; 60 kg ± 10% IBW)
Steady State Dose Time:	N/A	**Healthy Volunteers Only:**	Y
Length of Infusion:	N/A	**No. of Adverse Events:**	62
Dietary Restrictions:	No alcohol- or xanthine-containing beverages & food 24hrs pre-dose & throughout sample collection period. No grapefruit-containing beverages & food 7 days pre-dose & throughout the entire study.		
Activity Restrictions:	Subjects were seated & remained seated/semi-reclined 4hrs post-dose, except when prevented by adverse events. No strenuous activity during the housing period. Cautioned in activities of mental alertness/judgement/physical coordination 36 hours post-dose.		
Drug Restrictions:	No medication (including over-the-counter products, excluding vitamins taken as nutritional supplements for non-therapeutic indications) 7 days pre-study.		
Blood Sampling:	Before dosing (time 0), and 0.5,1,1.5,2,2.5,3,3.5,4,4.5, 5,5.5,6,7,8, 10, 16, 24,36,48,60 and 72 hours, post-dose		

Study Results

1) Clinical

Adverse Events:

Twenty-nine (29) subjects experienced 62 treatment drug-related adverse events. Thirty-eight (38) cases were determined 'probable' (headache 35, nausea 2 and vomiting 1) 15 were 'possible' (dizziness 3, feels hot 4, nausea 2, shaky arms 1, palpitations 1, feels tired, Itching 1, chest pain 1, and loose stools 1) and 9 were 'remote' (headache 1, dizziness 1, runny nose 1, nausea 1, abdominal pain 1, loose stool 1, lack of appetite, feverish 1 and pre-orbital redness 1) related to the study drug. All events were mild in severity and evenly distributed among the test (27) and reference (35).

Protocol Deviations:

Subjects # 5 and #51 completed the study but the analysis of their samples were stopped at the request of the sponsor because Subject #5 vomited (9.4 hours post-dose in Period I) and Subject #51 had adverse events (Period II). Subject #8 consumed Cola beverage 2.4 days post dose in Period I. There were some sampling time deviations. Actual sampling times were used for pharmacokinetic calculations. There were some minor delays in the storage of some collected samples in the freezer.

Dropouts:

SUBJECT NO.:	33	38	42	43
REASON:	Vomiting episode at 3.7 hrs post-dose	Personal reasons	Personal reasons	Personal reasons
PERIOD:	1	1	1	1
REPLACEMENT:	Y	Y	N	Y

SUBJECT NO.: 44
REASON: Personal reasons
PERIOD: 1
REPLACEMENT: Y

2) Analytical (Not to be Released Under FOI)
Pre-Study Assay Validation:

ANALYTE:	FELODIPINE
[redacted]	

Within-Study Assay Results:
Assay method, biological matrix and internal standards were similar to those of pre-study method validation.

Analyte	FELODIPINE
Sensitivity:	[redacted]
Standard Curve:	
QC Samples	
R**2 IS GREATER THAN:	
Specificity:	
Inter-day Accuracy (%)	
Inter-day Precision (% CV)	

Repeat Sample Analysis Summary:

Lost in Processing	22
Poor Chromatography	1
Anomalous Value	9
Highest/Lowest Standard Missing	5
Not Reportable	5
No Sample	5

Comments: The analytical method is incomplete because the submitted long-term stability data for felodipine did not cover the duration of study.

3) Pharmacokinetic:

Mean Plasma Concentration: Table 2 and Figure 1
Pharmacokinetic Parameters: Table 3
90% Confidence Intervals: Table 4

4) Statistical Analysis:

1. Arithmetic means and least square means were calculated for AUC_{0-T}, AUC_{0-INF}, and C_{MAX}
2. ANOVA was performed on log transformed AUC_{0-T}, AUC_{0-INF}, and C_{MAX}. The analysis of variance model included sequence, subject nested within sequence, period, and drug formulation as factors. A 5% level of significance was used for within-subject (i.e. period and formulation) and a 10% level of significance of between-subject comparisons (i.e. sequence). Each analysis of variance included calculations of LSM, differences between adjusted formulation means and SE associated with these differences. The statistical analyses were done using SAS GLM procedure.

Comments:

1. The reviewer recalculated the pharmacokinetic parameters and 90% confidence intervals. The reported values are in good agreement with those obtained by the reviewer.

2. The 90% confidence intervals for the log transformed AUC_{0-T} and AUC_{0-INF} are within acceptable limits. The 90% confidence intervals for the LCmax are outside the limits. There are no statistically significant period, sequence, or treatment effects for any of these parameters.

3. Nine (9) anomalous values were reported for felodipine. In all 9 cases, the median values were used by the firm. None were for Cmax. The reviewer recalculated the PK parameters using the original values and the outcome of the study did not change. The 90% confidence intervals for LCmax remained outside the acceptable limits.

4. No subjects with zero-hour drug level, first measurable level as Cmax or first scheduled post-dose time as Cmax.

5. The firm did not report the values of AUC_{0-INF}, Kel and T1/2 for Subject #30 (Period 2, Test) and Subject #41(Period 2, Reference) since a terminal log-linear phase in the concentration vs time profile was not observed. The reviewer agrees with this decision.

Conclusion:
The fasting study is not acceptable because the 90% confidence intervals for LCmax were outside the acceptable limits and long-term stability data did not cover the duration of the study.

Protocol No.: 991005, Comparative, Randomized, Single-Dose, 3-Way Crossover Bioavailability Study of Mutual and Astra Merck (Plendil®) 10 mg Felodipine Extended-Release Tablets in Healthy Adult Males Under Non-Fasting Conditions

Study Information

STUDY FACILITY INFORMATION

Clinical Facility:	_____
Medical Director:	_____ M.D.
Scientific Director:	_____ Pharm. D.
Clinical Study Dates:	03/23/00 to 04/23/00
Analytical Facility	_____
Principal Investigator:	_____, Ph.D.
Analytical Study Dates:	04/25/00 to 05/09/00
Storage Period:	47 Days (Long term stability – 51 days)

TREATMENT INFORMATION

Treatment ID:	A	B	C
Test or Reference:	T	T	R
Product Name:	Felodipine ER	Felodipine ER	Plendil®
Manufacturer:	Mutual Pharmaceutical	Mutual Pharmaceutical	Astra Merck
Batch/Lot Number:	BB7730042	BB7730042	H4386
Strength:	10 mg	10 mg	10 mg
Dosage Form:	Tablet	Tablet	Tablet
Dose Administered:	10 mg	10 mg	10 mg
Study Condition:	Fasting	Fed	Fed
Length of Fasting:	10 hours	10 hours	10 hours
Std. Breakfast:	N/A	Y	Y
Breakfast Specifics:	N/A	180 mL orange juice, 240 mL whole milk, 1 fried egg, 1 buttered English muffin, 1 slice American cheese, 1 rasher of Canadian bacon, 1 serving hash brown potatoes.	180 mL orange juice, 240 mL whole milk, 1 fried egg, 1 buttered English muffin, 1 slice American cheese, 1 rasher of Canadian bacon, 1 serving hash brown potatoes.
Standardized Lunch:	Y	Y	Y
Lunch Specifics:	Apple juice,Hungarian meatballs, rice, mixed vegetables, whole wheat roll, buttertart, butter, salt, pepper.	Apple juice,Hungarian meatballs, rice, mixed vegetables, whole wheat roll, buttertart, butter, salt, pepper.	Apple juice,Hungarian meatballs, rice, mixed vegetables, whole wheat roll, buttertart, butter, salt, pepper.
Standardized Dinner:	Y	Y	Y
Dinner Specifics:	Lemon lime "Up", chicken Kiev, mixed vegetables, mashed potatoes, whole wheat roll, butterscotch pudding cup, 1 pkg Fig Newton cookies, butter, salt, pepper.	Lemon lime "Up", chicken Kiev, mixed vegetables, mashed potatoes, whole wheat roll, butterscotch pudding cup, 1 pkg Fig Newton cookies, butter, salt, pepper.	Lemon lime "Up", chicken Kiev, mixed vegetables, mashed potatoes, whole wheat roll, butterscotch pudding cup, 1 pkg Fig Newton cookies, butter, salt, pepper.

RANDOMIZATION		DESIGN	
Randomized:	Y	**Design Type:**	Crossover
No. of Sequences:	6	**Replicated Treatment Design:**	N
No. of Periods:	3	**Balanced:**	Y
No. of Treatments:	3	**Washout Period:**	14 days

Randomization Scheme:

ABC: 1, 12,15,	CBA: 2, 8, 16	BCA: 4,5,9
CAB: 3,10,14	ACB: 6,7,11	BAC: 13, 17,18
4 subjects (#2,6,8 & 13) did not complete study		

DOSING		SUBJECTS	
Single or Multiple Dose:	single	**IRB Approval:**	Y
Steady State:	N	**Informed Consent Obtained:**	Y
Volume of Liquid Intake:	360 mL	**No. of Subjects Enrolled:**	18
Route of Administration:	Oral	**No. of Subjects Completing:**	14
Dosing Interval:	N/A	**No. of Subjects Plasma Analyzed:**	17
Number of Doses:	N/A	**No. of Dropouts:**	4
Loading Dose:	N/A	**Sex(es) Included:**	Male (18 - 40 years; 60 kg ± 10% IBW)
Steady State Dose Time:	N/A	**Healthy Volunteers Only:**	Y
Length of Infusion:	N/A	**No. of Adverse Events:**	30
Dietary Restrictions:	No alcohol- or xanthine-containing beverages & food 24hrs pre-dose & throughout sample collection period. No grapefruit-containing beverages & food 7 days pre-dose & throughout the entire study.		
Activity Restrictions:	Subjects were seated & remained seated/semi-reclined 4hrs post-dose, except when prevented by adverse events. No strenuous activity during the housing period. Cautioned in activities of mental alertness/judgement/physical coordination 36hrs post-dose.		
Drug Restrictions:	No medication (including over-the-counter products, excluding vitamins taken as nutritional supplements for non-therapeutic indications) 7 days pre-study.		
Blood Sampling:	Same as in Fasting Study		

Study Results

1) Clinical

Adverse Events:

Nine (9) subjects experienced 30 treatment drug-related adverse events. Twenty-three (23) cases were determined 'probable' (headache 19, vomiting 1, shivering 1, epigastric pain 1, and nausea 1), 6 were 'possible' (dizziness 4, arm muscular pain 1, and lightheadness 1) and 1 were 'remote' (feels tired) related to the study drug. All events were mild in severity and occurred with even distribution among the three treatment arms (Trt A = 8, Trt B= 13 and Trt C= 9).

Protocol Deviations:
The washout period of 14 days was reduced by 1 hour as a result of the observation Daylight Savings Time. Some samples were not placed in the freezer within 1.5 hours of collection. One subject (#8) consumed some chocolates. There were some sampling time deviations that were adjusted for actual times.

Dropouts:

SUBJECT NO.:	2	6	8	13
REASON:	Personal reasons	Personal reasons	Personal reasons	Adverse events
PERIOD:	2	2	2	1
REPLACEMENT:	N	N	N	N

2) Analytical (Not to be Released Under FOI)

Pre-Study Assay Validation - Same as in Fasting Study

Within-Study Assay Results: Assay method, biological matrix and internal standards were similar to pre-study method validation.

Analyte	FELODIPINE
Sensitivity:	
Standard Curve:	
QC Samples	
R**2 IS GREATER THAN:	
Specificity:	
Inter-day Accuracy (%)	
Inter-day Precision (% CV)	

Sample Reassay Summary:

Lost in Processing	13
Anomalous Value	13
Above Curve Limit	40
No Sample	19

Comments: The analytical method is acceptable.

3) Pharmacokinetic:
Mean Plasma Concentration: Table 5, Figure 2
Pharmacokinetic Parameters: Table 6
Ratio of Means: Table 7

4) Statistical Analysis:
Arithmetic means, geometric means and LSMs were calculated for AUC_{0-T}, AUC_{0-INF}, and C_{MAX}, and T_{MAX}. Ratios of means were calculated using the LSM for both ln-transformed and untransformed AUC_{0-T}, AUC_{0-INF}, and C_{MAX}.

Comments:

1. Thirteen (13) anomalous values were reported and the median values were used by the firm. Two values were for Cmax. The reviewer recalculated the PK parameters using the original values and the outcome of the study did not change.

2. No subjects had a zero-hour drug level or first scheduled post-dose time as Cmax.

3. For the AUC_{0-T}, AUC_{0-INF}, and C_{MAX}, the test/reference LSM and geometric means ratios were within the acceptable range of 0.80 - 1.25. All statistical analyses were verified by the reviewer.

4. The firm could not estimate AUC_{0-INF}, Kel and T1/2 for Subject #2 (Period 2, Reference) and the reviewer agrees with this observation.

5. Of the 18 subjects enrolled in the study, four did not complete the study. Subject #13 was withdrawn in Period I (test-fed) due to headache, nausea, vomiting and shivering. Subjects #2, 6, and 8 did not return for Period 3 for personal reasons. The firm's analysis included data from these 3 subjects. The reviewer recalculated ratios of means dropping these 3 subjects who did not complete all 3 study periods. The ratios of means remained within the acceptable limits.

Conclusion: The non-fasting study is acceptable.

Protocol No.: 2338, A Two-Way Crossover Multiple-Dose Open-Label Fasting Bioequivalence Study Comparing Felodipine 10 mg ER Tablets and Plendil® 10 mg Tablets in Normal Healthy Male Subjects

Study Information

STUDY FACILITY INFORMATION

Clinical Facility: [redacted]

Medical Director: [redacted] M.D., F.R.C.P., F.A.C.P.
Scientific Director: [redacted] Ph.D.
Clinical Study Dates: 04/07/00 to 05/05/00
Analytical Facility [redacted]

Principal Investigator: [redacted] Ph.D.
Analytical Study Dates: 05/05/00 to 05/16/00
Storage Period: 40 days (Long-term stability: 107 days)

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Felodipine Extended-Release	Plendil®
Manufacturer:	Mutual Pharmaceutical Co., Inc.	Astra Merck
Batch/Lot Number:	BB7730042	H4386
Strength:	10 mg	10 mg
Dosage Form:	Tablet	Tablet
Dose Administered:	10 mg	10 mg
Study Condition:	Fasting	Fasting
Length of Fasting:	10 hours	10 hours

RANDOMIZATION		DESIGN	
Randomized:	Y	**Design Type:**	Crossover
No. of Sequences:	2	**Replicated Treatment Design:**	N
No. of Periods:	2	**Balanced:**	Y
No. of Treatments:	2	**Washout Period:**	2 weeks

Randomization Scheme:

AB: 2,3,6,7,11,12,16,17,18, 25,28,29,33,34, 36, 37, 39, 41,42,44,45,**46**,47,48	BA: 1,**5**,4,8,9,10,13,14,15,**19**,20,**21**,22,**23**, **24**, **26**, 27, 30,31,**32**,35,38,40,43,

Subjects #5, #23, #24 #26 and #46 were dismissed due to adverse events. Subjects #7 and #32 withdrew for personal reasons. Subjects #19 and #21 were dropped for non-compliance.

DOSING		SUBJECTS	
Single or Multiple Dose:	multiple	**IRB Approval:**	Y
Steady State:	Y	**Informed Consent Obtained:**	Y
Volume of Liquid Intake:	360 mL	**No. of Subjects Enrolled:**	48
Route of Administration:	oral	**No. of Subjects Completing:**	39
Dosing Interval:	24 hr	**No. of Subjects Plasma Analyzed:**	39
Number of Doses:	7	**No. of Dropouts:**	9
Loading Dose:	N/A	**Sex(es) Included:**	Male (18 - 40 yrs and 60 kg ± 10% IBW)
Steady State Dose Time:	N/A	**Healthy Volunteers Only:**	Y
Length of Infusion:	N/A	**No. of Adverse Events:**	146

Dietary Restrictions: No alcohol-, grapefruit- and xanthine-containing foods and fluids from 48 hrs pre-study until the last blood draw.

Activity Restrictions: Subjects remained seated upright for the first 4 hrs post-dose, except if drowsiness, dizziness, or lightheadedness occurred, then, subjects were able to lie down on their right side. No strenuous activity at any time during the housing period.

Drug Restrictions: No prescription medication 30 days pre-study. No over-the -counter drugs at least 14 days pre-study and during the study period (esp. cold preparations, Aspirin, Bufferin, Excedrin, Anacin, etc, vitamin and antacid preparations)

Blood Sampling: Days 1,5, & 6 at 0 h (pre-dose) and on Day 7 at 0 h (pre-dose), 0.5,1, 1.5,2,2.5,3,3.5,4,4.5,5,5.5,6,6.5,7,8,9,10,16, and 24 hours, post-dose.

Study Results

1) Clinical

Adverse Events:

Thirty-eight (38) subjects experienced 146 drug-related adverse events. Sixteen (16) were considered to be 'probable' while the remaining 130 cases were 'possible' related to the study drug. Headache accounted for more than 57% (84/146) of the events. There were 14 cases of 1^0 AV block and 14 cases of sinus bradycardia. Other events include nausea, lightheadedness, diarrhea, constipation and stomach upset. Only one subject received pharmacologic treatment (Tylenol) for an adverse event (headache). All events were evenly distributed between the two treatments.

Protocol Deviations:

There were 67 (31 in Period I and 36 in Period II) reported deviations. Urinalysis was not performed on all subjects during medical screening. Thirty-six (36) were blood sampling time deviations ranging from 1 - 58 minutes and occurring from 0.5 - 24 hour post-dose. All calculations were carried out using actual sampling time points.

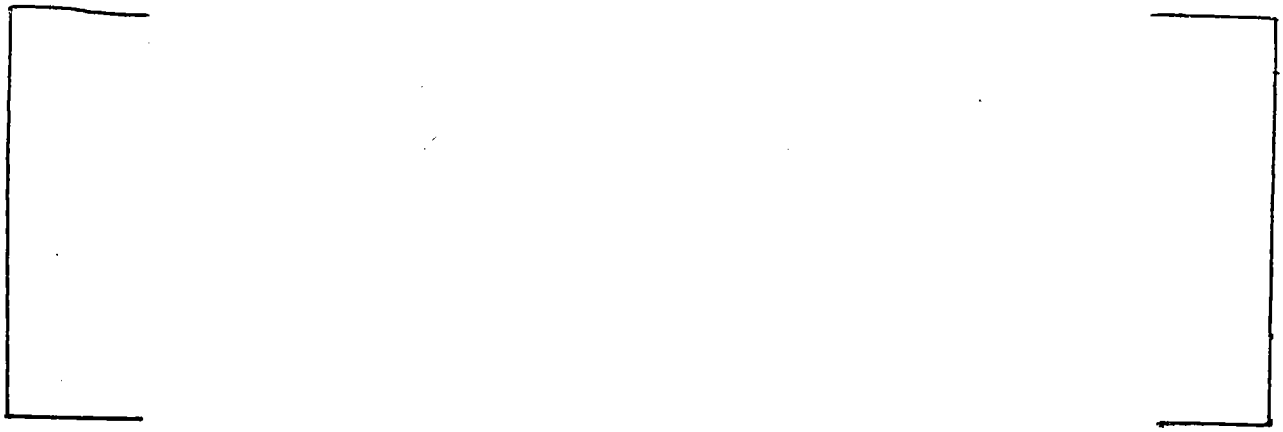
Dropouts:

SUBJECT NO.:	19	21	23	24
REASON:	Non-compliance	Non-compliance	Adverse events	Adverse events
PERIOD:	1	2	2	2
REPLACEMENT:	N	N	N	N
SUBJECT NO.:	26	32	46	5
REASON:	Adverse events	Personal reasons	Adverse events	Adverse events
PERIOD:	2	1	1	2
REPLACEMENT:	N	N	N	N
SUBJECT NO.:	7			
REASON:	Personal reasons			
PERIOD:	1			
REPLACEMENT:	N			

2) Analytical (Not to be Released Under FOI)

Pre-Study Assay Validation:

ANALYTE: FELODIPINE



Within-Study Assay Results:
Assay method, biological matrix and internal standards were similar to those of pre-study method validation.

Analyte	FELODIPINE
Sensitivity:	
Standard Curve:	
QC Samples	
R**2 IS GREATER THAN:	
Specificity:	
Inter-day Accuracy (%)	
Inter-day Precision (% CV)	

Sample Reassay Summary:

Above Limit of Quantitation	2
Processing Error	3
Pharmacokinetic Repeats	35

Comments: The analytical method is acceptable.

3) Pharmacokinetic:

Mean Plasma Concentration: Table 8, Figure 3
Pharmacokinetic Parameters: Table 9
90% Confidence Intervals: Table 10

4) Statistical Analysis:
Arithmetic means, geometric means and LSMs were calculated for AUC_{0-T}, C_{MAX}, C_{MIN}, and T_{MAX} and degree of fluctuation of Day 7. Ratios of arithmetic means were calculated for AUC_{0-T}, C_{MAX}, C_{MIN}, C_{AVE}, % Fluctuation and T_{MAX}. Analysis of variance (ANOVA) (with factors including treatment, period, sequence, and subject within sequence) were carried out. For analyses, effects were considered statistically significant at $< 5\%$ level. The statistical analyses were done using SAS GLM procedure.

Comments:

1. The mean peak plasma felodipine levels for the test and reference products were attained on Day #7 (3.5 hours) (Table 8).

2. The firm has confirmed steady-state attainment by performing ANOVA on log-transformed pre-dose levels obtained on days 5, 6, and 7 for both test and reference products. The reviewer agrees with the firm's decision.

3. Thirty-five (35) pharmacokinetic repeats were done. The original values were reported in 21 of the cases. The repeat values were reported for the remaining 14. None was for Cmax. The reviewer verified that if the original values were used instead of the repeat values in the latter cases, the outcome of the study would not change.

4. The reviewer's recalculated PK values were in agreement with those obtained by the firm and the 90% confidence intervals of all PK parameters are within the acceptable limits of 80 - 125%.

5. The study samples were analyzed by a different analytical laboratory (———). The long-term stability data (107 days) was submitted as study amendment (3/7/01). It covered the entire storage period of study samples (40 days).

Conclusion:
The multiple dose study is acceptable even though it is no longer neeeded as per BA/BE guidance.

Protocol No.: 991007, Comparative, Randomized, Single-Dose, 2-Way Crossover Bioavailability Study of Mutual and Astra Merck (Plendil®) 5 mg Felodipine Extended-Release Tablets in Healthy Adult Males Under Fasting Conditions

Study Information

STUDY FACILITY INFORMATION

Clinical Facility:	———
Medical Director:	——— M.D.
Scientific Director:	——— Pharm.D.
Clinical Study Dates:	04/19/00 to 05/03/00
Analytical Facility	———
Principal Investigator:	——— Ph.D.
Analytical Study Dates:	05/09/00 to 05/30/00
Storage Period:	41 days (Long-term stability: 51 days)

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Felodipine Extended-Release	Plendil(R)
Manufacturer:	Mutual Pharmaceutical Co., Inc.	Astra Merck
Manufacture Date:	01/06/2000	N/A

Expiration Date:	N/A	09/01
ANDA Batch Size:	———	N/A
Batch/Lot Number:	BB7720045	H4497
Potency:	100.7	102.6
Content Uniformity:	101.4	102.3
Strength:	5 mg	5 mg
Dosage Form:	Tablet	Tablet
Dose Administered:	5 mg	5 mg
Study Condition:	Fasting	Fasting
Length of Fasting:	10 hours	10 hours

RANDOMIZATION		DESIGN	
Randomized:	Y	**Design Type:**	Crossover
No. of Sequences:	2	**Replicated Treatment Design:**	N
No. of Periods:	2	**Balanced:**	Y
No. of Treatments:	2	**Washout Period:**	14 days

Randomization Scheme:

AB: 1,3,6,7,8,12,14,17,18,19,20,23,24,27,28,32,34,35,36,39,41,43

BA: 2,4,5,9,10,11,13,15,16,21,22,25,26,29,30,31,33,37,38,40,42,44

**Subjects # 15, 25, 28 and # 36 did not complete study. Samples from Subject #34 were not analyzed because the subject took extra 20 mL of water to facilitate pill swallowing.

DOSING		SUBJECTS	
Single or Multiple Dose:	Single	**IRB Approval:**	Y
Steady State:	N	**Informed Consent Obtained:**	Y
Volume of Liquid Intake:	360 mL	**No. of Subjects Enrolled:**	44
Route of Administration:	Oral	**No. of Subjects Completing:**	40
Dosing Interval:	N/A	**No. of Subjects Plasma Analyzed:**	39
Number of Doses:	N/A	**No. of Dropouts:**	4
Loading Dose:	N/A	**Sex(es) Included:**	Male (18 - 40 yrs and 60 kg ± 10% IBW)
Steady State Dose Time:	N/A	**Healthy Volunteers Only:**	Y
Length of Infusion:	N/A	**No. of Adverse Events:**	41

Dietary Restrictions: No alcohol- or xanthine-containing beverages & food 24hrs pre-dose & throughout sample collection period. No grapefruit-containing beverages & food 7 days pre-dose & throughout the entire study.

Activity Restrictions: Subjects were seated & remained seated/semi-reclined 4hrs post-dose, except when prevented by adverse events. No strenuous activity during the housing period. Cautioned in activities of mental alertness/judgement/physical coordination 36hrs post-dose.

Drug Restrictions: No medication (including over-the-counter products, excluding vitamins taken as nutritional supplements for non-therapeutic indications) 7 days pre-study.

Blood Sampling: Before dosing(time 0), and 0.5,1,1.5,2,2.5,3,3.5,4,4.5, 5,5.5,6,7,8, 9,10, 16, 24,36,48,60 and 72 hours, post-dose

Study Results

1) Clinical

Adverse Events:

Twenty (20) subjects experienced 41 treatment drug-related adverse events. One (1) case was determined 'probable' (headache), 36 were 'possible' (headache 14, dizziness 3, flatulence 1, weakness 2, tiredness 1, vomiting 3, feeling hot and cold 1, feeling hot 1, photosensitivity 1, sweating 1, tachycardia 1, sleepiness 1, cold sores 1, generalized erythema 2, and nausea 3) and 4 were 'remote' (hematechezia, headache 2, and vomiting) related to the study drug. The reported adverse events are mild and evenly distributed among the reference (19) and test (22) products.

Protocol Deviations:

Subject # 34 completed the study but his samples were not analyzed because he took extra water to swallow his pill in period 2. No samples were obtained from Subject #8 in period 2 (Reference) and Subject # 39 in period 1 (Test) at 60- and 72-hour post dose, respectively, because subjects did not show up for blood draws. There were some minor sampling time deviations. Actual sampling times were used for pharmacokinetic calculations. There were some minor delays in the storage of some collected samples in the freezer.

Dropouts:

SUBJECT NO.:	15	25	28	36
REASON:	Personal reasons	Consuming extra 190 mL water	Adverse events (headache and N/V)	Adverse events (headache and N/V)
PERIOD:	1	1	1	1
REPLACEMENT:	N	N	N	N

2) Analytical (Not to be Released Under FOI)

Pre-Study Assay Validation: Same as that for Felodipine 10 mg Fasting Study.

Within-Study Assay Results:

Assay method, biological matrix and internal standards were similar to those of Pre-study method validation.

Analyte	FELODIPINE
Sensitivity:	[redacted]
Standard Curve:	
QC Samples	
R**2 IS GREATER THAN:	
Specificity:	
Inter-day Accuracy (%)	
Inter-day Precision (% CV)	

Repeat Sample Analysis Summary:

Lost in Processing	21
Anomalous Value	6
No Sample	2

Comments: The analytical method is acceptable.

3) Pharmacokinetic:

Mean Plasma Concentration: Table 11 and Figure 4
Pharmacokinetic Parameters: Table 12
90% Confidence Intervals: Table 13

4) Statistical Analysis:

1. Arithmetic means and least square means were calculated for AUC_{O-T}, AUC_{O-INF}, and C_{MAX}

2. ANOVA was performed on log transformed AUC_{O-T}, AUC_{O-INF}, and C_{MAX}. The analysis of variance model included sequence, subject nested within sequence, period, and drug formulation as factors. A 5% level of significance was used for within-subject (i.e. period and formulation) and a 10% level of significance of between-subject comparisons (i.e. sequence). Each analysis of variance included calculations of LSM, differences between adjusted formulation means and SE associated with these differences. The statistical analyses were done using SAS GLM procedure.

Comments:

1. Six (6) anomalous values were reported and the median values were used by the firm. Four were for Cmax. The reviewer recalculated the PK parameters using the original values and the outcome of the study did not change.

2. No subjects with zero-hour drug level, first scheduled post-dose time point as C_{max} or first measurable drug concentration as C_{max}. The reviewer recalculated the pharmacokinetic parameters and found them in complete agreement with those of the firm.

3.. The reviewer's recalculated 90% confidence intervals for log-transformed AUCT, AUC_{0-INF}, and C_{max} for felodipine corresponded with those of the firm and are all within the within acceptable limits of 80 - 125%.

Conclusion:

The fasting study is acceptable.

Protocol No.: 991008, Comparative, Randomized, Single-Dose, 2-Way Crossover Bioavailability Study of Mutual and Astra Merck (Plendil®) 2.5 mg Felodipine Extended-Release Tablets in Healthy Adult Males Under Fasting Conditions

Study Information

STUDY FACILITY INFORMATION

Clinical Facility:	[redacted]
Medical Director:	[redacted] M.D.
Scientific Director:	[redacted], Pharm.D.
Clinical Study Dates:	05/25/00 to 06/08/00
Analytical Facility	[redacted]
Principal Investigator:	[redacted] Ph.D.
Analytical Study Dates:	06/14/00 to 06/29/00
Storage Period:	35 days (Long-term stability: 51 days)

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Felodipine Extended-Release	Plendil®
Manufacturer:	Mutual Pharmaceutical Co., Inc.	Astra Merck
Manufacture Date:	N/A	N/A
Expiration Date:	N/A	10/01
ANDA Batch Size:	[redacted]	N/A
Batch/Lot Number:	BB7710046	J5126
Potency:	97.3	99.4
Content Uniformity:	96.5	99.0
Strength:	2.5 mg	2.5 mg
Dosage Form:	Tablet	Tablet
Dose Administered:	2 x 2.5 mg	2 x 2.5 mg
Study Condition:	Fasting	fasting
Length of Fasting:	10 hours	10 hours

RANDOMIZATION		DESIGN	
Randomized:	Y	**Design Type:**	crossover
No. of Sequences:	2	**Replicated Treatment Design:**	N
No. of Periods:	2	**Balanced:**	Y
No. of Treatments:	2	**Washout Period:**	14 days

Randomization Scheme:

AB: 1,5,7,8,9,11,13,14,15,18,19,20,22,25,27,29,30,33,35,38,41,43

BA: 2,3,4,6,10,12,16,17,21,23,24,26,28,31,32,34,36,37,39,40,42,44

****Subjects # 15, 25, 28 and # 36 did not complete study. Samples from Subject #34 were not analyzed because the subject took extra 20 mL of water to facilitate pill swallowing.**

DOSING		SUBJECTS	
Single or Multiple Dose:	Single	**IRB Approval:**	Y
Steady State:	N	**Informed Consent Obtained:**	Y
Volume of Liquid Intake:	360 mL	**No. of Subjects Enrolled:**	44
Route of Administration:	Oral	**No. of Subjects Completing:**	40
Dosing Interval:	N/A	**No. of Subjects Plasma Analyzed:**	40
Number of Doses:	N/A	**No. of Dropouts:**	4
Loading Dose:	N/A	**Sex(es) Included:**	Male (18 - 40 years and 60 kg ± 10% IBW)
Steady State Dose Time:	N/A	**Healthy Volunteers Only:**	Y
Length of Infusion:	N/A	**No. of Adverse Events:**	20
Dietary Restrictions:	No alcohol- or xanthine-containing beverages & food 24hrs pre-dose & throughout sample collection period. No grapefruit-containing beverages & food 7 days pre-dose & throughout the entire study.		
Activity Restrictions:	Subjects were seated & remained seated/semi-reclined 4hrs post-dose, except when prevented by adverse events. No strenuous activity during the housing period. Cautioned in activities of mental alertness/judgement/physical coordination 36hrs post-dose.		
Drug Restrictions:	No medication (including over-the-counter products, excluding vitamins taken as nutritional supplements for non-therapeutic indications) 7 days pre-study.		
Blood Sampling:	Before dosing(time 0), and 0.5,1,1.5,2,2.5,3,3.5,4,4.5, 5,5.5,6,7,8, 9,10, 11,16, 24,36,48,60 and 72 hours, post-dose		

Study Results

1) Clinical

Adverse Events:

Fifteen (15) subjects experienced 20 treatment drug-related adverse events. Sixteen (headache - 15 and dizziness - 1) cases were considered 'probable', 2 (chest tightness and nausea) were 'possible' and 2 (pressure on forehead and loss of appetite) were 'remote' related to the study drug. All events were mild and fairly distributed between treatments.

Protocol Deviations:

Subject # 21 consumed xanthine-containing beverages 30 hours post-dose (Period 1). Subject # 34 skipped snack (Period 1). Subject #12 had low BP prior to dosing (Period 2). There were some minor sampling time deviations. Actual sampling times were used for pharmacokinetic calculations. There were some minor delays in the storage of some collected samples in the freezer.

Dropouts: None

2) Analytical (Not to be Released Under FOI)

Pre-Study Assay Validation: Same as that for Felodipine 10 mg Fasting Study.

Within-Study Assay Results:
Assay method, biological matrix and internal standards were similar to those of Pre-study method validation.

Analyte	FELODIPINE
Sensitivity:	
Standard Curve:	
QC Samples	
R**2 IS GREATER THAN:	
Specificity:	
Inter-day Accuracy (%)	
Inter-day Precision (% CV)	

Sample Analysis Summary:

Lost in Processing	29
Anomalous Value	6
No Sample	2

Comments: The analytical method is acceptable.

3) Pharmacokinetic:
Mean Plasma Concentration: Table 14 and Figure 5
Pharmacokinetic Parameters: Table 15
90% Confidence Intervals: Table 16

4) Statistical Analysis:

1. Arithmetic means and least square means were calculated for AUC_{O-T}, AUC_{O-INF}, and C_{MAX}

2. ANOVA was performed on log transformed AUC_{O-T}, AUC_{O-INF}, and C_{MAX}. The analysis of variance model included sequence, subject nested within sequence, period, and drug formulation as factors. A 5% level of significance was used for within-subject (i.e. period and formulation) and a 10% level of significance of between-subject comparisons (i.e. sequence). Each analysis of variance included calculations of LSM, differences between adjusted formulation means and SE associated with these differences. The statistical analyses were done using SAS GLM procedure.

Comments:

1. Six (6) anomalous values were reported and the median values were used by the firm. Three were for Cmax. The reviewer recalculated the PK parameters using the original values. The confidence interval for LCmax changed from 82.7 - 104.7% to 79.1 - 103.9% while the confidence intervals for AUCT and LAUCI did not change in the study.

2. The firm has not submitted SOP for repeat analysis.

Conclusion:
Fasting study on felodipine 2.5 mg is incomplete.

Table I : Formulation (Not to be released under FOI)

INGREDIENT	Felodipine ER mg /Tablet	Felodipine ER mg/Tablet	Felodipine ER mg /Tablet
Felodipine, USP	10.00	5.00	2.50
Polyethylene Glycol — NF			
Povidone,USP			
Hydroxypropyl Methylcellulose, USP			
Microcrystalline Cellulose, NF			
Silicon Dioxide, NF			
	[1]	[2]	[3]
Carnauba Wax			
TOTAL WEIGHT	457.02	457.02	457.02

[1] _____ consists of the following: hydroxypropyl methylcellulose, hydroxypropyl cellulose, titanium dioxide, polyethylene glycol, D&C yellow #10 lake, FD&C red no. 40 aluminum lake, FD&C blue no. 2 aluminum lake

[2] _____ consists of the following: hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, FD&C red no. 40 aluminum lake, polysorbate 80, D&C yellow no. 10 aluminum lake

[3] _____ consists of the following: hydroxypropyl methylcellulose, hydroxypropyl cellulose, titanium dioxide, polyethylene glycol, D&C yellow #10 lake, FD&C red no. 40 aluminum lake, FD&C blue no. 1 aluminum lake

_____ are used in manufacturing, but do not appear n the final product.

Test 2.5 mg tablet is round, light green, film-coated, unscored tablet debossed with MP 771
Reference 2.5 mg is sage green, round unscored convex tablets with code 450 on 1 side and PLENDIL on the other.
Test 5 mg tablet is round, light orange, film-coated, unscored tablet debossed with MP 772
Reference 5 mg is light red-brown, round unscored convex tablets with code 451 on 1 side and PLENDIL on the other.
Test 10 mg tablets are round, brown, film-coated, unscored tablet debossed with MP 773
Reference 10 mg is red-brown, round unscored convex tablets with code 452 on 1 side and PLENDIL on the other

Formulation Comments:

1. All inactive ingredients are within approved safety limits (FDA IIG, 1996).
2. The formulations of 2.5 mg and 5 mg strengths are proportionally similar to the 10 mg of the test product.

Table 17

In Vitro Dissolution Testing

Drug (Generic Name): Felodipine ER Tablets
Method : Mutual In-house

Dose Strength: 2.5mg, 5 mg & 10mg
Medium:
Volume:
Tolerance(Q):

No. Unit Tested: 12
Reference Drug: Plendil®
Assay Method:

Sampling Times (HOURS)	Ref. Product: Plendil® Tablets Lot Number: H4386 Strength: 10mg			Test Product: Felodipine ER Tablets Lot Number: BB 773 0042 Strength: 10mg		
	%Mean	Range	%RSD	%Mean	Range	%RSD
1 hour	11		4.9	12		7.1
2 hours	24		3.7	26		5.2
4 hours	52		2.8	57		3.3
6 hours	78		2.8	86		1.8
8 hours	96		2.2	99		1.3
9 hours	100		1.2	100		1.4
F_2 Comparison	68.5					
Sampling Times (HOURS)	Ref. Product: Plendil® Lot Number:H4497 Strength(mg):5mg			Test Product: Felodipine Lot Number:BB7720045 Strength(mg):5mg		
	%Mean	Range	%RSD	%Mean	Range	%RSD
1 hour	9		21.7	14		19.0
2 hours	21		19.6	27		16.0
4 hours	46		9.0	54		9.8
6 hours	71		7.2	79		9.3
8 hours	91		6.8	96		3.0
9 hours	99		3.3	101		1.4
F_2 Comparison	60.8					
Sampling Times (HOURS)	Ref. Product:Plendil® Lot Number:J5126 Strength(mg):2.5mg			Test Product: Felodipine Lot Number:BB7710046 Strength(mg): 2.5mg		
	%Mean	Range	%RSD	%Mean	Range	%RSD
1 hour	11		3.5	15		11.2
2 hours	24		3.5	29		6.2
4 hours	53		2.0	55		3.2
6 hours	78		2.1	80		6.2
8 hours	98		2.4	97		2.2
9 hours	103		1.1	100		0.9
F_2 Comparison	74					

F2 factor across different strengths		
	10 mg vs 5 mg	10 mg vs 2.5 mg
Test	72.0	73.6
Reference	66.6	86.9

Dissolution Comments

1. The test and reference products used in the dissolution testing and biostudies were from the same lots.

2. Currently, there is no USP Dissolution method for Felodipine ER tablets.

3. The firm used its in-house dissolution method and provided dissolution data only in one aqueous medium (←————————).

4. The dissolution testing should be conducted under the following conditions:

Apparatus:	Paddle at 50 and 75 rpm
Medium:	900 mL of aqueous media at various pH values (1-1.5, 4-4.5, 6-6.8 and 7-7.5)
Times:	1,2, and 4 hours, and every 2 hours thereafter, until 80% of the drug is released

In addition, the firm should generate dissolution profiles using 500 mL phosphate buffer pH 6.5 with 1% sodium lauryl sulphate and USP Apparatus II at a speed of 50 rpm.

Recommendations

I. The in vivo bioequivalence study conducted under fasting conditions by Mutual Pharmaceutical Co. on its Felodipine ER tablets, 10mg, lot # BB7730042, comparing it to the reference product, Plendil® ER tablets, 10mg, lot # H4386, manufactured by Merck, is unacceptable because 90% confidence interval for LCmax was outside of 80 – 125% limits.

II. The in vivo bioequivalence study conducted under non-fasting conditions by Mutual Pharmaceuticals on its Felodipine ER tablets, 10mg, lot # BB7730042, comparing it to the reference product, Plendil® ER tablets, 10mg, lot # H4386, manufactured by Merck, is acceptable.

III. The in vivo bioequivalence study conducted under steady state conditions by Mutual Pharmaceuticals on its Felodipine ER tablets, 10mg, lot # BB7730042, comparing it to the reference product, Plendil® ER tablets, 10mg, lot # H4386, manufactured by Merck, is acceptable.

IV. The in vivo bioequivalence study conducted under fasting conditions by Mutual Pharmaceuticals on its Felodipine ER tablets, 5 mg, lot # BB7720045, comparing it to the reference product, Plendil® ER tablets, 5 mg, lot # H4497, manufactured by Merck, is acceptable.

V. The in vivo bioequivalence study conducted under fasting conditions by Mutual Pharmaceuticals on its Felodipine ER tablets, 2.5 mg, lot # BB7710046, comparing it to the reference product, Plendil® ER tablets, 2.5 mg, lot # J5126, manufactured by Merck, is incomplete.

VI. The DBE requests that the dissolution testing should be conducted under the following conditions:

Apparatus:	Paddle at 50 and 75 rpm
Medium:	900 mL of aqueous media at various pH values (1-1.5, 4-4.5, 6-6.8 and 7-7.5)
Times:	1,2, and 4 hours, and every 2 hours thereafter, until 80% of the drug is released

In addition, the firm should generate dissolution profiles using 500 mL phosphate buffer pH 6.5 with 1% sodium lauryl sulphate and USP Apparatus II at a speed of 50 rpm.

VII. The firm should be informed of the recommendations and deficiencies.

3/14/2001

Patrick Nwakama, Pharm.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR

Date 3/14/2001

Concur:

Date 3/21/2001

for Dale P. Conner, Pharm.D,
Director,
Division of Bioequivalence

APPEARS THIS WAY
ON ORIGINAL

Table 2. Mean Plasma Concentrations (pg/mL) of FELODIPINE, n = 45
Treatment A = Felodipine Extended-Release, 10 mg tablet, Dose Administered = 1 x 10 mg, fasting
Treatment B = Plendil®, 10 mg tablet, Dose Administered = 1 x 10 mg, fasting

Time(hour)	Test Mean (A)	Test %CV (A)	Ref Mean (B)	Ref %CV (B)	T/R Mean (A)/(B)
0	0.	0.	0.	0.	**
0.5	69.59	106.21	127.88	111.17	0.544
1	419.53	59.44	742.	66.04	0.565
1.5	814.82	68.43	1555.83	56.26	0.524
2	1276.35	58.53	2116.42	54.47	0.603
2.5	1586.61	59.74	2238.81	53.35	0.709
3	1735.19	67.62	2312.91	54.79	0.75
3.5	1901.91	62.75	2349.11	54.46	0.81
4	1993.45	61.74	2398.6	54.19	0.831
4.5	2266.1	61.27	2660.02	55.0	0.852
5	2124.3	56.66	2306.77	58.39	0.921
5.5	1996.07	53.39	2093.87	58.54	0.953
6	1944.19	55.11	1933.97	57.05	1.005
7	1800.31	55.16	1742.3	59.77	1.033
8	1589.62	50.84	1506.36	58.88	1.055
10	1494.3	52.59	1287.85	44.23	1.16
16	807.68	48.32	700.06	40.6	1.154
24	558.34	51.41	435.69	45.17	1.281
36	385.21	49.24	300.09	51.21	1.284
48	217.11	59.14	160.41	56.	1.353
60	133.23	66.83	102.59	58.78	1.299
72	78.37	65.39	65.65	69.94	1.194

Table 3. FELODIPINE Arithmetic Mean Pharmacokinetic Parameters
Treatment A = Felodipine Extended-Release, 10 mg tablet, Dose Administered = 10 mg, fasting
Treatment B = Plendil®, 10 mg tablet, Dose Administered = 10 mg, fasting

Parameter	Test Mean (A)	Test %CV (A)	Ref Mean (B)	Ref %CV (B)	T/R Mean (A)/(B)
AUCT	40194.089	42.849	37553.622	40.794	1.07
AUCI	42762.636	42.057	39629.159	42.085	1.08
CMAX	2691.968	49.47	3009.718	51.414	0.89
TMAX	5.3	40.796	3.656	40.807	1.45
KEL	0.047	30.183	0.044	30.086	1.06
THALF	16.069	29.992	17.239	36.782	0.93

UNIT: AUC = pg.hr/mL CMAX = pg/mL TMAX = hr

Table 4. Summary Statistics for FELODIPINE
Treatment A = Felodipine Extended-Release, 10 mg tablet, Dose Administered = 10 mg, fasting
Treatment B = Plendil®, 10 mg tablet, Dose Administered = 10 mg, fasting
A vs B Least Squares Means

Parameter	A	B	Ratio	Lower 90% CI	Upper 90% CI
LAUCI	10.57	10.49	1.08	101.5	115.7
LAUCT	10.45	10.40	1.05	97.7	113
LCMAX	7.76	7.88	0.88	79.8	97.8

[same as firm's calculations]

Table 5. Mean Plasma Concentrations (pg/mL) of FELODIPINE, n= 17
Treatment A = Felodipine Extended-Release, 10 mg tablet, Dose Administered = 1 x 10 mg, fasting
Treatment B = Felodipine Extended-Release, 10 mg tablet, Dose Administered = 1 x 10 mg, fed
Treatment C = Plendil®, 10 mg tablet, Dose Administered = 1 x 10 mg, fed

Time(hour)	Test (B)(Fed) Mean (% CV)	Test (C) (Fed) Mean (% CV)	Test (A) Fast Mean (% CV)	T/R Ratio (B)/(C)	T/R Ratio (B)/(A)
0	0.	0.	0.	**	**
0.5	5.96 (254.1)	47.15(199.2)	30.08(108.7)	0.126	0.198
1	77.41(183.1)	503.77(169.5)	349.31(51.1)	0.154	0.222
1.5	357.72(201.8)	1168.2(125.4)	821.65(43.7)	0.306	0.435
2	898.19(149.3)	1901.1(117.4)	1713.48(59.9)	0.472	0.524
2.5	1565.69(92.4)	2184.98(90.7)	2145.56(61.2)	0.72	0.73
3	2625.33(76.5)	3478.9(71.4)	2426.97(54.1)	0.75	1.082
3.5	3766.42(55.3)	3982.41(53.7)	2716.61(57.5)	0.94	1.386
4	5837.73(64.1)	4568.46(61.1)	2697.47(50.6)	1.28	2.164
4.5	6727.34(68.1)	6249.56(65.3)	2968.52(52.9)	1.08	2.266
5	6816.98(76.4)	5857.54(77.1)	2710.53(48.3)	1.16	2.515
5.5	6141.29(85.8)	5561.38(73.4)	2454.94(42.2)	1.10	2.502
6	5243.41(82.2)	4540.28(83.5)	2355.81(40.5)	1.15	2.226
6.5	4052.23(74.6)	4249.95(90.9)	2070.49(39.1)	0.95	1.957
7	3587.36(63.3)	3698.73(90.8)	1929.83(39.8)	0.97	1.859
8	2737.62(64.2)	2983.91(76.8)	1839.87(42.7)	0.92	1.488
9	1980.27(62.9)	2263.89(74.6)	1566.8(46.1)	0.87	1.264
10	1461.21(59.2)	1695.15(75.7)	1474.73(51.0)	0.86	0.991
16	516.25(56.9)	555.89(59.8)	735.86(56.5)	0.93	0.702
24	292.0(65.6)	319.41(62.0)	473.84(63.3)	0.92	0.616
36	185.9(68.6)	212.59(67.1)	341.28(67.6)	0.87	0.545
48	105.52(70.7)	111.36(71.1)	170.83(57.5)	0.95	0.618
60	72.44(76.5)	75.19(75.1)	115.79(51.9)	0.96	0.626
72	49.06(73.5)	50.84(83.4)	74.79(61.4)	0.96	0.656

Table 6. FELODIPINE Arithmetic Mean Pharmacokinetic Parameters
Treatment A = Felodipine Extended-Release, 10 mg tablet, Dose Administered = 10 mg, fasting
Treatment B = Felodipine Extended-Release, 10 mg tablet, Dose Administered = 10 mg, fed
Treatment C = Plendil®, 10 mg tablet, Dose Administered = 10 mg, fed

Parameter	Test (B) Fed Mean (% CV)	Test (C) Fed Mean(% CV)	Test (A) Fast Mean(% CV)	T/R Ratio (B)/(C)	T/R Ratio (B)/(A)
AUCT	45742.5(53.5)	47736.4(53.9)	40584.9(42.8)	0.96	1.13
AUCI	48019.7(54.6)	49754.2(55.7)	42874.9(42.8)	0.96	1.12
CMAX	8117.0(66.1)	7247.4(59.9)	3304.5(48.4)	1.12	2.46
TMAX	4.69(31.6)	4.24(34.2)	4.27(29.7)	1.11	1.10
KEL	0.038(15.8)	0.04(25.9)	0.042(31.2)	0.95	0.91
THALF	18.89(17.5)	18.2(25.8)	18.68(39.0)	1.04	1.01

UNIT: AUC = pg.hr/mL CMAX = pg/mL TMAX = hr

Table 7. Summary Statistics for FELODIPINE
Treatment A = Felodipine Extended-Release, 10 mg tablet, Dose Administered = 10 mg, fasting
Treatment B = Felodipine Extended-Release, 10 mg tablet, Dose Administered = 10 mg, fed
Treatment C = Plendil®, 10 mg tablet, Dose Administered = 10 mg, fed

Least Squares Means [TRANSFORMED DATA]

Parameter	B	A	C	Ratio (B/A)	Ratio (B/C)
LAUCI	10.60	10.53	10.63	1.07	0.97
LAUCT	10.59	10.49	10.60	1.10	0.99
LCMAX	8.80	7.94	8.71	2.36	1.09

Table 8. Mean Plasma Concentrations (ng/mL) of FELODIPINE, n=39
Treatment A = Felodipine Extended-Release, 10 mg tablet, Dose Administered = 1 x 10 mg x 7 days, fasting
Treatment B = Plendil®, 10 mg tablet, Dose Administered = 10 mg, 1 x 10 mg x 7 days fasting

Time(hour)	Test Mean (A)	Test %CV (A)	Ref Mean (B)	Ref %CV (B)	T/R Ratio (A)/(B)
Day 1(0.00 h)	0.	0.	0.	0.	**
Day 5(0.00 h)	0.89	48.17	0.82	49.78	1.081
Day 6(0.00 h)	0.82	49.9	0.83	53.9	0.988
Day 7(0.00 h)	0.82	55.06	0.78	59.	1.05
0.50	0.89	51.51	0.93	56.96	0.961
1.00	1.24	46.41	1.68	60.48	0.734
1.50	1.6	46.29	2.32	56.91	0.69
2.00	2.08	50.88	2.82	58.75	0.738
2.50	2.56	53.55	3.3	63.98	0.775
3.00	2.72	52.32	3.46	65.19	0.786
3.50	2.94	51.68	3.47	61.88	0.847
4.00	3.04	55.62	3.42	60.75	0.889
4.50	3.21	58.87	3.57	67.57	0.898
5.00	3.38	55.74	3.62	60.85	0.934
5.50	3.09	44.97	3.23	55.91	0.956
6.00	2.96	45.25	3.10	56.15	0.99
6.50	2.77	47.45	2.76	53.03	1.004
7.00	2.56	48.03	2.55	52.68	1.007
8.00	2.3	46.21	2.19	43.11	1.048
9.00	2.09	52.79	2.01	45.7	1.037
10.0	2.01	50.37	1.85	49.07	1.085
16.0	1.35	55.01	1.3	73.31	1.042
24.0	0.84	42.17	0.88	70.22	0.951

Table 9. FELODIPINE Pharmacokinetic Parameters
Treatment A = Felodipine Extended-Release, 10 mg tablet, Dose Administered = 10 mg x 7 days, fasting
Treatment B = Plendil®, 10 mg tablet, Dose Administered = 10 mg x 7 days, fasting

A vs B Arithmetic Means

Parameter	A	B	Ratio
AUC(0-24 h)	42.6	44.13	0.96
TMAX	4.91	4.16	1.18
Cave	1.78	1.84	0.97
Cmax	3.74	4.22	0.89
Cmin	0.84	0.88	0.95
Degree of Fluctuation	162.03	181.84	0.89

UNIT: AUC = ng.hr/mL CMAX = ng/mL TMAX = hr

Table 10. Summary Statistics for FELODIPINE
Treatment A = Felodipine Extended-Release, 10 mg tablet, Dose Administered = 10 mg x 7 days, fasting
Treatment B = Plendil®, 10 mg tablet, Dose Administered = 10 mg x 7 days, fasting
A vs B Least Squares Means

Parameter	A	B	Ratio	Lower 90% CI	Upper 90% CI
LAUCT(0-24 h)	3.67	3.68	0.99	92	105
LCMAX	1.21	1.31	0.90	82	99
LCMIN	-0.26	-0.30	1.04	95	115
Lcave	1.6346	1.6605	0.98	92	105

Table 11. Mean Plasma Concentrations (pg/mL) of FELODIPINE, n = 39
Treatment A = Felodipine Extended-Release, 5 mg tablet, Dose Administered = 1 x 5 mg, fasting
Treatment B = Plendil®, 5 mg tablet, Dose Administered = 1 x 5 mg, fasting

TIME(HR)	TEST (A)		REFERENCE(B)		RATIO(A/B)%
0	0.00	(0.0)	0.00	(0.0)	N/A
0.5	61.58	(82.8)	112.09	(87.2)	0.549
1	285.74	(71.2)	469.98	(66.3)	0.608
1.5	457.38	(66.2)	798.46	(46.4)	0.573
2	688.55	(62.9)	1031.90	(44.0)	0.667
2.5	763.48	(60.3)	1019.28	(47.7)	0.749
3	825.47	(66.9)	987.27	(44.1)	0.836
3.5	856.25	(58.1)	940.16	(46.0)	0.911
4	881.95	(67.2)	982.13	(46.1)	0.898
4.5	1019.29	(66.1)	1176.18	(53.2)	0.867
5	960.00	(73.0)	1073.99	(53.6)	0.894
5.5	940.21	(75.6)	961.30	(49.7)	0.978
6	898.41	(71.7)	920.72	(53.4)	0.976
6.5	854.35	(71.1)	849.59	(55.4)	1.006
7	873.59	(74.9)	795.13	(51.7)	1.099
8	811.31	(60.7)	694.06	(53.8)	1.169
9	787.10	(60.8)	660.48	(54.9)	1.192
10	760.93	(49.7)	683.51	(54.8)	1.113
16	430.13	(39.5)	438.93	(67.0)	0.980
24	262.58	(55.2)	264.61	(66.5)	0.992
36	198.13	(64.2)	182.51	(59.2)	1.086
48	101.32	(70.5)	86.70	(63.3)	1.169
60	59.44	(70.5)	53.73	(68.8)	1.106
72	35.23	(84.4)	32.12	(81.0)	1.097

Table 12. FELODIPINE Arithmetic Mean Pharmacokinetic Parameters (n = 39)
Treatment A = Felodipine ER, 5 mg tablet, Dose Administered = 5 mg, fasting
Treatment B = Plendil®, 5 mg tablet, Dose Administered = 5 mg, fasting

Parameter	Test Mean (A)	Test %CV (A)	Ref Mean (B)	Ref %CV (B)	T/R Ratio (A)/(B)
AUCT	19796.0	42.83	19772.0	40.794	1.00
AUCI	20796.0	43.56	20697.0	42.085	1.01
CMAX	1282.1	56.57	1385.2	51.414	0.93
TMAX	5.71	48.5	4.436	40.807	1.29
KEL	0.047	33.2	0.0465	30.086	1.01
THALF	16.48	35.3	16.41	32.0	1.00

UNIT: AUC = pg.hr/mL CMAX = pg/mL TMAX = hr

Table 13. Summary Statistics for FELODIPINE
Treatment A = Felodipine ER, 5 mg tablet, Dose Administered = 5 mg, Fasting
Treatment B = Plendil ®, 5 mg tablet, Dose Administered = 5 mg, fasting

Parameter	A	B	Ratio	Lower 90% CI	Upper 90% CI
LAUCI	9.86	9.84	1.02	91.4	114.1
LAUCT	9.81	9.79	1.02	91.2	113.7
LCMAX	7.04	7.16	0.88	81.2	97.4

Table 14. Mean Plasma Concentrations (pg/mL) of FELODIPINE, n = 40
Treatment A = Felodipine Extended-Release, 2.5 mg tablet, Dose Administered = 2 x 2.5 mg, fasting
Treatment B = Plendil®, 2.5 mg tablet, Dose Administered = 2 x 2.5 mg, fasting

TIME (HR)	TEST TREATMENT A		REFERENCE TREATMENT B		RATIO (A/B)%
0	0.00	(0.0)	0.00	(0.0)	N/A
0.5	63.99	(80.0)	116.77	(96.2)	0.548
1	331.48	(70.5)	566.41	(74.7)	0.585
1.5	563.31	(59.9)	908.76	(72.0)	0.620
2	724.25	(56.4)	1069.94	(71.0)	0.677
2.5	836.00	(62.6)	1070.05	(66.8)	0.781
3	849.87	(57.6)	1065.10	(65.2)	0.798
3.5	869.37	(53.5)	1036.64	(59.9)	0.839
4	845.68	(54.8)	1003.89	(55.9)	0.842
4.5	1014.14	(59.0)	1141.48	(61.0)	0.888
5	994.32	(59.5)	1017.20	(55.9)	0.978
5.5	997.20	(63.1)	1003.24	(55.5)	0.994
6	921.67	(54.9)	940.69	(60.1)	0.898
6.5	847.16	(49.5)	920.52	(62.0)	0.920
7	807.89	(50.5)	874.22	(57.1)	92.4
8	725.34	(53.5)	724.02	(59.8)	1.002
9	656.22	(52.6)	651.40	(57.8)	1.007
10	675.28	(44.9)	638.44	(61.4)	1.058
11	611.19	(45.4)	544.77	(55.8)	1.122
16	400.79	(49.6)	336.88	(60.3)	1.190
24	239.70	(57.7)	212.76	(78.3)	1.127
36	174.03	(62.9)	156.08	(74.3)	1.115
48	93.33	(73.9)	87.20	(105.5)	1.070
60	57.76	(83.4)	55.94	(104.0)	103.3
72	35.46	(85.8)	34.41	(113.3)	1.031

Table 15. FELODIPINE Arithmetic Mean Pharmacokinetic Parameters (n = 40)
Treatment A = Felodipine ER, 2.5mg tablet, Dose Administered = 2 x 2.5 mg, fasting
Treatment B = Plendil®, 2.5 mg tablet, Dose Administered = 2 x 2.5 mg, fasting

PK PARAMETER	N	TEST TREATMENT A		N	REFERENCE TREATMENT B		RATIO (A/B)%
AUCT [pg•hr/mL]	40	18525.1	(45.2)	40	18342.3	(58.7)	1.01
AUCI [pg•hr/mL]	40	19530.6	(46.0)	40	19427.0	(60.5)	1.00
CMAX [pg/mL]	40	1249.77	(48.7)	40	1399.62	(60.2)	0.89
TMAX [hr]	40	5.063	(42.5)	40	3.813	(45.2)	1.33
KEL [1/hr]	40	0.04224	(27.7)	40	0.04099	(36.8)	1.03
THALF [hr]	40	18.034	(37.2)	40	19.375	(38.6)	0.93

UNIT: AUC = pg.hr/mL CMAX = pg/mL TMAX = hr

Table 16. Summary Statistics for FELODIPINE
Treatment A = Felodipine ER, 2.5 mg tablet, Dose Administered = 2 x 2.5 mg, Fasting
Treatment B = Plendil ®, 2.5 mg tablet, Dose Administered = 2 x 2.5 mg, fasting

A vs B Least Squares Means

Parameter	A	B	Ratio	Lower 90% CI	Upper 90% CI
LAUCI	9.80	9.77	1.03	94.5	111.2
LAUCT	9.74	9.72	1.02	94.5	110.8
LCMAX	7.04	7.14	0.90	79.1	103.9

(Firm's calculated LCmax : 82.7 – 104.7%)

CC: ANDA 75-896
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File 3/14/2001
HFD-655/ P.Nwakama

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Printed in final on //

Endorsements: (Final with Dates)
HFD-655/ PNwakama 3/14/2001
HFD-655/ Nerurkar 3/14/01
HFD-650/ D. Conner for Rose 3/21/2001

BIOEQUIVALENCY - INCOMPLETE Submission date: June 6, 2000
~~June 21, 2000~~ (KS) 3/27/01
August 14, 2000
August 29, 2000
March 7, 2001

1. **FASTING STUDY** (STF) (6/6/00)
Clinical:
Analytical: [ ]
Strengths: 10 mg
Outcome: UN

2. **FOOD STUDY** (STP) (6/6/00)
Clinical:
Analytical: [ ]
Strength: 10 mg
Outcome: AC

3. **MULTIPLE DOSE STUDY (STM)** (6/6/00)
Clinical:
Analytical: [ ]
Strength: 10 mg
Outcome: AC

4. **FASTING STUDY (STF)** (8/29/00)
Clinical:
Analytical: [ ]
Strengths: 5 mg
Outcome: AC

5. **STUDY AMENDMENT (STA)**
(8/14/2000)
Strengths: 5 mg
Outcome: AC

6. **FASTING STUDY (STF)** (8/29/00)
Clinical:
Analytical: [ ]
Strengths: 2.5 mg
Outcome: IC

7. **STUDY AMENDMENT (STA)**
(3/7/2001) (MULTI-DOSE STUDY)
Strengths: 10 mg
Outcome: AC

Outcome Decisions: **IC** - INCOMPLETE **AC** - ACCEPTABLE
UC - UNACCEPTABLE

FIGURE 1

FELODIPINE PLASMA CONCENTRATIONS (PG/ML) VERSUS TIME
SINGLE-DOSE FASTING STUDY #991004

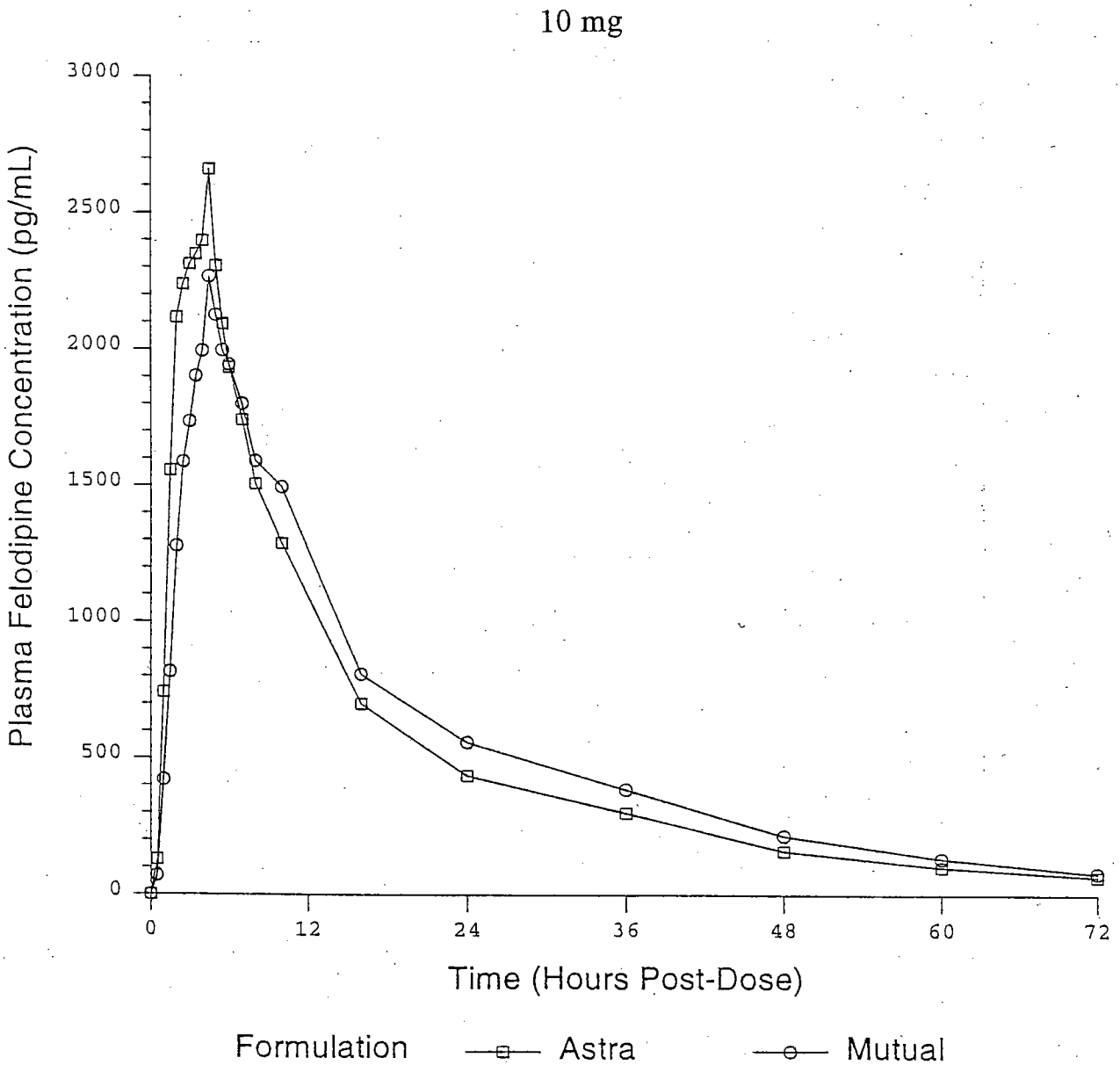


FIGURE 2

FELODIPINE PLASMA CONCENTRATIONS (PG/ML) VERSUS TIME
FED/FASTING SINGLE-DOSE STUDY #991005
(LINEAR PLOT)

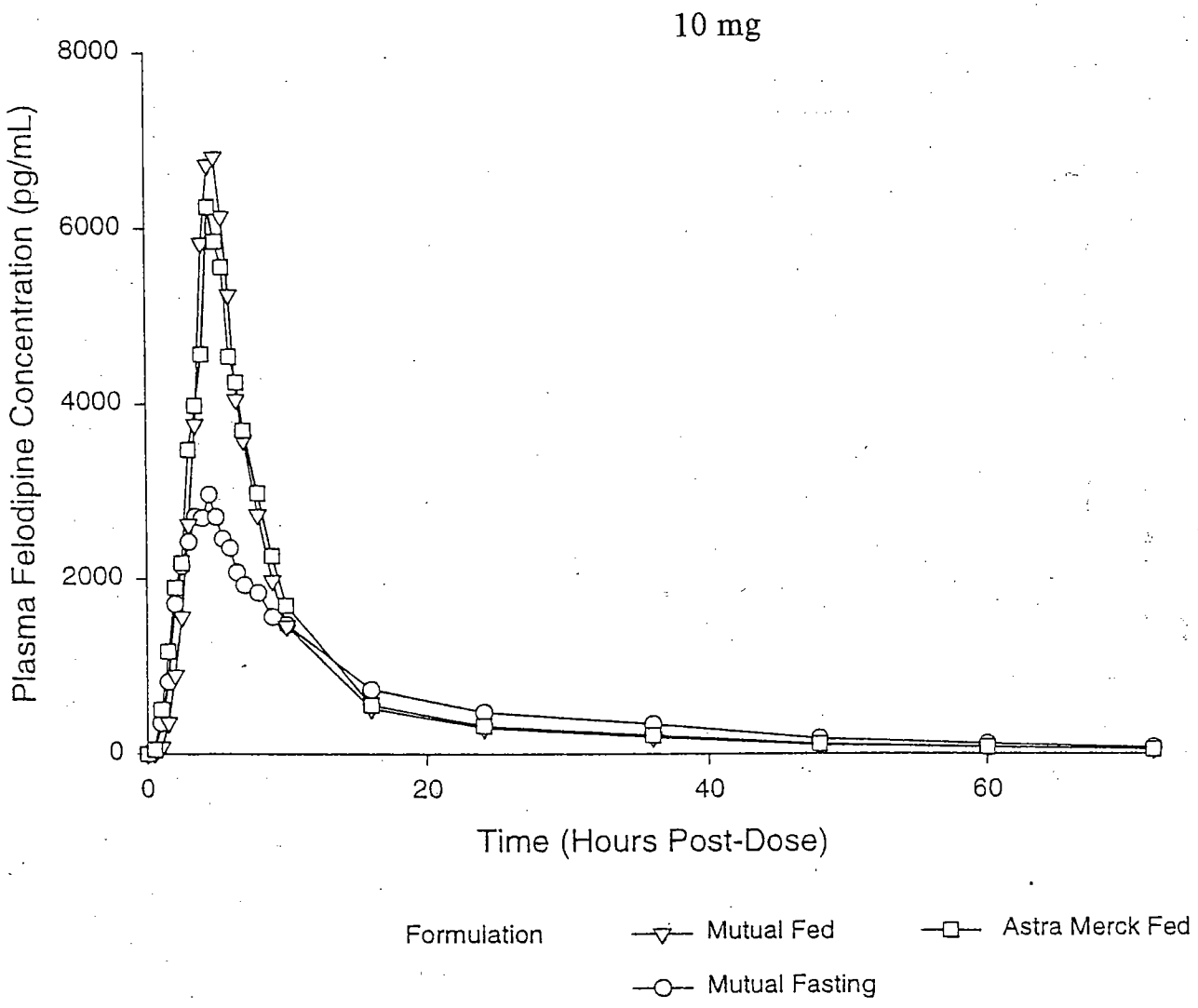


FIGURE 3
FELODIPINE PLASMA CONCENTRATIONS (NG/ML) VERSUS TIME
MULTIPLE-DOSE FASTING STUDY #2338

10 mg

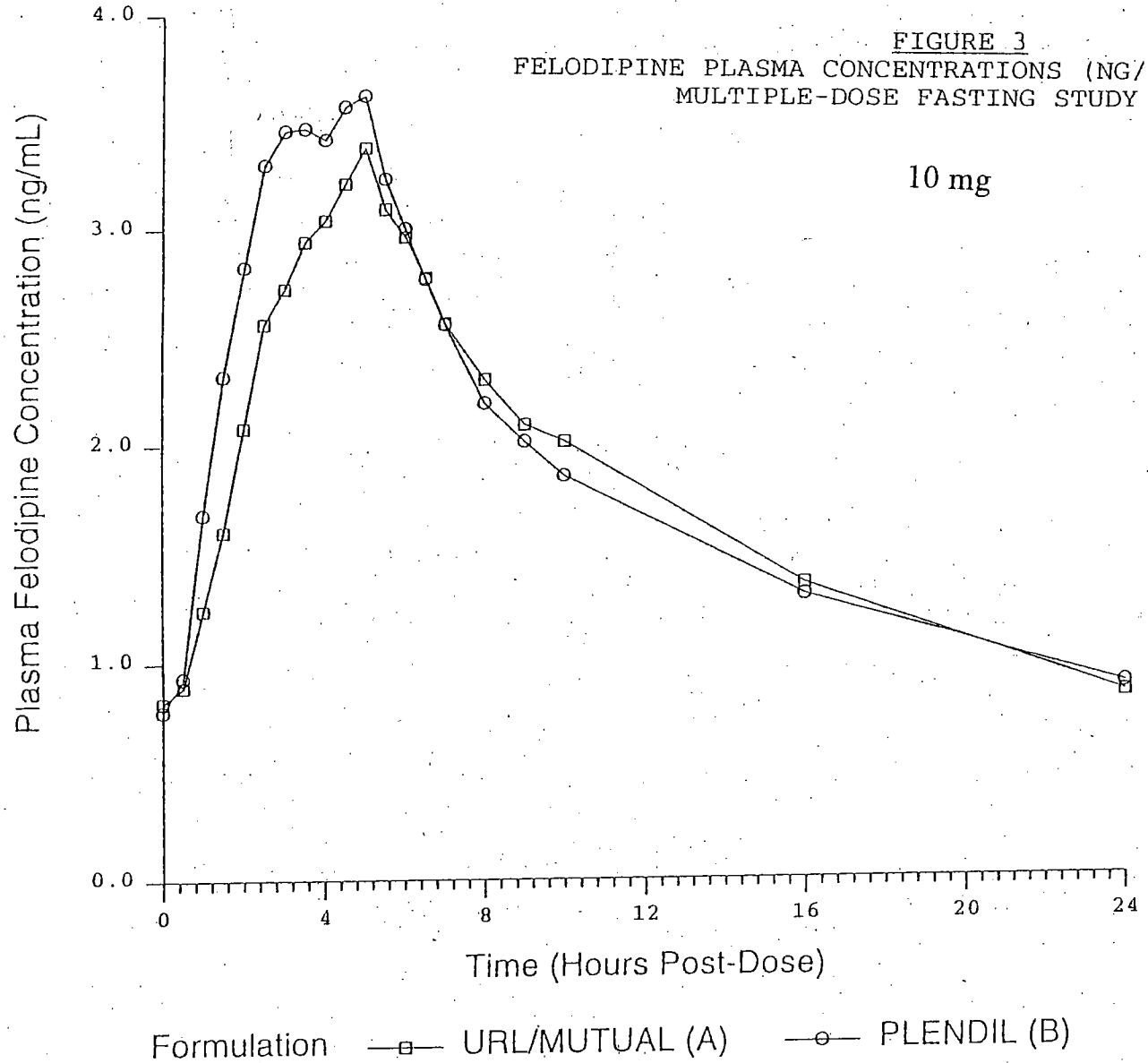


FIGURE 4
FELODIPINE PLASMA CONCENTRATIONS (PG/ML) VERSUS TIME
SINGLE-DOSE FASTING STUDY #991007
(LINEAR PLOT)

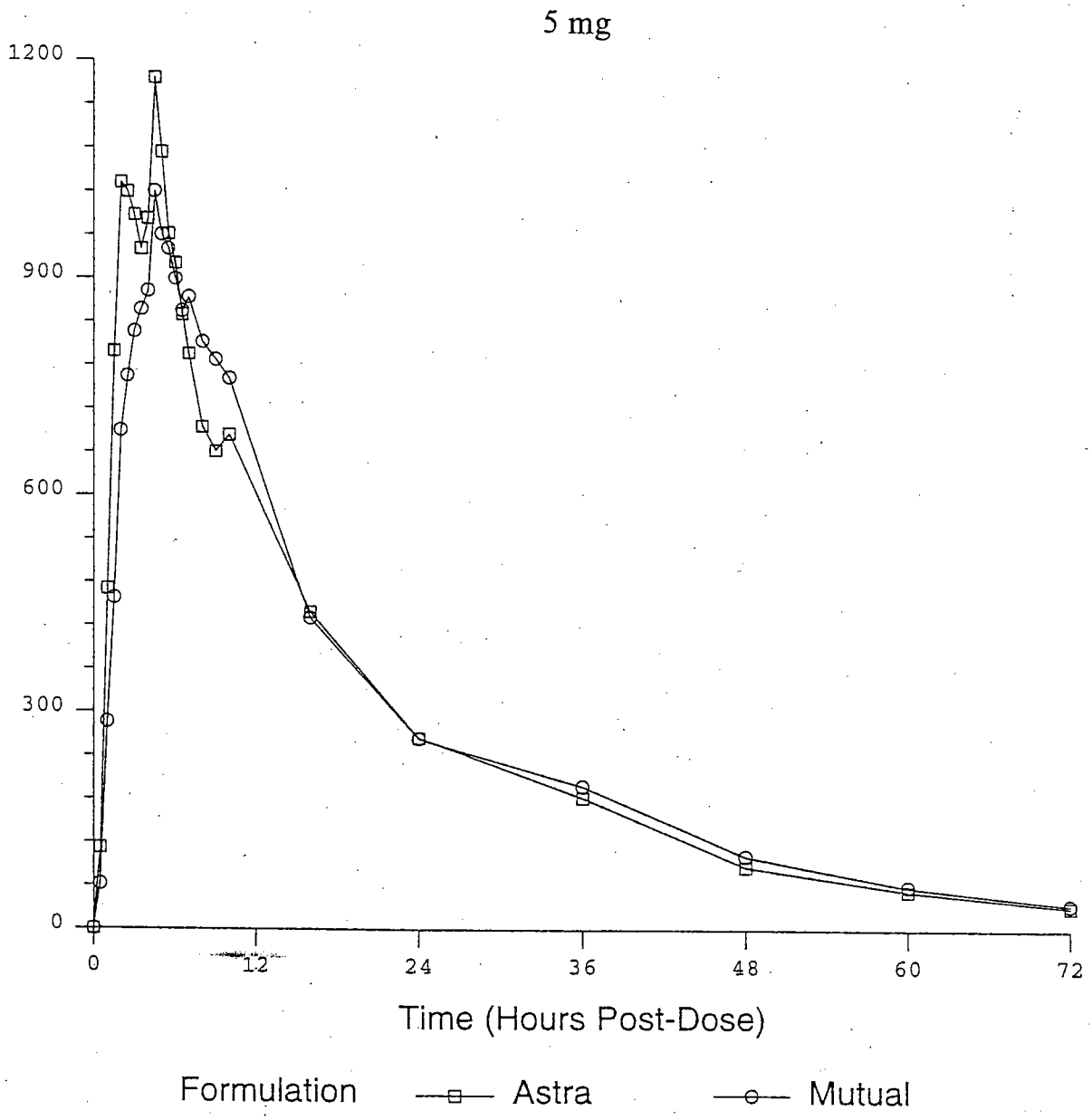
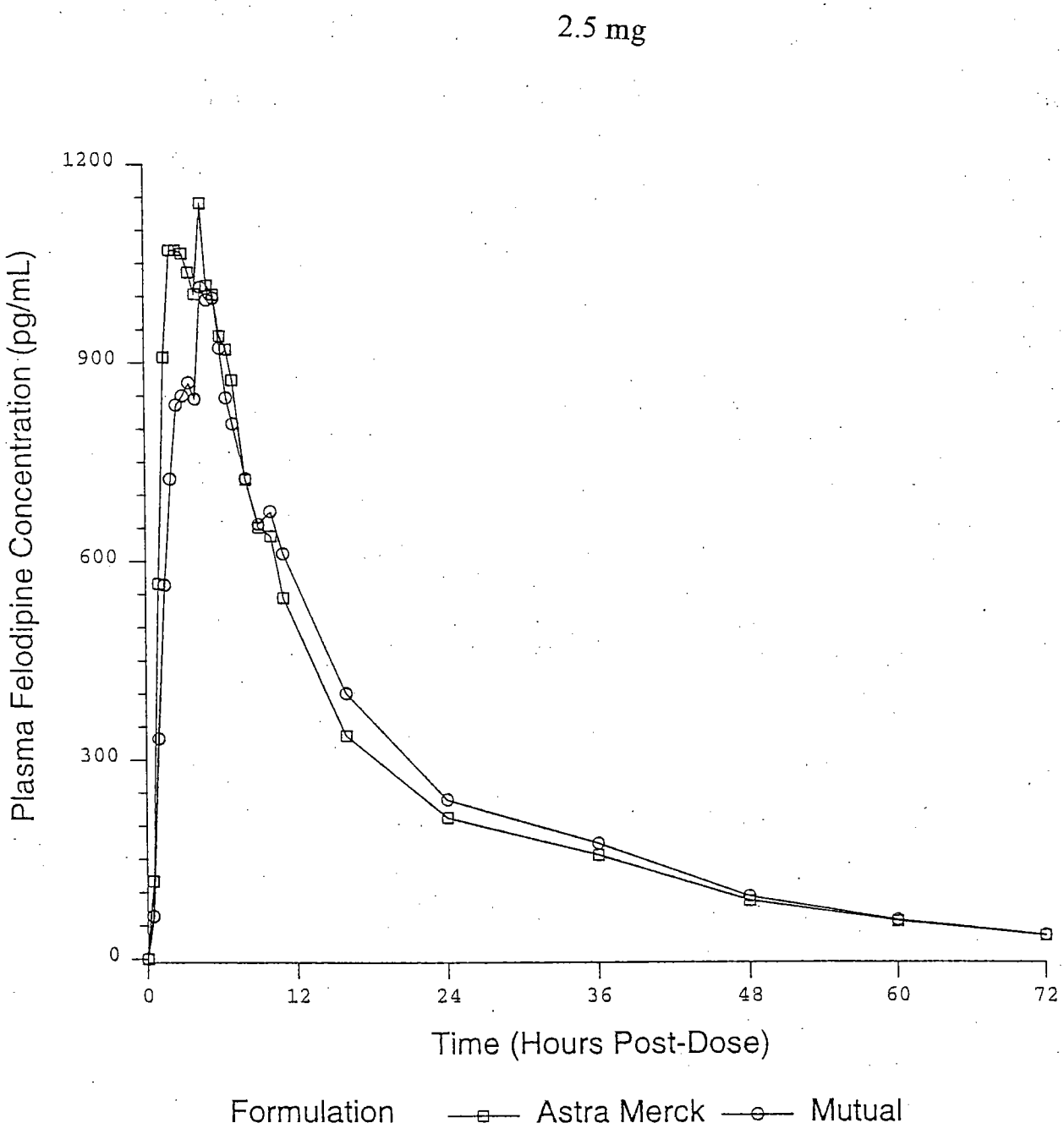


FIGURE 5

PLASMA FELODIPINE CONCENTRATIONS (PG/ML) VERSUS TIME
SINGLE-DOSE FASTING STUDY #991008



BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 75-896 APPLICANT: Mutual Pharmaceuticals

DRUG PRODUCT: Felodipine ER Tablets, 2.5 mg, 5 mg and 10 mg

The Division of Bioequivalence (DBE) has completed its review and has the following deficiencies have been identified:

1. The fasting study on 10 mg is not acceptable since the 90% confidence intervals for LCmax are outside the acceptable limits of 80 - 125% and the long-term stability data does not cover the duration of the study.

2. You have repeat assays. Please submit all relevant SOPs for anomalous values/pharmacokinetic repeats since assays cannot be repeated unless mentioned in the SOPs.

3. If the original assay values are used instead of the repeat assay values for anomalous/pharmacokinetic repeats, the 90% confidence intervals for LCmax in the fasting study on 2.5 mg would be outside the acceptable limits of 80 - 125%.

4. The DBE requests that the dissolution testing should be conducted under the following conditions:

Apparatus:	Paddle at 50 and 75 rpm
Medium:	900 mL of aqueous media at various pH values (1-1.5, 4-4.5, 6-6.8 and 7-7.5)
Times:	1,2, and 4 hours, and every 2 hours thereafter, until 80% of the drug is released

In addition, you should generate dissolution profiles using 500 mL phosphate buffer pH 6.5 with 1% sodium lauryl sulphate and USP Apparatus II at a speed of 50 rpm.

5. For future studies, please dose with 240 mL water.

Sincerely yours,

for Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

A8.1

Felodipine ER Tablets
2.5, 5, & 10 mg
ANDA #: 75896/AB
Reviewer: Patrick Nwakama
File Name: 75896A.0301

Mutual Pharmaceutical Company
1100 Orthodox Street
Philadelphia, PA 19124
Submission Date:
April 30, 2001 (Amendment)
June 25, 2001 (Amendment)

Review Of A Study Amendment

History of ANDA (#75-896) Submissions:

1. June 6, 2000 - Mutual submitted an original ANDA (#75-896) for its Felodipine ER 10 mg tablets which included three bioequivalence (Fasting, Non-Fasting and Multiple-Dose) studies. The non-fasting and multiple-dose studies were found acceptable while the fasting study was found unacceptable by the Division of Bioequivalence (DBE).

2. July 21, 2000 - The firm submitted a fasting bioequivalence study on its Felodipine ER 5 mg tablets which was found acceptable by the DBE.

3. August 14, 2000 - Following the OGD request to file all strengths of its Felodipine ER tablets under one ANDA (#75-896), the firm withdrew ANDA # 75931 for Felodipine ER 5 mg tablets and re-filed it under ANDA # 75-896.

4. August 29, 2000 - The firm submitted a fasting bioequivalence study on its 2.5 mg tablets which was found incomplete by the DBE.

5. March 23, 2001 - The OGD sent a deficiency letter containing the following DBE's deficiency comments

Deficiency #1:

The fasting study on 10 mg is not acceptable since the 90% confidence intervals for Lcmax are outside the acceptable limits of 80 – 125% and the long-term stability data does not cover the duration of the study.

FIRM'S RESPONSE

Mutual's original ANDA 75-896 on Felodipine ER was submitted in June 2000 before the final version of BA/BE guidance was issued October 2000. According to the firm, OGD permitted the rounding of CI values to meet the specified limits of 80 – 125%, provided that the study data were 79.5 or greater or 125.4% or less. The firm claims to know of at least one ANDA approved with rounded results submitted during the period between the draft and final versions of the BA/BE guidance. The firm also included its record of a

telephone conversation (4:30 pm; 3/24/2000) with Jennifer Fan, DBE's Project Manager, during which Ms. Fan informed the firm that 79.8 was currently rounded to 80.

The firm has submitted an analytical report amendment containing data that extends the long-term stability to 107 days which now exceeds the duration of study of 67 days.

REVIEWER'S COMMENT

The firm's response is acceptable.

Deficiency #2:

You have repeat assays. Please submit all relevant SOPs for anomalous values /PK repeats since assays cannot be repeated unless mentioned in the SOPs.

FIRM'S RESPONSE:

Repeat assays were performed by the Bioanalytical Department of ———— according to SOP AL-G-1520-09.A01 (attached). The PK department also requested additional repeat assays for anomalous values observed after visual inspection of the concentration-time profiles. Samples are reassayed in duplicate and the final result used in PK and statistical analyses is determined based on SOP AL-G-1520-09.AO1. A total of three repeat assays were requested by the PK Department for studies 991004 (10 mg fasted), 991005 (10 mg fed) and 991007 (5 mg fasted). No SOP was in place in the PK Department at the time the felodipine reports were finalized, however, one is currently under development.

REVIEWER'S COMMENT:

The firm has provided a copy of SOP# AL-G-1420-09.A01. This SOP was mentioned but not included in the original submission. The reviewer verified that all anomalous / PK repeats were handled according to the SOP. Therefore, the firm's response is acceptable.

Deficiency #3:

If the original assay values are used instead of the repeat assay values for anomalous values / PK repeats, the 90% confidence intervals for LCmax in the fasting study on 2.5 mg would be outside the acceptable limits of 80 – 125%.

FIRM'S RESPONSE:

All repeats for the 2.5 mg fasting study were analytical repeats determined by SOP-AL-G-1520-09.A01. There were no PK repeats.

REVIEWER'S COMMENT:

The analytical lab ——— followed a written SOP (AL-G-1420-09.A01), in handling all anomalous values in the 2.5 mg Fasting study as verified by the reviewer. Per the SOP, the median of the original and duplicates was reported as the final value. Using the final values reported by the firm, the reviewer verified that 90% confidence intervals for LCmax in the fasting study on 2.5 mg were within the acceptable limits of 80 – 125%. Therefore, the firm's response is acceptable.

Deficiency #4:

The DBE requests that the dissolution testing should be conducted under the following conditions:

Apparatus: Paddle at 50 and 75 rpm
Meduim: 900 mL of aqueous media at various pH values (1-1.5, 4-4.5, 6-6.8, and 7-7.5)
Times: 1,2 and 4 hours, and every 2 hours thereafter, until 80% of the drug is released.

In addition, you should generate dissolution profiles using 500 mL phosphate buffer pH 6.5 with 1% sodium lauryl sulphate and USP Apparatus II at a speed of rpm.

FIRM'S RESPONSE:

April 30, 2001(Amendment):
The firm is in the process of performing the dissolution testing as requested and will submit the results by June 2001.

June 25, 2001(Amendment):

The firm repeated the dissolution testing following to the DBE's recommendations but the dissolution results showed both the test and reference drug products to have little or no dissolution in all suggested media. The firm requested a teleconference meeting with the Division on how to proceed.

REVIEWER'S COMMENT:

Upon consultation with Dr. Tran, the reviewer did not see a need for a teleconference meeting with the firm and the dissolution data generated using Mutual's in-house dissolution method [———————————————————] are now acceptable. However, the specifications proposed by the firm are not acceptable. According to the CDER guidance for Industry – Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations" (Issued September 1997, Part VII B. 1), *"The recommended range at any dissolution time point specification is ± 10% deviation from the mean dissolution profile obtained from the*

clinical/bioavailability lots. In certain cases, reasonable deviations from the ± 10% range can be accepted provided that the range at any time point does not exceed 25%." Also, *"Specifications should be established based on average dissolution data for each lot under study,* ***equivalent to USP Stage 2 testing****. Specifications allow that all lots to pass at Stage 1 of testing may result in lots with less than optimal in vivo performance passing these specifications at USP Stage 2 or Stage 3."*

The firm's proposed specification ranges are greater than 25%. Based on the dissolution results submitted for the test product, and in agreement with the Guidance's procedure, the following interim specifications are recommended:

Sampling Time(hour)	% Dissolved
1 hour	[ ]
4 hours	
8 hours	

Deficiency #5:

For future studies, please dose with 240 mL water.

FIRM'S RESPONSE:

The firm acknowledged the request that for future studies, 240 mL of water should be used for dosing.

REVIEWER'S COMMENT:

The firm's response is acceptable.

RECOMMENDATIONS:

I. The in vivo bioequivalence study conducted under fasting conditions by Mutual Pharmaceutical Co. on its Felodipine ER tablets, 10mg, lot # BB7730042, comparing it to the reference product, Plendil® ER tablets, 10mg, lot # H4386, manufactured by Merck, is acceptable.

II. The in vivo bioequivalence study conducted under non-fasting conditions by Mutual Pharmaceuticals on its Felodipine ER tablets, 10mg, lot # BB7730042, comparing it to the reference product, Plendil® ER tablets, 10mg, lot # H4386, manufactured by Merck, is acceptable.

III. The in vivo bioequivalence study conducted under steady state conditions by Mutual Pharmaceuticals on its Felodipine ER tablets, 10mg, lot # BB7730042, comparing it to the reference product, Plendil® ER tablets, 10mg, lot # H4386, manufactured by Merck, is acceptable.

IV. The in vivo bioequivalence study conducted under fasting conditions by Mutual Pharmaceuticals on its Felodipine ER tablets, 5 mg, lot # BB7720045, comparing it to the reference product, Plendil® ER tablets, 5 mg, lot # H4497, manufactured by Merck, is acceptable.

V. The in vivo bioequivalence study conducted under fasting conditions by Mutual Pharmaceuticals on its Felodipine ER tablets, 2.5 mg, lot # BB7710046, comparing it to the reference product, Plendil® ER tablets, 2.5 mg, lot # J5126, manufactured by Merck, is acceptable.

VI. The in vitro dissolution testing conducted by Mutual Pharmaceuticals on its Felodipine ER tablets, 2.5 mg, 5 mg and 10 mg has been found acceptable.

The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in —

—.

The test product should meet the following interim specifications:

Sampling Time(hour)	% Dissolved
1 hour	[ ]
4 hours	
8 hours	

8/1/2001

Patrick Nwakama, Pharm.D.
Review Branch III
Division of Bioequivalence

RD INITIALED B. DAVIT BMD
FT INITIALED B. DAVIT Barbara M Davit Date 8.10.

Concur: Dale P. Conner Date 8/21/01
Dale P. Conner, Pharm.D,
Director,
Division of Bioequivalence

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-896 APPLICANT: Mutual Pharmaceuticals

DRUG PRODUCT: Felodipine ER Tablets, 2.5 mg, 5 mg and 10 mg

The Division of Bioequivalence (DBE) has completed its review and has no further questions at this time.

The Division of Bioequivalence acknowledges that the following dissolution testing is being incorporated into your stability and quality control programs:

The dissolution testing is conducted in [redacted].

However, it should be noted that the specifications proposed by you are not considered acceptable. According to the CDER guidance for Industry - Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations (issued September 1997, Part VII B. 1), *"The recommended range at any dissolution time point specification is ± 10% deviation from the mean dissolution profile obtained from the clinical /bioavailability lots. In certain cases, reasonable deviations from the ± 10% range can be accepted provided that the range at any time point does not exceed 25%."* Also, *"Specifications should be established based on average dissolution data for each lot under study, equivalent to USP Stage 2 testing. Specifications that allow all lots to pass at Stage 1 of testing may result in lots with less than optimal in vivo performance passing these specifications at USP Stage 2 or Stage 3."*

Your proposed specification ranges are greater than 25%. Based on the dissolution results submitted for the test product, and in agreement with the Guidance's procedure, the following interim specifications are recommended:

Sampling Time(hour)	% Dissolved
1 hour	[redacted]
4 hours	
8 hours	

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to

revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 75-896
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ P.Nwakama

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Endorsements: (Final with Dates)
HFD-658/ PNwakama 8/1/2001
HFD-658/ B.Davit 8.1.01
HFD-650/ SMazzella
HFD-650/ D. Conner 8/21/01

BIOEQUIVALENCY - ACCEPTABLE Submission date: April 30, 2001
June 25, 2001

OK 1. **STUDY AMENDMENT** (STA) Strengths: 2.5, 5, 10 mg
(4/30/2001) **Outcome: IC**

OK 2. **STUDY AMENDMENT** (STA) Strengths: 2.5, 5, 10 mg
(6/25/2001) **Outcome: AC**

Outcome Decisions: **AC** - ACCEPTABLE

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75-896 SPONSOR : Mutual Pharmaceuticals

DRUG AND DOSAGE FORM : Felodipine Extended-Release

STRENGTH(S) : 2.5 mg, 5 mg and 10 mg Tablets

TYPES OF STUDIES : Fasting, Non-Fasting & Multiple dose Studies

CLINICAL STUDY SITE : _____ (Fasting and Non-Fasting Studies)
_____ (Multiple-dose Study)

ANALYTICAL SITE : _____ (Fasting and Non-Fasting Studies)
_____ (Multiple-dose Study)

STUDY SUMMARY : Confidence Intervals in Fasting and Multi-dose Studies; and T/R ratios in the Non-Fasting study are within acceptable limits.

DISSOLUTION : Dissolution was conducted according to Firm's own method.

DSI INSPECTION STATUS

Inspection needed: Yes	Inspection status:	Inspection results:
First Generic Yes New facility ____ For cause ____ other ____	Inspection requested: Inspection completed: (date)	

PRIMARY REVIEWER: Patrick E. Nwakama, Pharm.D. BRANCH : III

INITIAL : PEN DATE : 8/1/2001

TEAM LEADER : Barbara Davit, Ph.D. BRANCH : III

INITIAL : BMD DATE : 8/1/01

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : DPC DATE : 8/21/01

A10.1

Bita

Felodipine ER Tablets
2.5, 5, & 10 mg
ANDA #: 75896
Reviewer: Patrick Nwakama
File Name: 75896A.1101

Mutual Pharmaceutical Company
1100 Orthodox Street
Philadelphia, PA 19124
Submission Date:
November 28, 2001

Review Of A Study Amendment

History of ANDA (#75-896) Submissions:

1. June 6, 2000 - Mutual submitted an original ANDA (#75-896) for its Felodipine ER 10 mg tablets which included three bioequivalence (Fasting, Non-Fasting and Multiple-Dose) studies. The non-fasting and multiple-dose studies were found acceptable while the fasting study was found unacceptable by the Division of Bioequivalence (DBE).

2. July 21, 2000 - The firm submitted a fasting bioequivalence study on its Felodipine ER 5 mg tablets which was found acceptable by the DBE.

3. August 14, 2000 - Following the OGD request to file all strengths of its Felodipine ER tablets under one ANDA (#75-896), the firm withdrew ANDA # 75931 for Felodipine ER 5 mg tablets and re-filed it under ANDA # 75-896.

4. August 29, 2000 - The firm submitted a fasting bioequivalence study on its 2.5 mg tablets which was found incomplete by the DBE.

5. March 23, 2001 - The OGD sent a deficiency letter containing the following DBE's deficiency comments.

6. April 30, 2001 - The firm responded satisfactorily to the cited deficiencies and informed the DBE that it is in the process of completing dissolution testing according to FDA-recommended method.

7. June 25, 2001 – The firm submitted its new dissolution testing results. The DBE found the dissolution testing acceptable but recommended different dissolution specifications. This was communicated to the firm as a deficiency by Chemistry.

Chemistry Deficiency:
The DBE has recommended the following specifications for the dissolution testing: —

— . The test product should meet the following specifications:

Sampling Time(hour)	% Dissolved
1 hour	[ ]
4 hours	
8 hours	

Please incorporate your requested dissolution specifications, as well as the comments provided by the Division of Bioequivalence (DBE) and we respectfully request a minor revision.

FIRM'S RESPONSE

The firm accepted the dissolution testing method specified by DBE but is requesting a slight modification of the dissolution specifications following a thorough review of its accumulated dissolution (release and stability) data.

Sampling Time(hour)	% Dissolved
1 hour	
4 hours	[ ]
8 hours	

The firm believes that a change in 4-hour dissolution specification from ——— % to ——— % is still in line with DBE's requirement of ≤ 25% range and would be more consistent with the quality properties of its drug product.

REVIEWER'S COMMENT

The firm's response is acceptable. The dissolution data from fresh biobatches (BB7730042, BB7720045, BB7710046) support the firm's proposed 4-hour specifications.

RECOMMENDATIONS:

I. The in vivo bioequivalence study conducted under fasting conditions by Mutual Pharmaceutical Co. on its Felodipine ER tablets, 10mg, lot # BB7730042, comparing it to the reference product, Plendil® ER tablets, 10mg, lot # H4386, manufactured by Merck, is acceptable.

II. The in vivo bioequivalence study conducted under non-fasting conditions by Mutual Pharmaceuticals on its Felodipine ER tablets, 10mg, lot # BB7730042, comparing it to the reference product, Plendil® ER tablets, 10mg, lot # H4386, manufactured by Merck, is acceptable.

III. The in vivo bioequivalence study conducted under steady state conditions by Mutual Pharmaceuticals on its Felodipine ER tablets, 10mg, lot # BB7730042, comparing it to the reference product, Plendil® ER tablets, 10mg, lot # H4386, manufactured by Merck, is acceptable.

IV. The in vivo bioequivalence study conducted under fasting conditions by Mutual Pharmaceuticals on its Felodipine ER tablets, 5 mg, lot # BB7720045, comparing it to the reference product, Plendil® ER tablets, 5 mg, lot # H4497, manufactured by Merck, is acceptable.

V. The in vivo bioequivalence study conducted under fasting conditions by Mutual Pharmaceuticals on its Felodipine ER tablets, 2.5 mg, lot # BB7710046, comparing it to the reference product, Plendil® ER tablets, 2.5 mg, lot # J5126, manufactured by Merck, is acceptable.

VI. The in vitro dissolution testing conducted by Mutual Pharmaceuticals on its Felodipine ER tablets, 2.5 mg, 5 mg and 10 mg has been found acceptable.

The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in ——— ———. The test product should meet the following interim specifications:

Sampling Time(hour)	% Dissolved
1 hour	[ ]
4 hours	
8 hours	

12/17/2001

Patrick Nwakama, Pharm.D.
Review Branch III
Division of Bioequivalence

6m 12/17/01

RD INITIALED B. DAVIT
FT INITIALED B. DAVIT Barbara M Davit Date 12/17/01

Concur: N Saluja Date 12/31/2001

for Dale P. Conner, Pharm.D,
Director,
Division of Bioequivalence

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-896 APPLICANT: Mutual Pharmaceuticals

DRUG PRODUCT: Felodipine ER Tablets, 2.5 mg, 5 mg and 10 mg

The Division of Bioequivalence (DBE) has completed its review and has no further questions at this time.

The Division of Bioequivalence acknowledges that the following dissolution testing is being incorporated into your stability and quality control programs:

The dissolution testing is conducted in [redacted].

Sampling Time(hour)	% Dissolved
1 hour	[redacted]
4 hours	
8 hours	

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

for Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 75-896
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ P.Nwakama 12/17/2001

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Endorsements: (Final with Dates)
HFD-658/ PNwakama
HFD-658/ B.Davit 12/17/01
HFD-650/ SMazzella
HFD-650/ D. Conner for MP 12/31/2001

BIOEQUIVALENCY - ACCEPTABLE Submission date: November 28, 2001

1. **STUDY AMENDMENT** (STA) Strengths: 2.5, 5, 10 mg
(11/28/2001) **Outcome: AC**

Outcome Decisions: **AC** - ACCEPTABLE

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75896 SPONSOR : Mutual Pharmaceuticals.

DRUG AND DOSAGE FORM : Felodipine Extended-Release

STRENGTH(S) : 2.5 mg, 5 mg and 10 mg Tablets

TYPES OF STUDIES : Fasting, Non-Fasting & Multiple dose Studies

CLINICAL STUDY SITE : _____ (Fasting & Non-fasting Studies)
_____ (Multiple-dose Study)

ANALYTICAL SITE : _____
_____ (Multiple-dose Study)

STUDY SUMMARY : The 90% CIs in the fasting and Multiple-dose Studies; and T/R ratios in the Non-Fasting study are within acceptable limits.

DISSOLUTION : Dissolution was conducted according to Firm's own method.

DSI INSPECTION STATUS

Inspection needed: Yes NO	Inspection status:	Inspection results:
First Generic Yes____	Inspection requested:	
New facility _____	Inspection completed: (date)	
For cause _____		
other _____		

PRIMARY REVIEWER : Patrick E. Nwakama, Pharm.D. BRANCH : III

INITIAL : _____ DATE : 12/17/2001

TEAM LEADER : Barbara Davit, Ph.D. BRANCH : III

INITIAL : BD DATE : 12/17/01

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

for INITIAL : _____ DATE : 12/31/2001

Dale Conner 1/28/02

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-896

ADMINISTRATIVE DOCUMENTS

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : June 12, 2000

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615) 6/12/00

SUBJECT: Examination of the bioequivalence study submitted with an ANDA for Felopipine Extended-release Tablets, 10 mg to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to USC 355 (j)(5)(B)(iv).

Mutual Pharmaceutical Co., Inc. has submitted ANDA 75-896 for Felodipine Extended-release Tablets, 10 mg. The ANDA contains a certification pursuant to 21 USC 355 (j)(2)(A)(vii)(iv) stating that patent(s) for the reference listed drug will not be infringed by the manufacturing or sale of the proposed product. Also it is a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the study submitted by Mutual on June 6, 2000, 2000 for its Felodipine product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

ANDA 75-896

In determining whether a bio study is "complete" to satisfy statutory requirements, the following items are examined:

1. Study design

   (a) Appropriate number of subjects
   (b) Description of methodology

2. Study results

   (a) Individual and mean data is provided
   (b) Individual demographic data
   (c) Clinical summary

The issue raised in the current situation revolves around whether the study can purport to demonstrate bioequivalence to the listed drug.

We would appreciate a cursory review and your answers to the above questions as soon as possible so we may take action on this application.

DIVISION OF BIOEQUIVALENCE:

__✓__ Study meets statutory requirements Clarke S. Chavez 6/20/00

_____ Study does **NOT** meet statutory requirements

Reason:

Director, Division of Bioequivalence

6/26/00
Date

BIOEQUIVALENCE CHECKLIST FOR APPLICATION COMPLETENESS

ANDA 75-896 **DRUG NAME** Felodipine **FIRM** Mutual Pharmaceutical Co. Inc Philadelphia, PA

DOSAGE FORM(s) Extended-Release Tablets

	YES	NO	REQUIRED AMOUNT	AMOUNT SENT	COMMENTS
Protocol	✓				Fasting 991005 Fed + Fasting 991004 Steady State 2338
Assay Methodology	✓				
Procedure SOP	✓				
Methods Validation	✓				
Study Results Ln/Lin	✓				
Adverse Events	✓				
IRB Approval	✓				
Dissolution Data	✓				
Pre-screening of patients	✓				
Chromatograms	✓				
Consent forms	✓				signed forms provided for Study #2338 (see add. comment (ii))
Composition	✓				
Summary of study	✓				
Individual Data & Graphs , Linear & Ln	✓				
PK/PD data disk	✓				
Randomization Schedule	✓				
Protocol Deviations	✓				

	YES	NO	REQUIRED AMOUNT	AMOUNT SENT	COMMENTS
Clinical site	✓				[ ]
Analytical site	✓				[ ]
Study investigators	✓				
Medical Records	✓				
Clinical Raw Data	✓				
Test Article Inventory	✓				
BIO Batch Size	✓				[ ]
Assay of active content drug	✓				
Content uniformity	✓				
Date of manufacture	✓				Q.C Release Dat 1/13/00
Exp. Date RLD	✓				09/01
Biostudy lot numbers	✓				Test Drug: BB7730042 Ref Drug: H4386
Statistics	✓				
Summary results provided by the firm indicate studies pass BE criteria	✓				Please see Additional Comment in Attachment I
Waiver requests for other strengths / supporting data	N/A		—		

Additional comments: (I) For BE criteria: please see Attachment I

(II) On Consent Forms: Signed consent forms for only the steady state Study (# 2338) have been included in the ANDA submission. Signed consent forms for fasting (Study # 991004) and non-fasting (Study # 991005) have not been provided in the ANDA submission.

APPEARS THIS WAY ON ORIGINAL

Recommendation: (COMPLETE) / **INCOMPLETE**

Reviewed by Chandra S. Chaurasia

Chandra S. Chaurasia

Date 6/20/2000

Revised 6/7/2000

Attachment I to ANDA 75-896: Evaluation of Bioequivalence Application Completeness

Felodipine Extended-Release Tablet
10 mg
ANDA 75-896
Reviewer: Chandra S. Chaurasia

Mutual Pharmaceutical Company, Inc.
Philadelphia, PA
Submission Date: June 6, 2000

Additional Comments on Evaluation of Bioequivalence Application Completeness

Mutual Pharmaceutical ANDA 75-896 for Felodipine Extended-release Tablets includes bioequivalence studies under fasting, food and fasting and steady state conditions. The sponsor has reported the following pharmacokinetic measures under these conditions:

PK Measures*	Protocol No. 991004: Fed and Fasting Conditions		Protocol No. 991005: Fasting Conditions		Protocol No. 2338: Steady State Conditions	
	Test/Ref	90% CI	$Test_{fed}/Ref_{fed}$	90% CI	Test/Ref	90% CI
Ln AUCt (ng•hr/mL)	1.05	97.7-113	0.99	N/A	0.98	92-105
Ln AUCi (ng•hr/mL)	1.08	101.5-115.7	0.97	N/A	-	-
Ln Cmax (ng/mL)	0.88	79.8-97.8	1.11	N/A	0.90	82-99
LnCmin (ng/mL)	N/A	N/A	N/A	N/A	1.04	95-115

**geometric mean values for ln-transformed data reported*

As noted in the Table above, under fasting conditions, the confidence interval values for LnCmax is outside the acceptable range of 80-125%. However, currently the Agency accepts truncation value for pharmacokinetic measures. Accordingly, the CI value of 79.8% for Cmax is rounded to 80%. Thus, the summary results provided by the firm indicate studies pass BE criteria.

Recommendation: (COMPLETE)/INCOMPLETE

Reviewed by Chandra S. Chaurasia Date: 6/20/02

Chandra S. Chaurasia 6/20/2002

Telecon

Date: 08/14/00

Time: 1400 H

ANDA #: 75-931

Firm: Mutual Pharmaceutical Company

Drug: Felodipine Extended-release Tablets, 5 mg

Participants: Gregg Davis, FDA and Robert Dettery, Mutual

Phone #: 215-288-6500

Agenda:

I called Robert and told him that in looking at previously submitted applications for felodipine extended-release tablets, it was noticed that Mutual has a pending application for this drug product in a 10 mg strength (N 75-896). The proposed strength (5 mg) and the pending strength (10 mg) have proportional formulations and should be submitted in the same application as per the Guidance for Industry, Variations in Drug Products that May Be Included in a Single ANDA. The proposed application should be collapsed into the pending ANDA 75-896 as a new strength amendment. The firm should withdraw this application and request that the information be considered as an amendment to ANDA 75-896.

After conferring with the Document Room, the submitted information can be withdrawn and transferred to an amendment to ANDA 75-896. The current ANDA number, 75-931, will remain in the MIS system as withdrawn and a note will refer inquiries to ANDA 75-896.

RECORD OF TELEPHONE CONVERSATION

A conference call was placed by FDA(U. Venkataram and B.M. Azarm) to Mutual Pharmaceuticals (Dr. Robert Simon, Helen Leibman, and Sharon Watson). The call was made to ask that the firm tighten the limits for

[redacted]

The firm complied and will submit the revised limits as a TELEPHONE AMENDMENT.

APPEARS THIS WAY
ON ORIGINAL

DATE: Feb.1, 2002

APPLICATION NUMBER
75896

TELECON

INITIATED BY AGENT FOR SPONSOR

PRODUCT NAME
Felodipine

Firm Name:
Mutual Pharmaceuticals

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Robert Dettery

TELEPHONE NUMBER
215-288-6500

SIGNATURE

Orig: ANDA
Cc: Division File
Chem. II telecon binder

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OGD APPRCVAL ROUTING SUMMARY

ANDA # 75-896 Applicant Mutual Pharmaceutical Co.
Drug Felodipine Extended-release Tablets Strength(s) 2.5mg, 5mg, 10mg

APPROVAL (TENTATIVE APPROVAL) SUPPLEMENTAL APPROVAL (NEW STRENGTH) OTHER

REVIEWER:	DRAFT Package	FINAL Package
1. Martin Shimer Chief, Reg. Support Branch	Date 12/12/2003 Initials MMS	Date _____ Initials _____

Contains GDEA certification: (Yes) No (required if sub after 6/1/92)
Determ. of Involvement? Yes No
Pediatric Exclusivity System
RLD = NDA# 19-834
Patent/Exclusivity Certification: (Yes) No
Date Checked _____
If Para. IV Certification- did applicant
Nothing Submitted
Notify patent holder/NDA holder (Yes) No
Written request issued
Was applicant sued w/in 45 days: (Yes) No
(Study Submitted) - granted each
Has case been settled: (Yes) No Date settled: 11/12/2003, decision has been appealed
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes No (No determination made yet)
Type of Letter: (TA)
Comments: Most Recent court decision has found Mutual's product infringed the '081 patent & Mutual may not be Approved until (exp of '081 on 4/3/2007. Mutual has appealed the Decision ∴ OGD will NOT ask Mutual to Δ patent cert from P IV to P III

2. Project Manager, Stanley Shepperson Team 8 Review Support Branch	Date _____ Initials _____	Date _____ Initials _____

Original Rec'd date 6-6-00
Date Acceptable for Filing 6-6-00
Patent Certification (type) Para 3 + Para 4
Date Patent/Exclus.expires 6-19-01 + 10-30-07
Citizens' Petition/Legal Case Yes No
(If YES, attach email from PM to CP coord)
First Generic Yes No
Acceptable Bio reviews tabbed Yes No
EER Status Pending (Acceptable) OAI
Date of EER Status ~~11-26-01~~ 12-1-03
Date of Office Bio Review 8-21-01
Date of Labeling Approv. Sum 8-12-03
Date of Sterility Assur. App. N/A
Methods Val. Samples Pending Yes (No) per OGD policy
MV Commitment Rcd. from Firm (Yes) No comm letter
Modified-release dosage form: (Yes) No
Interim Dissol. Specs in AP Ltr: Yes (No) - TA.
Previously reviewed and tentatively approved Date _____
Previously reviewed and CGMP def./NA Minor issued Date _____
Comments:

3. Gregg Davis Deputy Dir., DLPS	Date 2/3/04 Initials _____	Date _____ Initials _____

RLD = Plendil Extended-Release Tablets 2.5mg, 5mg 10mg
AstraZeneca Pharmaceuticals, LP NDA 19-834 (004, 003, -002)

4. Div. Dir./Deputy Dir. Chemistry Div. I or II Comments: cmc satisfactory.		Date 1/9/04 Initials _____

Note: ANDA received on 6/6/00 provided for the 10mg strength only. On 8/14/00 OGD accepted an amendment to add the 5mg strength. On 8/29/00, OGD accepted an amendment for the 2.5 mg strength.

REVIEWER: **FINAL ACTION**

5. Frank Holcombe **First Generics Only** Date 2/2/04
Assoc. Dir. For Chemistry Initials SG
Comments: (First generic drug review)
SATISFACTORY

6. Peter Rickman Date 2/6/04 Initials PR for
Director, DLPS
Para.IV Patent Cert: Yes No ; Pending Legal Action: Yes No ; Petition: Yes No
Comments: Acceptable OPS dated 12/1/03 (Verified 2/3/04) No O.A.I. alerts noted - Bioequivalence studies (fasting, non-fasting, and steady-state on 10mg strength, fasting on 5 mg strength), and (fasting on 2.5 mg strength) found acceptable 8/10/04. Interim dissolution specifications also found acceptable. Bio studies conducted by OSI inspectional history - Office-wide bio enhanced on 8/21/02. These facilities have an acceptable and acceptable. labeling found acceptable for tentative approval on 5/12/03. CMC found acceptable 12/16/03. Methods validation was completed + found acceptable. 2/6/2004 First generic CMC audit has been completed. Robert Request

6. Robert L. West Date 2/6/2004
~~Acting~~ Deputy Director, OGD Initials
Para.IV Patent Cert: Yes No ; Pending Legal Action: Yes No ; Petition: Yes No
Comments: Mutual made a paragraph IV certification to the '081 patent for each strength (10mg, 5mg, and 2.5mg). Mutual was sued for infringement by AstraZeneca. On November 12, 2003, the district court ruled in favor of AstraZeneca. Mutual has appealed this decision.

This ANDA is recommended for tentative approval.

7. Gary Buehler Date 2/6/04
Director, OGD Initials GB
Comments: Tentative
First Generic Approval PD or Clinical for BE Special Scientific or Reg.Issue

8. Project Manager, Team Stan Shepperson Date 2/6/04
Review Support Branch Initials SS
P/A Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
2pm Time notified of approval by phone 2pm Time approval letter faxed
FDA Notification:
2/6/04 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

OGD APPROVAL ROUTING SUMMARY

ANDA # 75-896 Applicant Mutual Pharmaceutical Co., Inc
Drug Felodipine ER Tablets USP Strength(s) 2.5mg, 5mg, 10mg

APPROVAL ☑ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER:	DRAFT Package	FINAL Package
1. Martin Shimer Chief, Reg. Support Branch	Date 1 Nov 2004 Initials MS	Date 11/2/04 after Initials

Contains GDEA certification: Yes ☑ No ☐ Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92) Pediatric Exclusivity System
RLD = NDA# 19-834
Patent/Exclusivity Certification: Yes ☑ No ☐ Date Checked Previously granted
If Para. IV Certification- did applicant Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☑ No ☐ Written request issued ☐
Was applicant sued w/in 45 days: Yes ☑ No ☐ Study Submitted ☐
Has case been settled: Yes ☑ No ☐ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☑ No ☐
Date of latest Labeling Review/Approval Summary
Any filing status changes requiring addition Labeling Review Yes ☐ No ☑
Type of Letter:
Comments: Mutual sued on '081 & lost initially in DC on 11/12/2003. This decision vacated by Appellate Court that found Mutual does not infringe the '081 patent. Stanley Mutual eligible for 180 day on ~~all~~ strength. 180 triggered on 10/29/04

2. Project Manager, Shepperson Team 6 Review Support Branch	Date 11-4-04 Initials SMS	Date Initials

Original Rec'd date
Date Acceptable for Filing
Patent Certification (type)
Date Patent/Exclus.expires
Citizens' Petition/Legal Case Yes ☐ No ☐
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☐

EER Status Pending ☐ Acceptable ☐ OAI ☐
Date of EER Status
Date of Office Bio Review
Date of Labeling Approv. Sum 10-20-04
Labeling Acceptable Email Rec'd Yes ☒ No ☐
Labeling Acceptable Email filed Yes ☒ No ☐
Date of Sterility Assur. App.
Methods Val. Samples Pending Yes ☐ No ☐
MV Commitment Rcd. from Firm Yes ☐ No ☐

Acceptable Bio reviews tabbed Yes ☐ No ☐ Modified-release dosage form: Yes ☐ No ☐
Suitability Petition/Pediatric Waiver Interim Dissol. Specs in AP Ltr: Yes ☐
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☒ Date 2-6-2004
Previously reviewed and CGMP def. /NA Minor issued ☐ Date
Comments:

3. David Read **(PP IVs Only)** Pre-MMA Language included ☐ OGD Regulatory Counsel, Post-MMA Language Included ☐ Comments: N/A		Date Initials

4. Div. Dir./Deputy Dir. Chemistry Div. I II OR III Comments: Previously TA'ed. 2/6/04 No CMC changes		Date 11/1/04 Initials

REVIEWER: FINAL ACTION

5. Frank Holcombe **First Generics Only** Date_____
Assoc. Dir. For Chemistry Initials_____
Comments: (First generic drug review)
N/A. Completed at the time of the tentative approval issued 2/6/04.

6. Vacant RLD = Plendil Extended-release tablets NDA 19-834 (002, 003, 002)
Deputy Dir., DLPS AstraZeneca Pharmaceuticals LP 2.5mg, 5mg, 10mg Date_____
Initials_____

7. Peter Rickman Date 11/2/04
Director, DLPS Initials Per request for
Para.IV Patent Cert: Yes ☐ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes☐ No☐
Comments: Acceptable EES dated 12/1/03 (verified 11/2/04) No OAI alerts noted. Refer to the administrative sign-off form completed at the time of the tentative approval issued on 2/6/04. On 10/1/04, Mutual requested final approval of the ANDA based upon a favorable U.S. Court of Appeals decision. Mutual also stated that it had made no significant changes to the composition of the ANDA. On 10/5/04, Mutual submitted updated FPL 2°a, Changes in the RLD labeling. FPL found acceptable for approval 10/20/04, CMC found acceptable for approval 10/29/04. Methods validation was not requested.

8. Robert L. West Date 11/2/2004
Deputy Director, OGD Initials Per Robert West
Para.IV Patent Cert: Yes☒ No☐; Pending Legal Action: Yes☒ No☐; Petition: Yes☐ No☒
Comments: Mutual made a paragraph IV certification to the '081 patent for each strength. Mutual was sued for infringement by AstraZeneca and lost in the district court. However, Mutual appealed the decision and the decision was overturned by the Appeals Court. Mutual is eligible for 180-day generic drug exclusivity for all 3 strengths. The trigger for the exclusivity was on 10/29/04. This application is recommended for approval.

9. Gary Buehler Date 11/2/04
Director, OGD Initials Per
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg. Issue ☐

10. Project Manager, Team Stan Sheppersen 11/2/04 Date_____
Review Support Branch Initials_____
N/A Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
1pm Time notified of approval by phone 1pm Time approval letter faxed
FDA Notification:
11/2/04 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
11/2/04 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

File V:/division/dlps/approvrou9.doc

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-896

CORRESPONDENCE

United Research Laboratories, Inc.
Mutual Pharmaceutical Company, Inc.

1100 Orthodox Street
Philadelphia, PA 19124

215-288-6500
www.urlmutual.com

75:896
Ack for filing
S. Middleton
505(j)(2)(A) 7/18/00

labeling review drafted 7/27/00
A. Vezza

June 6, 2000

Office of Generic Drugs/CDER/FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: Abbreviated New Drug Application
Felodipine ER Tablets, 10mg

Dear Sir:

In accordance with section 505(j) of the Federal Food Drug and Cosmetic Act, Mutual Pharmaceutical Company, Inc. is submitting for FDA review and approval a 21 Volume Abbreviated New Drug Application for Felodipine ER Tablets in the 10 mg strength. This product will be labeled with the established generic name (no proprietary name) and will be packaged in bottles of 30, 100, 250, 500, and 1000 tablets.

AstraZeneca's Plendil® Extended-Release Tablets, 10mg, is the listed drug. The labeling that Mutual proposes is patterned after the Plendil® Extended-Release Tablets insert, revision 12/98.

We certify that we are concurrently sending a true copy of this abbreviated application (without the labeling section and bioequivalency results) to Ms. Debra Pagano, NDA/ANDA Program Manager, FDA Philadelphia District Office. In accordance with the October 14, 1994 letter from CDER, this submission does not include information that will be evaluated by district investigators (e.g., certain written procedures, equipment lists, etc.).

With this application, under separate cover, we are submitting the results of three *in vivo* bioequivalency studies, comparing AstraZeneca's Plendil® Extended-Release Tablets, 10mg, with Mutual's Felodipine ER Tablets, 10mg, under fed, fasting, and steady state conditions.

Please note that two (2) separately bound copies of the Analytical Methods Section (Section XV) are included with this application, in accordance with 21 CFR 314.50(e)(2)(i). Mutual Pharmaceutical commits to resolve any issue identified in the methods validation process after approval.

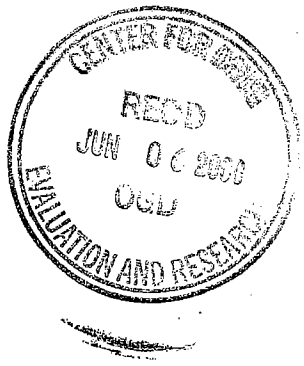
Finally, Mutual authorizes _____, to act on our behalf with regards to this application.

This application will include a bioequivalence ESD electronic submission. The diskette will be sent as new correspondence within 30 days.

Sincerely,

Robert Dettery
Vice-President, Regulatory Affairs
Mutual Pharmaceutical Company, Inc.

cc: Ms. Debra Pagano
PHI-DO NDA/ ANDA Program Manager



URL MUTUAL

United Research Laboratories, Inc.
Mutual Pharmaceutical Company, Inc.

1100 Orthodox Street
Philadelphia, PA 19124
215-288-6500
www.urlmutual.com

PS

July 7, 2000

Office of Generic Drugs/CDER/FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESPONDENCE

NEW CORRESP
NC

RE: ANDA 75-896; Felodipine ER Tablets, 10mg

Dear Sir or Madam:

Mutual Pharmacuetical Company, Inc. is submitting the bioequivalence ESD electronic submission.

Mutual Pharmaceutical Company, Inc certifies that to the best of our knowledge and ability, the electronic submission is identical to that in the hard copy.

Please feel free to contact me with any questions or comment regarding this submission. Thank you.

Sincerely,

Robert Dettery

Robert Dettery
Vice President, Regulatory Affairs
Mutual Pharmaceutical Company, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUL 10 2000
OGD

ANDA 75-896

Mutual Pharmaceutical Company, Inc.
Attention: Robert Dettery
1100 Orthodox Street
Philadelphia, PA 19124

JUL 20 2000

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Felodipine Extended-release Tablets, 10 mg

DATE OF APPLICATION: June 6, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: June 6, 2000

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

  1) Each owner of the patent or the representative designated by the owner to receive the notice;

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a court order or judgement or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Nasser Mahmud, Chief, Regulatory Support Branch, at (301) 827-5862.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Tim Ames
Project Manager
(301) 827-5849

Sincerely yours,

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-896
DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/

Endorsement: HFD-615/NMahmud, Chief, RSB date 7/20/00
HFD-615/SMiddleton, CSO date 7/20/00
Word File
V:/FIRMSAM\MUTUAL\LTRS&REV\75896.ACK
FT/mjl/7/19/00
ANDA Acknowledgment Letter!

United Research Laboratories, Inc.
Mutual Pharmaceutical Company, Inc.

1100 Orthodox Street
Philadelphia, PA 19124

215-288-6500
www.urlmutual.com

July 21, 2000

Office of Generic Drugs/CDER/FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: Abbreviated New Drug Application
Felodipine ER Tablets, 5mg

Dear Sir:

In accordance with section 505(j) of the Federal Food Drug and Cosmetic Act, Mutual Pharmaceutical Company, Inc. is submitting for FDA review and approval a seven (7) Volume Abbreviated New Drug Application for Felodipine ER Tablets in the 5 mg strength. This product will be labeled with the established generic name (no proprietary name) and will be packaged in bottles of 30, 100, 250, 500, and 1000 tablets.

AstraZeneca's Plendil® Extended-Release Tablets, 5mg, is the listed drug. The labeling that Mutual proposes is patterned after the Plendil® Extended-Release Tablets insert, revision 10/99.

We certify that we are concurrently sending a true copy of this abbreviated application (without the labeling section and bioequivalency results) to Ms. Debra Pagano, NDA/ANDA Program Manager, FDA Philadelphia District Office. In accordance with the October 14, 1994 letter from CDER, this submission does not include information that will be evaluated by district investigators (e.q., certain written procedures, equipment lists, etc.).

With this application, we are submitting the results of one (1) *in vivo* bioequivalency study, comparing AstraZeneca's Plendil® Extended-Release Tablets, 5mg, with Mutual's Felodipine ER Tablets, 5mg, under fasting conditions.

Please note that two (2) separately bound copies of the Analytical Methods Section (Section XV) are included with this application, in accordance with 21 CFR 314.50(e)(2)(i). Mutual Pharmaceutical commits to resolve any issue identified in the methods validation process after approval.

Please also note that Mutual Pharmaceutical Company has previously submitted ANDA 75-896 for Felodipine ER Tablets, 10mg. We intend to file a separate ANDA in the near future for Felodipine ER Tablets, 2.5mg.

Finally, Mutual authorizes [redacted] to act on our behalf with regards to this application.

This application will include a bioequivalence ESD electronic submission. The diskette will be sent as new correspondence within 30 days.

Sincerely,

Robert Dettery
Vice-President, Regulatory Affairs
Mutual Pharmaceutical Company, Inc.

cc: Ms. Debra Pagano
PHI-DO NDA/ ANDA Program Manager

APPEARS THIS WAY
ON ORIGINAL

URL MUTUAL

United Research Laboratories, Inc.
Mutual Pharmaceutical Company, Inc.

1100 Orthodox Street
Philadelphia, PA 19124
215-288-6500
www.urlmutual.com

August 14, 2000

Office of Generic Drugs/CDER/FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

MAJOR AMENDMENT
(CMC, Bioequivalence, Labeling)

WD

ORIG AMENDMENT

WITHDRAWN

N/WD N/AC

RE: ANDA 75-931; Felodipine ER Tablets, 5 mg
ANDA 75-896; Felodipine ER Tablets, 10 mg

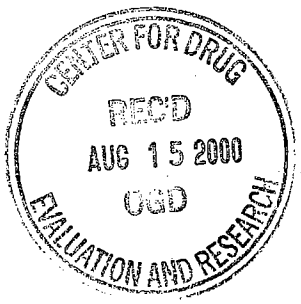
Dear Sir/Madam:

On July 24, 2000 Mutual Pharmaceutical Company submitted an abbreviated new drug application for Felodipine ER Tablets, 5mg, which was assigned ANDA # 75-931.

Per my August 14, 2000 telecon with the Mr. Greg Davis, Regulatory Support Branch, OGD, Mutual Pharmaceutical wishes to submit the Felodipine ER Tablets, 5mg, as a major amendment to the previously submitted application for Felodipine ER Tablets, 10mg (ANDA 75-896). The abbreviated new drug application for Felodipine ER Tablets, 10mg, was submitted on June 6, 2000. By this action, Mutual also hereby withdraws our application as ANDA 75-931.

I understand that the Paragraph IV notification requirements, per 21 CFR 314.95, as they pertain to the Felodipine ER Tablets, 5 mg, begin with the July 24, 2000 submission date. Mutual's voluntary withdrawal of its ANDA 75-931 is specifically contingent upon the FDA's agreement that the submission date of the Paragraph IV Certification for the 5mg tablets will remain as July 24, 2000. If the Agency does not agree that the Paragraph IV Certification date for the purposes of determining priority of Paragraph IV submissions under 21 CFR 314.107(c)(1)-(2) is July 24, 2000, then Mutual does not agree to the withdrawal of the 5mg ANDA 75-931.

We certify that we are concurrently sending a true copy of this amendment to Ms. Debra Pagano, NDA/ANDA Program Manager, FDA Philadelphia District Office.



Please feel free to contact me with any questions or comments regarding this submission.

Sincerely,

Robert Dettery
Vice-President, Regulatory Affairs
Mutual Pharmaceutical Company, Inc.

cc: Ms. Debra Pagano
PHI-DO NDA/ ANDA Program Manager

APPEARS THIS WAY
ON ORIGINAL

mB RS

URL MUTUAL

United Research Laboratories, Inc.
Mutual Pharmaceutical Company, Inc.

1100 Orthodox Street
Philadelphia, PA 19124

215-288-6500
www.urlmutual.com

August 18, 2000

Office of Generic Drugs/CDER/FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Minor Amendment
(Electr

NEW CORRESP
N C

RE: ANDA 75-896; Felodipine ER Tablets, 5mg and 10mg

Dear Sir:

Mutual Pharmaceutical Company, Inc. is submitting the bioequivalence ESD electronic submission. Based on a August 16, 2000 telecon between Sushama Bhuta (Mutual) and Richard Sponaugle, we are submitting an EVA submission that has been edited in the ESD to reflect the submission status from "original" to "amendment."

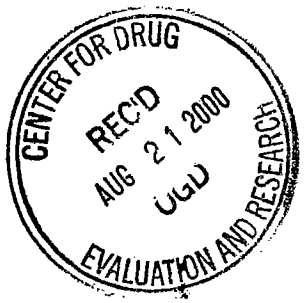
Mutual Pharmaceutical Company, Inc. certifies that to the best of our knowledge and ability, the electronic submission is identical to that in the hard copy.

Please feel free to contact me with any questions or comments regarding this submission. Thank you.

Sincerely,

Robert Dettery

Robert Dettery
Vice-President, Regulatory Affairs
Mutual Pharmaceutical Company, Inc.



URL MUTUAL

United Research Laboratories, Inc.
Mutual Pharmaceutical Company, Inc.

1100 Orthodox Street
Philadelphia, PA 19124
215-288-6500
www.urlmutual.com

Office of Generic Drugs/CDER/FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

PATENT AMENDMENT

AUG 29 2000

Re: ANDA 75-896; Felodipine ER Tablets, 5 mg and 10 mg

Dear Sir or Madam:

NEW CORRESP
NC

In accordance with 21 CFR 314.95(b) and (e), Mutual Pharmaceutical Company wishes to amend our above-referenced application to document that official Notice of Certification has been given to AstraZeneca Pharmaceuticals as the patent and NDA holder for Patent No. 4,803,081. Mutual received written confirmation from FDA on July 20, 2000 that ANDA 75-896 was substantially complete and acceptable for filing. The notice was sent to AstraZeneca via registered mail on August 7, 2000. Enclosed please find a copy of the notice and a copy of the registered return receipt postcard that documents the receipt of the notice by AstraZeneca on August 17, 2000.

Please note that the notice sent on August 7, 2000 was specifically for Mutual's Felodipine ER 10 mg tablets. We have subsequently amended ANDA 75-896 to add the 5 mg tablet dosage strength. A separate Notice of Certification was sent to AstraZeneca Pharmaceuticals within 30 days of the amendment for this additional strength, but we have not yet received documentation of its receipt. Mutual will submit a separate Patent Amendment covering the 5 mg strength once this documentation is received.

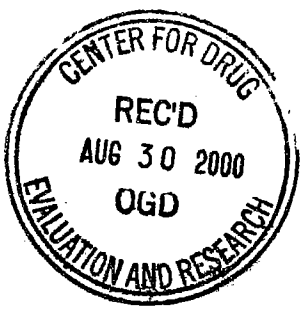
A copy of this submission is also being provided to the FDA, Philadelphia District Office.

Please direct any future comments or questions regarding this submission to my attention.

Sincerely,

Robert Dettery
Vice President, Regulatory Affairs

C: D. Pagano, PHI-DO



URL MUTUAL

United Research Laboratories, Inc.
Mutual Pharmaceutical Company, Inc.

1100 Orthodox Street
Philadelphia, PA 19124
215-288-6500
www.urlmutual.com

August 29, 2000

NDA DRUG AMENDMENT
AA

Office of Generic Drugs/CDER/FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
AUG 31 2000
OGD

RE: Major Amendment for ANDA 75-896
Felodipine ER Tablets, 2.5mg, 5mg, and 10mg

Dear Sir:

In accordance with section 505(j) of the Federal Food Drug and Cosmetic Act, Mutual Pharmaceutical Company, Inc. is submitting for FDA review and approval a nine (9) Volume application, submitted as a major amendment for ANDA 75-896, for Felodipine ER Tablets in the 2.5 mg strength. This product will be labeled with the established generic name (no proprietary name) and will be packaged in bottles of 30, 100, 250, 500, and 1000 tablets.

AstraZeneca's Plendil® Extended-Release Tablets, 2.5mg, is the listed drug. The labeling that Mutual proposes is patterned after the Plendil® Extended-Release Tablets insert, revision 10/99.

We certify that we are concurrently sending a true copy of this abbreviated application (without the labeling section and bioequivalency results) to Ms. Debra Pagano, NDA/ANDA Program Manager, FDA Philadelphia District Office. In accordance with the October 14, 1994 letter from CDER, this submission does not include information that will be evaluated by district investigators (e.q., certain written procedures, equipment lists, etc.).

With this application, we are submitting the results of one (1) *in vivo* bioequivalency study, comparing AstraZeneca's Plendil® Extended-Release Tablets, 2.5mg, with Mutual's Felodipine ER Tablets, 2.5mg, under fasting conditions.

Please note that two (2) separately bound copies of the Analytical Methods Section (Section XV) are included with this application, in accordance with 21 CFR 314.50(e)(2)(i). Mutual Pharmaceutical commits to resolve any issue identified in the methods validation process after approval.

Finally, Mutual authorizes _____, to act on our behalf with regards to this application.

This application will include a bioequivalence ESD electronic submission. The diskette will be sent as new correspondence within 30 days.

Sincerely,

Robert Dettery
Vice-President, Regulatory Affairs
Mutual Pharmaceutical Company, Inc.

cc: Ms. Debra Pagano
PHI-DO NDA/ ANDA Program Manager

United Research Laboratories, Inc.
Mutual Pharmaceutical Company, Inc.

1100 Orthodox Street
Philadelphia, PA 19124

215-288-6500
www.urlmutual.com

September 12, 2000

Office of Generic Drugs/CDER/FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

PATENT AMENDMENT

NEW CORRESP
NC

rr for 2.5mg
Notice is adequate
Still awaiting rr for 5mg
9/25/a

Re: ANDA 75-896; Felodipine ER Tablets, 2.5 mg, 5 mg and 10 mg

Dear Sir or Madam:

In accordance with 21 CFR 314.95(b) and (e), Mutual Pharmaceutical Company wishes to amend our above-referenced application to document that official Notice of Certification has been given to AstraZeneca Pharmaceuticals as the patent and NDA holder for Patent No. 4,803,081.

Mutual submitted an amendment to ANDA 75-896 on August 29, 2000 for the purpose of adding the 2.5 mg dosage strength to the application. That amendment included a Paragraph IV Certification to the '081 patent and on August 31, 2000 a notice to that effect was sent to AstraZeneca via registered mail. Enclosed please find a copy of the notice and a copy of the registered return receipt postcard that documents the receipt of the notice by AstraZeneca on September 6, 2000.

Please note that the notice sent on August 31, 2000 was specifically for Mutual's Felodipine ER 2.5 mg tablets. (Mutual previously notified AstraZeneca about the 10 mg dosage strength, for which we submitted a Patent Amendment on August 29, 2000.) We had also amended ANDA 75-896 to add the 5 mg tablet dosage strength. A separate Notice of Certification was sent to AstraZeneca Pharmaceuticals within 30 days of the amendment for that additional strength, but we have not yet received documentation of its receipt. Mutual will submit a separate Patent Amendment covering the 5 mg strength once this documentation is received.

A copy of this submission is also being provided to the FDA, Philadelphia District Office.

Please direct any future comments or questions regarding this submission to my attention.

Sincerely,

Robert Dettery

Robert Dettery
Vice President, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
SEP 13 2000
OGD

C: D. Pagano, PHI-DO

United Research Laboratories, Inc.
Mutual Pharmaceutical Company, Inc.

1100 Orthodox Street
Philadelphia, PA 19124
215-288-6500
www.urlmutual.com

September 28, 2000

Office of Generic Drugs/CDER/FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESPONDENCE

NEW CORRESP
NC
1 Bio

Re: ANDA 75-896; Felodipine ER Tablets, 2.5mg, 5mg, and 10mg

Dear Sir or Madam:

Mutual Pharmaceutical Company, Inc. is submitting the bioequivalence ESD electronic submission.

Mutual Pharmaceutical Company, Inc. certifies that to the best of our knowledge and ability, the electronic submission is identical to that in the hard copy.

Please feel free to contact me with any questions or comments regarding this submission. Thank you.

Sincerely,

Robert Dettery
Vice President, Regulatory Affairs
Mutual Pharmaceutical Company, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
SEP 29 2000
OGD

URL MUTUAL

United Research Laboratories, Inc.
Mutual Pharmaceutical Company, Inc.

1100 Orthodox Street
Philadelphia, PA 19124
215-288-6500
www.urlmutual.com

November 15, 2000

N/A

ORIG AMENDMENT

Office of Generic Drugs/CDER/FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: ~~Minor~~ Amendment for ANDA 75-896
Felodipine ER Tablets, 2.5mg, 5mg, and 10mg

Aug 14, 2000 ?

Dear Sir:

On ~~June~~ 6, 2000, Mutual Pharmaceutical Company, Inc., submitted the above referenced ANDA for ~~F~~elodipine ER Tablets, 10mg. This was followed by two (2) major amendments on ~~July~~ 24, 2000 and August 29, 2000 for the submission of the 5mg strength and 2.5mg strength, respectively.

Mutual now realizes there may have been an error in Section VII, Components and Composition. We would like to amend the application to correct the error. The enclosed Exhibit A should be used in lieu of page 8537 of the original application for Felodipine ER Tablets, 10mg. The enclosed Exhibit B should be used in lieu of page 1727 of the major amendment for the Felodipine ER Tablets, 5mg. The enclosed Exhibit C should be used in lieu of page 1743 of the major amendment for the Felodipine ER Tablets, 2.5mg.

We are concurrently sending a true copy of this minor amendment to Ms. Debra Pagano, NDA/ANDA Program Manager, FDA Philadelphia District Office.

Sincerely,

Susan B. Wilson

Susan B. Wilson
Regulatory Affairs Associate
Mutual Pharmaceutical Company, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
NOV 17 2000
OGD

cc: Ms. Debra Pagano
PHI-DO NDA/ ANDA Program Manager

United Research Laboratories, Inc.
Mutual Pharmaceutical Company, Inc.

1100 Orthodox Street
Philadelphia, PA 19124
215-288-6500
www.urlmutual.com

NEW CORRESP

NC

November 17, 2000

Office of Generic Drugs/CDER/FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

PATENT AMENDMENT

Re: ANDA 75-896; Felodipine ER Tablets, 2.5 mg, 5 mg and 10 mg

Dear Sir or Madam:

On June 6, 2000 Mutual Pharmaceutical Company, Inc. submitted the above referenced ANDA for Felodipine ER Tablets, 10 mg. This was followed by two major amendments on July 24, 2000 and August 29, 2000 for the submission of the 5 mg strength and the 2.5 mg strength respectively. These submissions contained Paragraph IV Certifications against U. S. Patent 4,803,081 (the '081 patent).

Mutual Pharmaceutical Company wishes to inform you that the holder of the '081 patent, AstraZeneca, has filed a Complaint for Patent Infringement against Mutual in the U.S. District Court for the Eastern District of Pennsylvania. A copy of this Complaint, which was filed on September 18, 2000 is enclosed in this Patent Amendment.

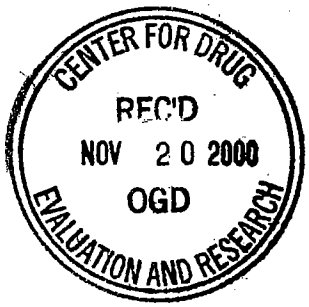
A copy of this submission is also being provided to the FDA, Philadelphia District Office.

Please direct any future comments or questions regarding this submission to my attention.

Sincerely,

Robert Dettery
Vice President, Regulatory Affairs

C: D. Pagano, PHI-DO



United Research Laboratories, Inc.
Mutual Pharmaceutical Company, Inc.

1100 Orthodox Street
Philadelphia, PA 19124
215-288-6500
www.urlmutual.com

ORIG AMENDMENT
N/AC FPL
BIOAVAILABILITY

labeling review drafted 3/15/01 A. Vezza

March 7, 2001

Office of Generic Drugs/CDER/FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

MAJOR AMENDMENT
(CMC, Bioequivalence, and Labeling Deficiencies)

Re: ANDA 75-896; Felodipine Extended-Release Tablets, 2.5mg, 5mg, and 10mg

Dear Sir/Madam:

On November 16, 2000, your Office corresponded by fax with Mutual Pharmaceutical Company regarding the above-referenced abbreviated new drug application. The correspondence listed major deficiency comments about the Chemistry, Manufacturing and Controls section and labeling.

This submission represents Mutual's response to the major deficiency letter for ANDA 75-896.

A. CHEMISTRY DEFICIENCIES:

√1. *Components of ——— need to be included in the component and composition statement. Please revise and resubmit.*

Mutual has revised the Component and Composition statement to include the components of ———. Please refer to Exhibit A for the revised Components and Composition statement for Felodipine ER Tablets, 2.5mg, 5mg, and 10mg.

√2. *On page 8547, you included two specifications of NMT —% and NMT —% for ———. Please clarify.*

Mutual has revised its specification in accordance with the ———. Please find attached in Exhibit B, Mutual's revised ——— test method and corresponding specification form. The following is a summary of the specifications:

[ ]

Redacted 8 page(s)

of trade secret and/or

confidential commercial

information from

3/7/2001 MUTUAL LETTER

3. *There appears to be a typographical error in reporting the dosage form and fill size of the drug product on page 9343. The dosage form is reported incorrectly as capsules. The 60 count package reported on page 9343 is not part of the packaging system reported on page 9342.*

Mutual acknowledges the typographical error on page 9343 of the original submission and this page has been revised to reflect the correct drug product and dosage form. Please refer to Exhibit Q. Please replace page 624 with page 9343 or the original ANDA submission for Felodipine ER Tablets, 10mg.

4. *A satisfactory compliance evaluation for the firms referenced in the ANDA is required for approval. We have requested an evaluation from the Office of Compliance.*

Mutual acknowledges that a satisfactory compliance evaluation for the firms referenced in the ANDA is required for approval. Mutual also acknowledges that an evaluation from the Office of Compliance has been requested.

5. *Additionally, please note that chemistry, manufacturing and controls information regarding the 2.5 and 5mg products (amendments dated August 14 and 29, 2000) have not been reviewed. Please review the deficiencies identified in Section A for relevance to these products. Revise any pertinent documentation and resubmit.*

Mutual acknowledges that the amendments submitted for the 2.5mg and 5mg products have not been reviewed. Mutual has reviewed the chemistry deficiencies identified in Section A and has submitted the revised documents for the 2.5mg and 5mg strengths.

LABELING DEFICIENCIES

Regarding the labeling deficiencies listed in the August 28, 2000 letter to AstraZeneca and the November 16, 2000 letter to Mutual, we have made the requested revisions. We are submitting twelve (12) final printed container labels and insert labeling as Exhibit R. A side-by-side comparison of the revised labels and labeling with that from our last submission is also included in Exhibit R.

BIOEQUIVALENCE

Mutual would also like to take this opportunity to submit report amendments, additional pages, and replacement pages for the bioequivalence studies conducted on Felodipine ER Tablets, 10mg.

Please find the report amendments as Exhibit S:

Addendum I for Study #2338 (from ———————)
Analytical Report Amendment for Project # 991004 (from———————)

Please find the replacement pages as Exhibit T. The replacement pages are as follows:

Page #	*Replaces Original ANDA Page #*
800	2695
801	2708
802	3251

Please find the additional pages as Exhibit U.

Page #	*Additional Page in Original ANDA*
803	2708A
804	2852A
805	4271A

This concludes Mutual's response to the Major Deficiency Letter for ANDA 75-896. A duplicate Field Submission copy of this Major Amendment has been provided to the FDA, Philadelphia District Office.

Please direct any questions or comments concerning this amendment to my attention. Thank you.

Sincerely,

Susan B. Wilson

Susan B. Wilson
Regulatory Affairs Associate, Mutual Pharmaceutical Company, Inc.

cc: D. Pagano, PHI-DO

United Research Laboratories, Inc.
Mutual Pharmaceutical Company, Inc.

1100 Orthodox Street
Philadelphia, PA 19124

215-288-6500
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April 30, 2001

AMENDMENT
N/AB

Office of Generic Drugs/CDER/FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

BIOEQUIVALENCY AMENDMENT

Re: ANDA 75-896; Felodipine Extended-Release Tablets, 2.5 mg, 5 mg, and 10 mg

Dear Sir or Madam:

On March 23, 2001 Mutual Pharmaceutical Company received a deficiency letter pertaining to the above-referenced application. That letter listed five deficiencies that were identified by the Division of Bioequivalence. Mutual's response to those deficiencies is as follows:

1. *The fasting study on 10 mg is not acceptable since the 90% confidence intervals for LCmax are outside the acceptable limits of 80 – 125% and the long-term stability data does not cover the duration of the study.*

Mutual believes that this comment was prompted by the Guidance to Industry – Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations, which was issued October 2000. However, ANDA 75-896 was submitted in June 2000 before this guidance was available. At the time the bioequivalency study was performed and at the time the ANDA was submitted, OGD permitted the rounding of confidence interval values to meet the specified limits of 80-125%, provided that the study data were 79.5% or greater, or 125.4% or less.

Mutual is aware of at least one other ANDA that was approved after the issuance of the draft version of the above-referenced guidance based on the rounding of the confidence interval data from 79.8% to 80%. This approval was confirmed by Mutual's regulatory consultant, [redacted] who agreed that OGD has previously accepted rounded results when all other *in vivo* study requirements were met and the *in vitro* data was acceptable. Our consultant also confirmed that the ANDA approved with rounded results was submitted after the draft version, but before the final version, of the bioequivalency guidance. This is exactly the same situation as Mutual's Felodipine application.

Prior to submission of ANDA 75-896, Mutual made an inquiry to the Division of Bioequivalence concerning the rounding of confidence intervals. Ms. Jennifer Fan confirmed that rounding to whole numbers was an acceptable practice. Please refer to Exhibit 1-1 for a memo of the telephone conversation between Ms. Fan and Dr. Jie Du, Mutual's Director of Biopharmaceutics.

In addition, Mutual has obtained written opinions regarding this issue from ——— ———, the Contract Research Organization that performed the bioequivalence study, and from Dr. ———, a consultant that FDA has frequently used for bioequivalence matters. Please refer to Exhibits 1-2 and 1-3 respectively.

Therefore, based on the established practice at the time Mutual submitted this application, Mutual respectfully requests that OGD reconsider its position and determine that the calculated confidence limit of 79.8 support acceptance of the fasting bioequivalence study at 80-125%.

Regarding the long-term stability data not covering the duration of the study, please refer to Mutual's Major Amendment, dated March 7, 2001, specifically Exhibits S, T, and U. These exhibits included an analytical report amendment from ——— which contains stability data for a 107 day period. This exceeds the 67 day duration of the study.

2. *You have repeat assays. Please submit all relevant SOPs for anomalous values/pharmacokinetic repeats since assays cannot be repeated unless mentioned in the SOPs.*

We respectfully refer you to Exhibit 1-2, in which this comment is answered by ——— ———.

3. *If the original assay values are used instead of the repeat assay values for anomalous/pharmacokinetic repeats, the 90% confidence intervals for LCmax in the fasting study on 2.5 mg would be outside the acceptable limits of 80 – 125%.*

Again, we respectfully refer you to Exhibit 1-2, in which this comment is answered by ———

4. *The DBE requests that the dissolution testing should be conducted under the following conditions:*

Apparatus:	*Paddle at 50 and 75 rpm*
Medium:	*900 mL of aqueous media at various pH values (1-1.5, 4-4.5, 6-6.8, and 7-7.5)*
Times:	*1,2, and 4 hours, and every 2 hours thereafter, until 80% of the drug is released*

In addition, you should generate dissolution profiles using 500 mL phosphate buffer pH 6.5 with 1% sodium lauryl sulphate and USP Apparatus II at a speed of rpm.

Mutual is in the process of performing the dissolution testing that you requested in this comment. This is a huge amount of work, for which we will not have all the results until about June 2001. We will submit the results at that time as another Bioequivalency Amendment.

5. For future studies, please dose with 240 mL water.

We acknowledge your comment that for future studies, 240 mL of water should be used for dosing.

Since this is a Bioequivalency Amendment, we are not providing a Field Submission copy to the District Office.

Please direct any further questions or comments regarding this application to my attention. Thank you.

Sincerely,

Robert Dettery
Vice President, Regulatory Affairs

Cc: L. Ogunbiyi

United Research Laboratories, Inc.
Mutual Pharmaceutical Company, Inc.

1100 Orthodox Street
Philadelphia, PA 19124

215-288-6500
www.urlmutual.com

June 25, 2001

VIA FAX AND STANDARD MAIL

BIOAVAILABILITY
ORIG AMENDMENT
N/AB

Office of Generic Drugs/CDER/FDA
Attn: Steve Mazzella, HFD-650
Metro Park North II
7500 Standish Place
Rockville, MD 20855

Re: ANDA 75-896, Felodipine ER Tablets, 2.5 mg, 5 mg, and 10 mg

Dear Mr. Mazzella:

This letter is in follow-up to our telecon on June 22, 2001. As you know, on March 23, 2001 OGD faxed Mutual Pharmaceutical Company a deficiency letter for our ANDA 75-896, Felodipine ER Tablets. In that letter, Mutual was requested to perform additional dissolution testing under several varying conditions. In addition, Mutual was specifically directed to continue testing dissolution time points until 80% of the drug substance was released from the drug product.

Upon performing these dissolution tests, Mutual's Analytical Research and Development (ARD) department encountered difficulty in obtaining 80% of the drug substance in solution. In some cases, dissolution samples were taken up to 30 hours with the result that little or no drug substance was found to be present.

Attached is a summary of some of the dissolution results that we have obtained after testing Felodipine ER Tablets under the conditions mentioned in the deficiency letter. Mutual would like to be able to provide the dissolution information that OGD requested in the deficiency letter, but we are not sure how to proceed given these results.

Mutual requests a telephone meeting between our ARD department and OGD's Division of Bioequivalence. The purpose of this meeting would be to discuss the results that we have obtained to date and to request guidance regarding how we should best proceed in order to provide the data requested in the deficiency letter.

Please telephone me at 215-807-1044 to arrange a date and time for this meeting to occur. Thank you.

CENTER FOR DRUG
EVALUATION AND RESEARCH
JUL 02 2001
OGD

Sincerely,

Robert Dettery
Vice President, Regulatory Affairs

United Research Laboratories, Inc.
Mutual Pharmaceutical Company, Inc.

1100 Orthodox Street
Philadelphia, PA 19124

215-288-6500
www.urlmutual.com

August 8, 2001

NC/Bio

Office of Generic Drugs/CDER/FDA
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855

CONTROLLED CORRESPONDENCE

Re: ANDA 75-896, Felodipine ER Tablets, 2.5 mg, 5 mg, and 10 mg

Dear Sir or Madam:

On March 23, 2001 Mutual Pharmaceutical Company received a faxed deficiency letter, listing five deficiencies from the Division of Bioequivalence, regarding the above-referenced application. Mutual responded to that deficiency letter on April 30, 2001 but noted that the requested additional dissolution testing would require several months to complete.

On June 25, 2001 Mutual corresponded with the Division of Bioequivalence regarding the additional dissolution testing that we were requested to perform in the March 23rd deficiency letter. We explained the difficulties that were encountered in performing these tests, such as the drug substance not going into solution after 30 hours of stirring, and we requested a meeting in order to obtain guidance from the Division regarding how to best proceed.

Based on my August 8, 2001 telephone conversation with Steve Mazzella, DBE Project Manager, Mutual now believes that the additional dissolution testing, which was requested of us in the March 23rd deficiency letter, is no longer necessary. Therefore, Mutual is sending this controlled correspondence to inform OGD that we withdraw our request for a meeting with the Division of Bioequivalence, and that we consider our response to the March 23, 2001 deficiency letter to be complete.

Sincerely,

Robert Dettery

Robert Dettery
Vice President, Regulatory Affairs

URL MUTUAL

United Research Laboratories, Inc.
Mutual Pharmaceutical Company, Inc.

1100 Orthodox Street
Philadelphia, PA 19124

215-288-6500
www.urlmutual.com

August 15, 2001

NC NEW CORRESP

Ms. Bonnie McNeal
Office of Generic Drugs/CDER/FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESPONDENCE

RE: ANDA 75-896; Felodipine ER Tablets, 2.5mg, 5mg and 10mg

Dear Ms. McNeal:

Per your telephone request, I am submitting two "desk" copies of the Current Methods of Testing and corresponding Analytical Reports for the above referenced product as needed for the purpose of Method Validation.

It should be noted that the raw material Method of Testing and Analytical Report are being simultaneously submitted as an Amendment. The Method of Testing and Analytical Reports for the finished tablets were previously submitted on March 7, 2001, as part of a Major Amendment.

Please feel free to contact me with any questions or comment regarding this submission. Thank you.

Sincerely,

Amy McKelvey-Haas

Amy McKelvey-Haas
Regulatory Affairs Associate
Mutual Pharmaceutical Company, Inc.

CENTER FOR DRUG
AUG 16 2001
OGD
EVALUATION AND RESEARCH

Noted. NAI.
B. McNeal
8/24/01

United Research Laboratories, Inc.
Mutual Pharmaceutical Company, Inc.

1100 Orthodox Street
Philadelphia, PA 19124

215-288-6500
www.urlmutual.com

August 15, 2001

Office of Generic Drugs/CDER/FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

AMENDMENT
(CMC)

NDA ORIG AMENDMENT
N/AA

Re: ANDA 75-896; Felodipine Tablets 2.5 mg, 5mg and 10 mg

Dear Sir or Madam:

Mutual wishes to amend the above-referenced application to submit an updated Method of Testing and the Analytical Report for the active pharmaceutical ingredient.

[redacted]

This concludes Mutual's Minor Amendment to ANDA 75-896. A duplicate copy of this submission is being provided to the Philadelphia, Pre-Approval Manager.

Please direct any further questions or comments regarding this submission to my attention. Thank you.

Sincerely,

Amy McKelvey-Haas

Amy McKelvey-Haas
Regulatory Affairs Associate
Mutual Pharmaceutical Company, Inc.

CENTER FOR DRUG
EVALUATION AND RESEARCH
AUG 20 2001
OGD

United Research Laboratories, Inc.
Mutual Pharmaceutical Company, Inc.

1100 Orthodox Street
Philadelphia, PA 19124

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September 24, 2001

DRUG ABBREVIATION
N/Am

Office of Generic Drugs/CDER/FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Minor Amendment
(Chemistry)

RE: ANDA 75-896; Felodipine Extended-Release Tablets, 2.5 mg, 5 mg, and 10mg

On August 15, 2001, your office faxed correspondence to Mutual Pharmaceutical Company regarding the above-referenced application. This letter and the accompanying documentation represent Mutual's response to this deficiency letter.

A. Chemistry Deficiencies:

1. [redacted]

2. [redacted]

3. [redacted]

CENTER FOR DRUG
SEP 26 2001
EVALUATION AND RESEARCH

Redacted 2 page(s)

of trade secret and/or

confidential commercial

information from

9/24/2001 MUTUAL LETTER

URL MUTUAL

United Research Laboratories, Inc.
Mutual Pharmaceutical Company, Inc.

1100 Orthodox Street
Philadelphia, PA 19124

215-288-6500
www.urlmutual.com

FACSIMILE

To: Document Control Room
Fax #: 301-827-4337
Date: 11/28/01
Pages: 3, including this cover sheet.

OPSC AMENDMENT
N/FA

I am faxing the following cover letter from Mutual Pharmaceutical's FAX AMENDMENT to our ANDA 75-896. The exhibits are too voluminous to include by fax. The entire submission is being sent via Fedex for arrival at the Document Control Room Thursday morning.

APPEARS THIS WAY
ON ORIGINAL

From the desk of...

Robert Dettery
Vice-President, Regulatory Affairs
Mutual Pharmaceutical Company
1100 Orthodox Street
Philadelphia, PA 19124

215-807-1044
Fax: 215-807-1095

United Research Laboratories, Inc.
Mutual Pharmaceutical Company, Inc.

1100 Orthodox Street
Philadelphia, PA 19124

215-288-6500
www.unimutual.com

November 28, 2001

Office of Generic Drugs/CDER/FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855
Fax # 301-827-4337

FAX AMENDMENT
(Chemistry)

NC

Re: ANDA 75-896, Felodipine ER Tablets, 2.5 mg, 5 mg, and 10 mg

Dear Sir or Madam:

On November 13, 2001 your Office faxed a correspondence to Mutual Pharmaceutical Company stating minor deficiencies regarding the above-referenced application. Mutual was requested to respond within 30 days in the form of a FAX AMENDMENT. This letter represents Mutual's response to your November 13, 2001 correspondence.

A. Chemistry Deficiencies

1. The Division of Bioequivalence has recommended the following specifications for the dissolution testing: ——— The test product should meet the following specifications:

Sampling Time (hour)	*% Dissolved*
1 hour	[ ]
4 hours	
8 hours	

Please incorporate the dissolution specifications and testing method into your stability and finished product testing specifications.

Mutual acknowledges your requested dissolution specifications, as well as the comments provided by the Division of Bioequivalence (DBE), and we respectfully request a minor revision.

Mutual proposes the same dissolution parameters that you specified ———, but with the following dissolution specifications:

Sampling Time (hour)	**% Dissolved**
1 hour	[ ]
4 hours	
8 hours	

Our request to slightly change the 4th hour dissolution specification from that which you recommended, is based on a thorough review of the dissolution data (release and stability) accrued to date. We believe the ——— specification would be more consistent with the quality attributes of our Felodipine ER Tablets and still be consistent with DBE's requirement of having a range not in excess of 25%.

In anticipation of your concurrence, we have revised our finished product and stability Method of Testing and Analytical Reports accordingly, which we are providing as Exhibit A.

2. *Please revise and resubmit the Method Validation Package to include the dissolution specifications and testing method recommended by the Division of Bioequivalence. The validation report should be resubmitted accordingly.*

We are puzzled by this request, which seems to indicate that additional method validation is needed because of the revised dissolution specifications. Mutual wishes to note that the actual dissolution parameters (*i.e.*, media, volume, temperature, apparatus, and speed) have not changed from the method we originally validated. Furthermore, that validation, which demonstrated our method is precise, specific, rugged, linear, and accurate, covered the range of specifications across all time points.

The specification changes, both as you proposed and as Mutual wishes to revise, are changes to product performance criteria and do not require validation. We have, however, revised our Method Validation reports to include the new Drug Release specifications. These reports are enclosed as Exhibit B.

B. *In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:*

Please provide available room temperature data that includes dissolution data determined in accordance with the Division of Bioequivalence recommendations.

Mutual acknowledges your comment and has prepared revised Stability Summary reports for each submission batch of Felodipine ER Tablets. These reports, which are enclosed as Exhibit C, incorporate the revised dissolution specifications while displaying the existing room temperature stability results. It is evident that our current stability results pass the revised specifications. Future stability tests for dissolution will also be performed by the method and specifications given in Exhibit A.

Per your fax, this response is being submitted as a FAX AMENDMENT to ANDA 75-896. A copy of this submission is also being provided to the FDA, Philadelphia District.

Sincerely,

Robert Dettery

Robert Dettery
Vice President, Regulatory Affairs

C: D. Pagano, PHI-DO

United Research Laboratories, Inc.
Mutual Pharmaceutical Company, Inc.

1100 Orthodox Street
Philadelphia, PA 19124

215-288-6500
www.urlmutual.com

February 5, 2002

Office of Generic Drugs/CDER/FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

TELEPHONE AMENDMENT
(Chemistry)

ORIG AMENDMENT FA

RE: ANDA 75-896; Felodipine ER Tablets, 2.5 mg, 5 mg, and 10 mg

Dear Sir/Madam:

Mutual Pharmaceutical Company wishes to amend our above-referenced application for the purpose of reducing the release and stability limits for [redacted].

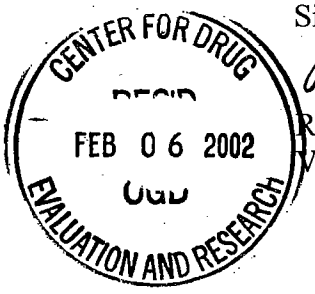
This change to our [redacted] was requested during a telephone call from the Office of Generic Drugs on February 1, 2002. Consequently, this amendment is being submitted as a Telephone Amendment to ANDA 75-896.

Enclosed is a copy of the revised Felodipine Extended-Release Tablets Method of Testing and Analytical Reports for release and stability testing.

We certify that we are concurrently sending a true copy of this amendment to the Food and Drug Administration, Philadelphia District Office.

Please feel free to contact me with any questions or comments regarding this submission.

Sincerely,



Robert Dettery
Vice-President, Regulatory Affairs

cc: Ms. Debra Pagano, PHI-DO

United Research Laboratories, Inc.
Mutual Pharmaceutical Company, Inc.

1100 Orthodox Street
Philadelphia, PA 19124

215-288-6500
www.urlmutual.com

September 24, 2002

via fax and Certified Mail

NEW CORRESP
NC

Office of Generic Drugs/CDER/FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

NEW CORRESPONDENCE

Re: ANDA 75-896; Felodipine Extended-Release Tablets, 2.5 mg, 5 mg, and 10 mg

Dear Sir or Madam:

On March 27, 2002 Mutual Pharmaceutical Company received a fax correspondence regarding the above-referenced abbreviated new drug application. That correspondence listed a few minor deficiencies that made the application Not Approvable under Section 505 of the Act.

In accordance with 21 CFR 314.120(a)(1), Mutual wishes to notify the Office of Generic Drugs of our intention to amend ANDA 75-896 in response to the minor deficiencies. We are diligently preparing significant data and information that will address those deficiencies, and we anticipate submitting that minor amendment within the next three months.

Therefore, Mutual respectfully requests that the review period for ANDA 75-896 be extended to allow us sufficient time to formulate our minor amendment.

A copy of this New Correspondence is being provided to the FDA, Philadelphia District Office.

Sincerely,

Robert Dettery
Vice President, Regulatory Affairs

Cc: D. Pagano, PHI-DO

RECEIVED
OCT 0 3 2002
OGD / CDER

ANDA 75-896

JAN - 2 2003

CERTIFIED MAIL-RETURN RECEIPT REQUESTED

Mutual Pharmaceutical Company, Inc.
Attention: Robert Dettery
1100 Orthodox Street
Philadelphia, PA 19124

Dear Sir:

This letter is in reference to your Abbreviated New Drug Application (ANDA) dated June 6, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Felodipine Extended-release Tablets, 10 mg.

We refer you to our "Not Approvable" letter March 27, 2002, which detailed the deficiencies identified during our review of your ANDA. The Agency may consider an ANDA applicant's failure to respond to a "Not Approvable" letter within 180 days to be a request by the applicant to withdraw the ANDA under 314.120(b). Your amendment to the application is overdue. You must amend your application within 10 days of receipt of this letter. Otherwise, an action to withdraw the application will be initiated per 21 CFR 314.99.

If you do not wish to pursue approval of this application at this time, you should request withdrawal in accord with 21 CFR 314.65. A decision to withdraw the application would be without prejudice to refiling.

If you have further questions you may contact Martin H. Shimer, Project Manager, Regulatory Support Branch, at (301) 827-5862.

Please send all correspondence to the following address:

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Sincerely yours,

Wm Peter Rickmam
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA # 75-896
DUP/Division File
HFD-610/PRickman
Endorsement:
HFD-617/Gregg Davis, Chief, RSB
HFD-617/MShimer, CSO, 1-1-03

V:\FIRMSAM\MUTUAL\LTRS&REV\75896.OTH

F/T by cll/12/31/02

10 DAY LETTER!

APPEARS THIS WAY
ON ORIGINAL

United Research Laboratories, Inc.
Mutual Pharmaceutical Company, Inc.

1100 Orthodox Street
Philadelphia, PA 19124

215-288-6500
www.urlmutual.com

NAE MHB 1-27-03

January 14, 2003

Office of Generic Drugs/CDER/FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

NC

AMENDMENT TO ANDA
(Chemistry)

Re: ANDA 75-896; Felodipine Extended-Release Tablets, 2.5 mg, 5 mg, and 10 mg

Dear Sir or Madam:

Mutual Pharmaceutical Company acknowledges receipt of your letter, dated January 2, 2003, which we received on January 8, 2003. That letter was a reminder that Mutual was overdue in providing a response to the March 27, 2002 "Not Approvable" letter pertaining to ANDA 75-896 for Felodipine Extended-Release Tablets, 2.5mg, 5mg, and 10mg.

Mutual has reviewed the issues put forth in your correspondence and we have concluded that the existing analytical method has been creating [redacted] which are addressed by a new analytical method. We are presently validating this new analytical method and we respectfully request additional time to prepare our response. We anticipate having this response ready for submission no later than four months from now, but hopefully sooner.

Mutual does not wish to withdraw this application. To the contrary, we are looking forward to satisfying your concerns and, thereby, clear the way for final ANDA approval.

A copy of this amendment is being provided to the FDA, Philadelphia District Office.

Please address any further questions or comments to my attention. Thank you.

Sincerely,

Robert Dettery

Robert Dettery
Vice President, Regulatory Affairs

Cc: K. Campbell, PHI-DO

United Research Laboratories, Inc.
Mutual Pharmaceutical Company, Inc.

1100 Orthodox Street
Philadelphia, PA 19124

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labeling review drafted 5/7/03 A. Vega

April 11, 2003

ORIG AMENDMENT
N/AF
FPL

Office of Generic Drugs/CDER/FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

AMENDMENT TO ANDA
(Labeling)

Re: ANDA 75-896; Felodipine Extended-Release Tablets, 2.5 mg, 5 mg, and 10 mg

Dear Sir or Madam:

Mutual Pharmaceutical Company wishes to amend our above-referenced abbreviated new drug application for the purpose of revising the proposed labeling. The revisions that have been made to the labeling were based on labeling changes approved May 22, 2002 for the reference listed drug, Plendil® extended-release tablets.

Enclosed please find twelve specimens of the final printed labeling for Mutual's Felodipine Extended-Release Tablets, 2.5 mg, 5 mg, and 10 mg. Also enclosed is a side-by-side comparison of our original insert and this revised insert with the changes noted.

Please note that Mutual acknowledges that there is a "Not Approvable" letter, dated March 27, 2002 that remains unanswered. As indicated in our New Correspondence, dated September 24, 2002 and our ANDA amendment, dated January 10, 2003, we intend to respond to that Not Approvable letter, probably within the next 4-6 weeks.

Please address any further questions or comments to my attention. Thank you.

Sincerely,

Robert Dettery
Vice President, Regulatory Affairs

RECEIVED
APR 14 2003
OGD / CDER

United Research Laboratories, Inc.
Mutual Pharmaceutical Company, Inc.

1100 Orthodox Street
Philadelphia, PA 19124

215-288-6500
www.urlmutual.com

May 13, 2003

NEW CORRESP

NC

Office of Generic Drugs/CDER/FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

TELEPHONE AMENDMENT
(Labeling)

Re: ANDA 75-896; Felodipine ER Tablets, 2.5 mg, 5 mg, and 10 mg

Dear Sir:

Mutual Pharmaceutical Company is submitting this Telephone Amendment to the above-referenced application for the purpose of committing to revise the storage condition statement on our labels and insert. This revision was requested by Ms. Lillie Golson in a telephone conversation on May 12, 2003.

Mutual commits to change the storage condition statement to read as follows:

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]

This revision will be made to our container labels and package insert prior to our initial commercial distribution of this product following ANDA approval.

Please feel free to contact me with any further questions or comments regarding this submission.

Sincerely,

Robert Dettery
Vice President, Regulatory Affairs

Cc: L. Golson, OGD

RECEIVED
MAY 14 2003
OGD / CDER

United Research Laboratories, Inc.
Mutual Pharmaceutical Company, Inc.

1100 Orthodox Street
Philadelphia, PA 19124

215-288-6500
www.urlmutual.com

GPAG AMENDMENT
N/Am

September 10, 2003

Office of Generic Drugs/CDER/FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

MINOR AMENDMENT
(Chemistry)

Re: ANDA 75-896; Felodipine Extended-Release Tablets, 2.5 mg, 5 mg, and 10 mg

Dear Sir or Madam:

On March 27, 2003 your Office corresponded with Mutual Pharmaceutical Company (Mutual) regarding the above-referenced application. In that correspondence, chemistry deficiencies were listed regarding [redacted] in the finished product. This letter represents Mutual's response to those chemistry deficiencies.

The March 27, 2003 letter stated the chemistry deficiencies as follows:

[redacted]

SEP 11 2003

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

9/10/2003 MUTUAL LETTER

A copy of this amendment is being provided to the FDA, Philadelphia District Office.

Please address any further questions or comments to my attention. Thank you.

Sincerely,

Robert Dettery
Vice President, Regulatory Affairs

Cc: K. Campbell, PHI-DO

United Research Laboratories, Inc.
Mutual Pharmaceutical Company, Inc.

1100 Orthodox Street
Philadelphia, PA 19124

215-288-6500
www.urlmutual.com

November 26, 2003

Office of Generic Drugs/CDER/FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

NEW CORRESP
NC

NEW CORRESPONDENCE

Re: ANDA 75-896; Felodipine Extended-Release Tablets, 2.5 mg, 5 mg, and 10 mg

Dear Sir or Madam:

This New Correspondence is submitted in response to a telephone inquiry by Mr. Stanley Shepperson, Project Manager, regarding the above-referenced application. Specifically, Mr. Shepperson inquired about the status of the patent infringement lawsuit between Mutual Pharmaceutical Company and AstraZeneca, the holder of U.S. Patent 4,803,081.

Please be advised that On November 12, 2003, U.S. District Judge Michael M. Baylson entered a Final Judgement in favor of AstraZeneca and against Mutual Pharmaceutical. In addition, the Court ordered that ANDA 75-896 may not be approved until the '081 patent expires. I am enclosing a copy of the District Court's Memorandum and Order.

Mutual has appealed this decision and we anticipate a favorable resolution within the next few months. Until then, the Court's Order prevents Mutual from receiving Final Approval on our ANDA 75-896 and a Tentative Approval may be the only possibility at this time.

Please feel free to contact me with any questions or comments about this application.

Sincerely,

Robert Dettery
Vice President, Regulatory Affairs

RECEIVED
NOV 28 2003
OGD/CDER

United Research Laboratories, Inc.
Mutual Pharmaceutical Company, Inc.

1100 Orthodox Street
Philadelphia, PA 19124

215-288-6500
www.urlmutual.com

ORIG AMENDMENT

XP

ORIG AMENDMENT
N/A

October 1, 2004

Office of Generic Drugs/CDER/FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

MINOR AMENDMENT -
FINAL APPROVAL REQUESTED

Re: ANDA 75-896; Felodipine Extended-Release Tablets 2.5 mg, 5 mg, and 10 mg

Dear Sir or Madam:

On June 6, 2000 Mutual Pharmaceutical Company (Mutual) submitted the above-referenced abbreviated new drug application for Felodipine Extended-Release Tablets, 2.5 mg, 5 mg, and 10 mg. The reference listed drug that was referenced in this application was Plendil Tablets by AstraZeneca Pharmaceuticals LP. Mutual's application contained a patent certification under Section 505(j)(2)(A)(vii)(IV) of the Act, stating non-infringement to U.S. Patent No. 4,803,081 (the '081 patent) that was listed in the Orange Book for Plendil Tablets.

On September 18, 2000 litigation was brought against Mutual in the U.S. District Court for the Eastern District of Pennsylvania involving a challenge to the '081 patent (AstraZeneca AB, Aktiebolaget Hassle, KBI-E Inc., KBI Inc., and AstraZeneca LP v. Mutual Pharmaceutical Company, Inc., Civil Action No. 00-CV-4731). Mutual submitted a Patent Amendment to ANDA 75-896 on November 17, 2000 notifying your office that this litigation had ensued. Mutual also notified the agency that on November 12, 2003 U.S. District Judge Michael M. Baylson entered a Final Judgement in favor of AstraZeneca and against Mutual, based on infringement of the '081 patent.

On February 6, 2004 the Office of Generic Drugs informed Mutual that our ANDA 75-896 had received **tentative approval**, but final approval could not be granted pending a favorable appellate court decision or the expiration of the '081 patent. Furthermore, Mutual was instructed to reactivate our application 90 days prior to the date that we believe our ANDA will be eligible for final approval by submitting a minor amendment that included an explanation of why we have that belief and identifying any changes in the conditions under which the ANDA was tentatively approved.

Mutual is very pleased to report that on September 30, 2004 the U.S. Court of Appeals for the Federal Circuit overturned the District Court decision and ruled non-infringement by Mutual of the '081 patent. A copy of the Judgement by the Court of Appeals is enclosed as Exhibit 1. As a result of this ruling, Mutual believes our ANDA 75-896 will be eligible for final approval within 90 days.

Regarding the conditions under which ANDA 75-896 received tentative approval, Mutual hereby states that there have been no significant changes in the chemistry, manufacturing, and controls by which Felodipine Extended-Release Tablets will be manufactured, as compared to that which was tentatively approved. In addition, there have been no changes to the labeling other than what has been previously discussed with the Office of Generic Drugs during the review of this application.

We are looking forward to receiving our final approval for ANDA 75-896. Please contact me directly at 215-807-1044 if you require any further information.

Sincerely,

Robert Dettery
Vice President, Regulatory Affairs

Encl. (1)

APPEARS THIS WAY
ON ORIGINAL

United Research Laboratories, Inc.
Mutual Pharmaceutical Company, Inc.
1100 Orthodox Street
Philadelphia, PA 19124
215-288-6500
www.urlmutual.com

Noted NAI
A. Vegga 10/7/04

October 4, 2004

Office of Generic Drugs/CDER/FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

NEW CORRESPONDENCE

MC

Re: ANDA 75-896; Felodipine Extended-Release Tablets 2.5mg, 5mg, and 10mg

Dear Sir or Madam:

On October 1, 2004 Mutual Pharmaceutical Company, Inc. submitted a Minor Amendment – Final Approval Requested to the above-referenced abbreviated new drug application. In that submission, I stated that there were no labeling changes other than those previously discussed with OGD as part of the ANDA review. I now wish to report that my statement regarding the labeling was inaccurate.

In June 2004, the labeling for the Reference Listed Drug, Plendil® ER Tablets, was revised. Mutual has revised our insert accordingly in order to match the RLD's labeling. In addition, Mutual has made minor style changes to our container labels. These changes will be submitted to our application under separate cover as a labeling amendment.

Please feel free to contact me if you have any questions.

Sincerely,

Robert Dettery/s/s

Robert Dettery
Vice-President, Regulatory Affairs

United Research Laboratories, Inc.
Mutual Pharmaceutical Company, Inc.
1100 Orthodox Street
Philadelphia, PA 19124
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Safety review
drafted 10/18/04
A. Vezza

October 5, 2004

Office of Generic Drugs/CDER/FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Amendment to ANDA
(Labeling)
ORIG AMENDMENT
N/A-F

Re: ANDA 75-896; Felodipine Extended-Release Tablets, 2.5mg, 5mg and 10mg

Dear Sir or Madam:

Mutual Pharmaceutical Company, Inc. wishes to amend our above-referenced abbreviated new drug application for the purpose of revising the proposed labeling. Based on a review of CDER's website, June 2004, the insert labeling for the Reference Listed Drug, Plendil ER Tablets, was revised. Mutual has revised our insert labeling accordingly. In addition, Mutual has made minor style changes to our container labels.

Enclosed please find twelve specimens of the final printed labeling for Mutual's Felodipine Extended-Release Tablets, 2.5mg, 5mg, and 10mg. For ease of review, Mutual has included annotated side-by-side comparisons of the RLD's current insert with Mutual's proposed insert, Mutual's current insert with Mutual's proposed insert and Mutual's current container label with the proposed container label.

Please address any questions or comments to my attention. Thank you.

Sincerely,

Sherry Schultz
Manager, Regulatory Affairs
Mutual Pharmaceutical Company, Inc.

RECEIVED
OCT 06 2004
OGD/CDER

RECEIVED
OCT 08 2004
OGD/CDER

United Research Laboratories, Inc.
Mutual Pharmaceutical Company, Inc.
1100 Orthodox Street
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October 29, 2004

NIMC

Office of Generic Drugs/CDER/FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

NEW CORRESPONDENCE

Re: ANDA 75-896; Felodipine Extended-Release Tablets, 2.5 mg, 5 mg, and 10 mg

Dear Sir or Madam:

On October 1, 2004 Mutual Pharmaceutical Company submitted a Minor Amendment – Final Approval Requested to the above-referenced application. In that submission, Mutual stated that the U.S. Court of Appeals for the Federal Circuit overturned the District Court decision and ruled non-infringement by Mutual of the '081 patent.

Mutual has now received the judgement from the District Court lifting the order that prevented the approval of our ANDA 75-896. A copy of this judgement accompanies this New Correspondence.

Mutual respectfully requests the Office of Generic Drugs to issue Final Approval our ANDA 75-896 as soon as possible.

Sincerely,

Robert Dettery /s/s

Robert Dettery
Vice President, Regulatory Affairs