

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

Approval Package for:

APPLICATION NUMBER:

75-128

Generic Name: Nifedipine Extended-release Tablets,
30mg

Sponsor: Elan Pharmaceutical Research Corporation

Approval Date: March 10, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:
75-128**

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**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75-128

APPROVAL LETTER

MAR 10 2000

ANDA 75-128

Elan Pharmaceutical Research Corporation
Attention: Roger Wayne Wiley
1300 Gould Drive
Gainesville, GA 30504

Dear Sir:

This is in reference to your abbreviated new drug application dated April 30, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Nifedipine Extended-release Tablets, 30 mg.

Reference is also made to your amendments dated August 24 and December 3, 1999 and January 6, 2000 and February 4, 2000.

The listed drug product referenced in your application is subject to periods of patent protection which expire June 8, 2008 and November 23, 2010, (Patent Nos. 4,892,741 and 5,264,446). Your application contains a patent certification under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, or sale of nifedipine will not infringe on the patent or that the patent is otherwise invalid. You further informed the Agency that Bayer Corporation initiated a patent infringement suit against you in United States District Court for the Northern District of Georgia [Gainesville Division] (Bayer AG and Bayer Corporation v. Elan Pharmaceutical Research Corporation), Civil Action No. 2:97-CV-0143-WCO).

The Agency also recognizes that the 30-month period identified in Section 505(j)(5)(B)(iii) of the Act, during which time FDA was precluded from approving your application, has expired.

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 Nifedipine Extended-release Tablets, 30 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Adalat® CC Extended-release Tablets of Bayer Corporation). Your dissolution testing should be incorporated into the stability and quality control program using the same

method proposed in your application. The "interim" dissolution test and tolerances are:

The dissolution testing should be conducted in _____ using _____ The test product should meet the following tentative specifications:

<u>Time Points</u>	<u>% Released</u>
1 hr	NMT _____
2 hr	_____
4 hr	_____
10 hr	NLT _____

The "interim" dissolution test and tolerances should be finalized by submitting dissolution data for the first three production size batches in a supplemental application. A "Special Supplement - Changes Being Effected" (zero) should be submitted when there are no revisions to the interim specifications or when the final specifications are tighter than the interim specifications. In all other instances a Prior Approval supplement should be submitted.

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.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

Page 3

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

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

3/10/00

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75-128

**TENTATIVE APPROVAL
LETTER**

MAY 28 1999

Elan Pharmaceutical Research Corporation
Attention: Roger Wayne Wiley
1300 Gould Drive
Gainesville, GA 30504

Dear Sir:

This is in reference to your abbreviated new drug application dated April 30, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Nifedipine Extended-release Tablets, 30 mg.

Reference is also made to your amendments dated July 30, 1997; and October 23, 1998 and April 12, 1999.

We have completed the review of this abbreviated application and have concluded that, based upon the information you have presented to date, the drug product is safe and effective for use as recommended in the submitted labeling. 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), and 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 referenced in your application, Adalat CC Extended-release Tablets of Bayer Corporation, is subject to periods of patent protection which expire on June 8, 2008, (U.S. Patent No. 4,892,741) and November 23, 2010, (U.S. Patent No. 5,264,446). Your application contains a patent certification under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, or sale of this drug product will not infringe on either of the patents. Section 505(j)(5)(B)(iii) of the Act provides that approval of an abbreviated application shall be made effective immediately unless an action for patent infringement is brought before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(I) is received by both the referenced new drug application (NDA) and

patent holders. You have notified the Agency that Elan Pharmaceutical Research Corporation (Elan) has complied with the requirements of Section 505(j)(2)(B) of the Act and that the patent and NDA holders initiated a patent infringement suit against Elan in the United States District Court for the Northern District of Georgia [Gainesville Division] (Bayer AG and Bayer Corporation v. Elan Pharmaceutical Research Corporation) Civil Action No. 2:97-CV-0143-WCO). Therefore, final approval cannot be granted until:

1. a. the expiration of the 30-month period provided for in section 505(j)(5)(B)(iii) since the date of receipt of the 45-day notice required under section 505(j)(2)(B)(i), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or,
 - b. the date of court decision [505(j)(5)(B)(iii)(I), (II), or (III)], which has been interpreted by the Agency to mean the date of the final order or judgement of that court from which no appeal can be or has been taken, or,
 - c. the patents have expired, and
2. The Agency is assured there is no new information that would affect whether final approval should be granted.

Because the Agency is granting a tentative approval for this application, please submit an amendment at least 60-days but not more than 90-days prior to the date you believe your application will be eligible for final approval. This amendment should be designated clearly in your cover letter as a MINOR amendment and it should identify the circumstances which have occurred that affect the effective date of final approval. The amendment must also provide:

1. a copy of a final order or judgement from which no appeal may be taken (which might not be the one from the district court), 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, and
2. a. updated information related to final-printed labeling or chemistry, manufacturing and controls data, or any other change in the conditions outlined in this abbreviated application, or

- b. a statement that no such changes have been made to the application since the date of tentative approval.

Any changes in the conditions outlined in this abbreviated application and the status of the manufacturing and testing facilities' compliance with current good manufacturing procedures are subject to Agency review before final approval of the application will be made.

In addition to, or instead of, the amendments referred to above; the Agency may, at any time prior to the final date of approval, request that you submit amendments containing the information requested above. Failure to submit these amendments may result in rescission of this tentative approval determination, or delay in issuance of the final approval letter.

The drug product that is the subject of this abbreviated application 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 before the effective final approval date is prohibited under section 501 of the Act. Also, until the Agency issues the final approval letter, this drug product will not be listed in the Agency's "Approved Drug Products with Therapeutic Equivalence Evaluations" list, commonly referred to as the "Orange Book".

The amendment should be designated as a MINOR AMENDMENT in your cover letter. Before you submit the amendment, please contact Kassandra Sherrod, Project Manager, at (301) 827-5849, for further instructions.

Sincerely yours,

151 9/26/99

Roger L. Williams, M.D.
Deputy Center Director for
Pharmaceutical Science
Center for Drug Evaluation and Research

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75-128

FINAL PRINTED LABELING(S)

APPROVED
MAY 10 2000

NDC 0093-1021-01

NIFEDIPINE
Extended-release
Tablets
30 mg

30 mg

Each tablet contains:
Nifedipine

R only

TEVA

LOT NO.

EXP.

Read accompanying directions carefully.

Usual dosage: See package insert

Dispense in light, light-resistant containers as defined in USP¹.

Store below 30°C (86°F).

Protect from light and moisture.

Tablets should be swallowed whole, not bitten or divided.
KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

ISS. 11/99

Manufactured By:

Ean Pharm. Ltd.,

Antony,

SICL Co Westmash, Ireland

Manufactured For:

TEVA PHARMACEUTICALS USA

Sellersville, PA 19380

L1340

N 0093-1021-01 4



000149

10 2007

APPROVED

NIFEDIPINE
Extended-release
Tablets 30 mg

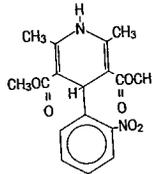
Rx only

IN/LF/108
Iss. 11/99

1021

DESCRIPTION

Nifedipine Extended-release Tablets is an extended-release tablet dosage form of the calcium channel blocker nifedipine. Nifedipine is 3,5-pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-dimethyl ester, $C_{17}H_{19}NO_6$, and has the structural formula:



Nifedipine is a yellow crystalline substance, practically insoluble in water but soluble in ethanol. It has a molecular weight of 346.3. Nifedipine Extended-release Tablets contain 30 mg of nifedipine for once-a-day oral administration.

Each tablet also contains the following inactive ingredients: hydroxypropyl methylcellulose, microcrystalline cellulose, colloidal silicon dioxide, and magnesium stearate. The inert ingredients in the film coating are: hydroxypropyl methylcellulose, polyethylene glycol, iron oxide and titanium dioxide. The ingredients of the printing ink are: dehydrated alcohol, shellac, iron oxide black, deionized water, 2-ethoxyethanol, alcohol SDA, lecithin, medicinal antifoam A.

CLINICAL PHARMACOLOGY

Nifedipine is a calcium ion influx inhibitor (slow-channel blocker or calcium ion antagonist) which inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. The contractile processes of vascular smooth muscle and cardiac muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Nifedipine selectively inhibits calcium ion influx across the cell membrane of vascular smooth muscle and cardiac muscle without altering serum calcium concentrations.

Mechanism of Action: The mechanism by which nifedipine reduces arterial blood pressure involves peripheral arterial vasodilatation and consequently, a reduction in peripheral vascular resistance. The increased peripheral vascular resistance that is an underlying cause of hypertension results from an increase in active tension in the vascular smooth muscle. Studies have demonstrated that the increase in active tension reflects an increase in cytosolic free calcium. Nifedipine is a peripheral arterial vasodilator which acts directly on voltage-dependent calcium channels in vascular smooth muscle. The inhibition of calcium influx through these channels results in an inhibition of calcium influx through these channels. Stores of intracellular calcium in vascular smooth muscle are limited and thus dependent upon the influx of extracellular calcium for contrac-

Following inactive ingredients: hydroxypropyl methylcellulose, microcrystalline cellulose, colloidal silicon dioxide, and magnesium stearate. The inert ingredients in the film coating are: hydroxypropyl methylcellulose, polyethylene glycol, iron oxide and titanium dioxide. The ingredients of the printing ink are: dehydrated alcohol, shellac, iron oxide black, deionized water, 2 ethoxyethanol, alcohol SD4, lecithin, medicinal antifloat A.

CLINICAL PHARMACOLOGY

Nifedipine is a calcium ion influx inhibitor (slow-channel blocker or calcium ion antagonist) which inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. The contractile processes of vascular smooth muscle and cardiac muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Nifedipine selectively inhibits calcium ion influx across the cell membrane of vascular smooth muscle and cardiac muscle without altering serum calcium concentrations.

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Nifedipine is a peripheral arterial vasodilator which acts directly on vascular smooth muscle. The binding of nifedipine to voltage-dependent calcium channels in vascular smooth muscle results in an inhibition of calcium influx through these channels. Stores of intracellular calcium in vascular smooth muscle are limited and thus dependent upon the influx of extracellular calcium for contraction to occur. The reduction in calcium influx by nifedipine causes arterial vasodilatation and decreased peripheral vascular resistance which results in reduced arterial blood pressure.

Pharmacokinetics and Metabolism

Nifedipine is completely absorbed after oral administration. The bioavailability of nifedipine as Nifedipine Extended-release Tablets relative to immediate-release nifedipine is in the range of 84% - 89%. After ingestion of Nifedipine Extended-release Tablets under fasting conditions, plasma concentrations peak at about 2.5-5 hours with a second small peak or shoulder evident at approximately 6-12 hours post dose. The elimination half-life of nifedipine administered as Nifedipine Extended-release Tablets is approximately 7 hours in contrast to the known 2 hour elimination half-life of nifedipine administered as an immediate-release capsule.

When Nifedipine Extended-release Tablets are administered as multiples of 30 mg tablets over a dose range of 30 mg to 90 mg, the area under the curve (AUC) is dose proportional; however, the peak plasma concentration for the 90 mg dose given as 3 x 30 mg is 29% greater than predicted from the 30 mg and 60 mg doses.

Two 30 mg Nifedipine Extended-release Tablets may be interchanged with a 60 mg Nifedipine Extended-release tablet. Three 30 mg Nifedipine Extended-release Tablets, however, result in substantially higher C_{max} values than those after a single 90 mg Nifedipine Extended-release tablet. Three 30 mg tablets should, therefore, not be considered interchangeable with a 90 mg tablet.

Once daily dosing of Nifedipine Extended-release Tablets under fasting conditions results in decreased fluctuations in the plasma concentration of nifedipine when compared to i.i.d. dosing with immediate-release nifedipine capsules. The mean peak plasma concentration of nifedipine following a 90 mg nifedipine extended-release tablet, administered under fasting conditions, is approximately 115 ng/mL. When Nifedipine Extended-release Tablets are given immediately after a high fat meal in healthy volunteers, there is an average increase of 60% in the peak plasma nifedipine concentration, a prolongation in the time to peak concentration, but no significant change in the AUC. Plasma concentrations of nifedipine when Nifedipine Extended-release Tablets are taken after a fatty meal result in slightly lower peaks compared to the same daily dose of the immediate-release formulation administered in three divided doses. This may be, in part, because Nifedipine Extended-release Tablets are less bioavailable than the immediate-release formulation.

Nifedipine is extensively metabolized to highly water soluble, inactive metabolites accounting for 60% to 80% of the dose excreted in the urine. Only traces (less than

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Nifedipine is extensively metabolized to highly water soluble, inactive metabolites accounting for 60% to 80% of the dose excreted in the urine. Only traces (less than 0.1% of the dose) of the unchanged form can be detected in the urine. The remainder is excreted in the feces in metabolized form, most likely as a result of biliary excretion.

No studies have been performed with Nifedipine Extended-release Tablets in patients with renal failure; however, significant alterations in the pharmacokinetics of nifedipine immediate-release capsules have not been reported in patients undergoing hemodialysis or chronic ambulatory peritoneal dialysis. Since the absorption of nifedipine from Nifedipine Extended-release Tablets could be modified by renal disease, caution should be exercised in treating such patients.

Because hepatic biotransformation is the predominant route for the disposition of nifedipine, its pharmacokinetics may be altered in patients with chronic liver disease. Nifedipine Extended-release Tablets have not been studied in patients with hepatic disease; however, in patients with hepatic impairment (liver cirrhosis) nifedipine has a longer elimination half-life and higher bioavailability than in healthy volunteers.

The degree of protein binding of nifedipine is high (92%-98%). Protein binding may be greatly reduced in patients with renal or hepatic impairment.

After administration of Nifedipine Extended-release Tablets to healthy elderly men and women (age > 60 years), the mean C_{max} is 36% higher and the average plasma concentration is 70% greater than in younger patients.

Clinical Studies: Nifedipine Extended-release Tablets produced dose-related decreases in systolic and diastolic blood pressure as demonstrated in two double-blind, randomized, placebo-controlled trials in which over 350 patients were treated with Nifedipine Extended-release Tablets 30, 60 or 90 mg once daily for 6 weeks. In the first study, Nifedipine Extended-release Tablets were given as monotherapy and in the second study, Nifedipine Extended-release Tablets were added to a beta-blocker in patients not controlled on a beta-blocker alone. The mean trough (24 hours post-dose) blood pressure results from these studies are shown below:

Nifedipine ER
DOSE
30 mg
60 mg
90 mg

in younger patients.
Clinical Studies: Nifedipine Extended-release Tablets produced dose-related decreases in systolic and diastolic blood pressure as demonstrated in two double-blind, randomized, placebo-controlled trials in which over 350 patients were treated with Nifedipine Extended-release Tablets 30, 60 or 90 mg once daily for 6 weeks. In the first study, Nifedipine Extended-release Tablets were given as monotherapy and in the second study, Nifedipine Extended-release Tablets were added to a beta-blocker in patients not controlled on a beta-blocker alone. The mean trough (24 hours post-dose) blood pressure results from these studies are shown below:

		MEAN REDUCTIONS IN TROUGH SUPINE BLOOD PRESSURE (mmHg) SYSTOLIC/DIASTOLIC	
		STUDY 1	
Nifedipine Extended-release Tablets	DISEASE	MEAN TROUGH REDUCTION*	DISEASE
30 mg	60	5.3/2.9	30 mg
60 mg	57	8.0/4.1	60 mg
90 mg	55	12.5/6.1	90 mg
		STUDY 2	
Nifedipine Extended-release Tablets	DISEASE	MEAN TROUGH REDUCTION*	DISEASE
30 mg	58	7.6/3.8	30 mg
60 mg	63	10.1/5.3	60 mg
90 mg	62	10.2/5.8	90 mg

* Trough response subtracted.

The trough/peak ratios estimated from 24 hour blood pressure monitoring ranged from 41%-78% for diastolic and 46%-91% for systolic blood pressure.

Hemodynamics: Like other slow-channel blockers, nifedipine exerts a negative inotropic effect on isolated myocardial tissue. This is rarely, if ever, seen in intact animals or man, probably because of reflex responses to its vasodilating effects. In man, nifedipine decreases peripheral vascular resistance which leads to a fall in systolic and diastolic pressures, usually minimal in normotensive volunteers (less than 5-10 mm Hg-systolic), but sometimes larger. With Nifedipine Extended-release Tablets, these decreases in blood pressure are not accompanied by any significant change in heart rate. Hemodynamic studies of the immediate-release nifedipine formulation in patients with normal ventricular function have generally found a small increase in cardiac index without major effects on ejection fraction, left ventricular end-diastolic pressure (LVEDP) or volume (LVEDV). In patients with impaired ventricular function, most acute studies have shown some increase in ejection fraction and reduction in left ventricular filling pressure.

Electrophysiologic Effects: Although, like other members of its class, nifedipine causes a slight depression of sinoatrial node function and atrioventricular conduction in isolated myocardial preparations, such effects have not been seen in studies in intact animals or in man. In formal electrophysiologic studies, predominantly in

MEAN TROUGH
REDUCTION
1/8/78
10/2/83

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INDICATIONS AND USAGE

Nifedipine Extended-release Tablets are indicated for the treatment of hypertension. They may be used alone or in combination with other antihypertensive agents.

CONTRAINDICATIONS

Known hypersensitivity to nifedipine.

WARNINGS

Excessive Hypotension: Although in most patients the hypotensive effect of nifedipine is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients using concomitant beta-blockers. Severe hypotension and/or increased fluid volume requirements have been reported in patients who received immediate-release capsules together with a beta-blocking agent and who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of nifedipine and a beta-blocker, but the possibility that it may occur with nifedipine alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In nifedipine-treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for nifedipine to be washed out of the body prior to surgery.

Increased Angina and/or Myocardial Infarction:

Rarely, patients, particularly those who have severe obstructive coronary artery disease, have developed well documented increased frequency, duration and/or severity of angina or acute myocardial infarction upon starting nifedipine or at the time of dosage increase. The mechanism of this effect is not established.

Beta-Blocker Withdrawal: When discontinuing a beta-blocker it is important to taper its dose, if possible, rather than stopping abruptly before beginning nifedipine. Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina probably related to

diate-release nifedipine formulations in patients with normal ventricular function have generally found a small increase in cardiac index without major effects on ejection fraction, left ventricular end-diastolic pressure (LVEDP) or volume. In patients with impaired ventricular function, most acute studies have shown some increase in ejection fraction and reduction in left ventricular filling pressure.

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Beta-Blocker Withdrawal: When discontinuing a beta-blocker it is important to taper its dose, if possible, rather than stopping abruptly before beginning nifedipine. Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of nifedipine treatment will not prevent this occurrence and on occasion has been reported to increase it.

Congestive Heart Failure: Rarely, patients (usually while receiving a beta-blocker) have developed heart failure after beginning nifedipine. Patients with light aortic stenosis may be at greater risk for such an event, as the unloading effect of nifedipine would be expected to be of less benefit to these patients, owing to their fixed impedance to flow across the aortic valve.

PRECAUTIONS

General - Hypotension: Because nifedipine decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of Nifedipine Extended-release Tablets is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure (See WARNINGS).

Peripheral Edema: Mild to moderate peripheral edema occurs in a dose-dependent manner with Nifedipine Extended-release Tablets. The placebo subtracted rate is approximately 8% of 30 mg daily, 12% of 60 mg and 19% of 90 mg daily. This edema is a localized phenomenon, thought to be associated with vasodilation of dependent arterioles and small blood vessels and not due to left ventricular dysfunction or generalized fluid retention. With patients whose hypertension is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Information for Patients: Nifedipine Extended-release Tablets should be swallowed whole and taken on an empty stomach. It should not be administered with food. Do not chew, divide or crush tablets.

Laboratory Tests: Rare, usually transient, but occasionally significant elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted. The relationship to nifedipine therapy is uncertain in most cases, but probable in some. These laboratory abnormalities have rarely been associated with clinical symptoms; however, cholestasis with or without jaundice has been reported. A small increase (<5%) in mean alkaline phosphatase was noted in patients treated with Nifedipine Extended-release Tablets. This was an isolated finding and it rarely resulted in values which fell outside the normal range. Rare instances of allergic hepatitis have been reported with nifedipine treatment. In controlled studies, Nifedipine Extended-release Tablets did not adversely affect serum uric acid, glucose, cholesterol or potassium.

Nifedipine, like other calcium channel blockers, decreases platelet aggregation *in vitro*. Limited clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregation and increase in bleeding time in some nifedipine patients. This is thought to be a function of inhibition of calcium transport across the platelet membrane. No clinical significance for these findings has been demonstrated. Positive direct Coombs' test with or without hemolytic anemia has been reported but a causal relationship between nifedipine administration and positivity of this laboratory test, including hemolysis, could not be determined.

Although nifedipine has been used safely in patients with renal dysfunction and has been reported to exert a beneficial effect in certain cases, rare reversible elevations in BUN and serum creatinine have been reported in patients with pre-existing chronic renal insufficiency. The relationship to nifedipine therapy is uncertain in most cases but probable in some.

Drug Interactions: Beta-adrenergic blocking agents: (See WARNINGS). Nifedipine Extended-release Tablets were well tolerated when administered in combination with a beta blocker in 187 hypertensive patients in a placebo-controlled clinical trial. However, there have been occasional literature reports suggesting that the combination of nifedipine and beta-adrenergic blocking drugs may increase the likelihood of congestive heart failure, severe hypotension, or exacerbation of angina in patients with cardiovascular disease.

Digitalis: Since there have been isolated reports of patients with elevated digoxin levels, and there is a possible interaction between digoxin and Nifedipine Extended-release Tablets, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing Nifedipine Extended-release Tablets to avoid possible over- or under-digitalization.

Coumarin Anticoagulants: There have been rare reports of increased prothrombin time in patients taking coumarin anticoagulants to whom nifedipine was administered. However, the relationship to nifedipine therapy is uncertain.

Quinidine: There have been rare reports of an interaction between quinidine and nifedipine (with a decreased plasma level of quinidine).

Cimetidine: Both the peak plasma level of nifedipine and the AUC may increase in the presence of cimetidine. Ranitidine produces smaller non-significant increases. This effect of cimetidine may be mediated by its known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of nifedipine. If nifedipine therapy is initiated in a patient currently receiving cimetidine, cautious titration is advised.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Nifedipine was administered orally to rats for

platelet membrane. No clinical significance for these findings has been demonstrated. Positive direct Coombs' test with or without hemolytic anemia has been reported but a causal relationship between nifedipine administration and positivity of this laboratory test, including hemolysis, could not be determined.

Although nifedipine has been used safely in patients with renal dysfunction and has been reported to exert a beneficial effect in certain cases, rare reversible elevations in BUN and serum creatinine have been reported in patients with pre-existing chronic renal insufficiency. The relationship to nifedipine therapy is uncertain in most cases but probable in some.

Drug Interactions: Beta-adrenergic blocking agents: (See WARNINGS). Nifedipine Extended-release Tablets were well tolerated when administered in combination with a beta blocker in 187 hypertensive patients in a placebo-controlled clinical trial. However, there have been occasional literature reports suggesting that the combination of nifedipine and beta-adrenergic blocking drugs may increase the likelihood of congestive heart failure cases. The relationship to combination of angina in patients with cardiovascular disease.

Digitalis: Since there have been isolated reports of patients with elevated digoxin levels, and there is a possible interaction between digoxin and Nifedipine Extended-release Tablets, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing Nifedipine Extended-release Tablets to avoid possible over- or under-digitalization.

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Carcinogenesis, Mutagenesis, Impairment of Fertility: Nifedipine was administered orally to rats for two years and was not shown to be carcinogenic. When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose. *In vivo* mutagenicity studies were negative.

Pregnancy: Pregnancy Category C. In rodents, rabbits and monkeys, nifedipine has been shown to have a variety of embryotoxic, placental toxic and fetotoxic effects, including stunted fetuses (rats, mice and rabbits), digital anomalies (rats and rabbits), rib deformities (mice), cleft palate (mice), small placentas and underdeveloped chorionic villi (monkeys), embryonic and fetal deaths (rats, mice and rabbits), prolonged pregnancy (rats; not evaluated in other species), and decreased neonatal survival (rats; not evaluated in other species). On a mg/kg or mg/m² basis, some of the doses associated with these various effects are higher than the maximum recommended human dose and some are lower, but all are within an order of magnitude of it. The digital anomalies seen in nifedipine-exposed rabbit pups are strikingly similar to those seen in pups exposed to phenytoin, and these are in turn similar to the pharyngeal deformities that are the most common malformation seen in human children with *in utero* exposure to phenytoin.

There are no adequate and well-controlled studies in pregnant women. Nifedipine Extended-release Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Nifedipine is excreted in human milk. Therefore, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

ADVERSE REACTIONS
The incidence of adverse events during treatment with Nifedipine Extended-release Tablets in doses up to 80 mg daily were derived from multi-center placebo-controlled clinical trials in 370 hypertensive patients. Atenolol 50 mg once daily was used concomitantly in 187 of the 370 patients on Nifedipine Extended-release Tablets and in 64 of the 126 patients on placebo. All adverse events reported during Nifedipine Extended-release Tablets therapy were tabulated inde-

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ADVERSE REACTIONS
The incidence of adverse events during treatment with Nifedipine Extended-release Tablets in doses up to 90 mg daily were derived from multi-center placebo-controlled clinical trials in 370 hypertensive patients. Atenolol 50 mg once daily was used concomitantly in 187 of the 370 patients on Nifedipine Extended-release Tablets and in 64 of the 126 patients on placebo. All adverse events reported during Nifedipine Extended-release Tablets therapy were tabulated independently of their causal relationship to medication.

The most common adverse event reported with Nifedipine Extended-release Tablets was peripheral edema. This was dose related and the frequency was 18% on Nifedipine Extended-release Tablets 30 mg daily, 22% on Nifedipine Extended-release Tablets 60 mg daily and 29% on Nifedipine Extended-release Tablets 90 mg daily versus 10% on placebo. Other common adverse events reported in the above placebo-controlled trials include:

Adverse Event	Nifedipine Extended-release Tablets (%) (n=370)	PLACEBO (%) (n=126)
Headache	19	13
Flushing/heat sensation	4	0
Dizziness	4	2
Ringswelling	2	4
Constipation	2	0

Where the frequency of adverse events with Nifedipine Extended-release Tablets and placebo is similar, causal relationship cannot be established.

The following adverse events were reported with an incidence of 3% or less in daily doses up to 90 mg:

- Body as a Whole/Systemic:** chest pain, leg pain
Central Nervous System: paresthesia, vertigo
Dermatologic: rash
Gastrointestinal: constipation
Musculoskeletal: leg cramps
Respiratory: epistaxis, rhinitis
Urogenital: impotence, urinary frequency

Other adverse events reported with an incidence of less than 1% were:

- Body as a Whole/Systemic:** cellulitis, chills, facial edema, neck pain, pelvic pain, pain
Cardiovascular: atrial fibrillation, bradycardia, cardiac arrest, extrasystole, hypotension, palpitations, phlebitis, postural hypotension, tachycardia, cutaneous angiodoses
Central Nervous System: anxiety, confusion, decreased libido, depression, hypertonia, insomnia, somnolence
Dermatologic: pruritus, sweating
Gastrointestinal: abdominal pain, diarrhea, dry mouth, dyspepsia, esophagitis, flatulence, gastrointestinal hemorrhage, vomiting
Hematologic: lymphadenopathy
Metabolic: gout, weight loss
Musculoskeletal: arthralgia, arthritis, myalgia

	Extended-release Tablets (310)	PLACEOB (n=126)
19	13	13
18	0	0
17	2	2
16	4	4
15	4	4
14	4	4
13	2	2
12	1	1
11	0	0
10	0	0
9	0	0
8	0	0
7	0	0
6	0	0
5	0	0
4	0	0
3	0	0
2	0	0
1	0	0

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Hematologic: lymphadenopathy

Metabolic: gout, weight loss

Musculoskeletal: arthralgia, arthritis, myalgia

Respiratory: dyspnea, increased cough, rales, pharyngitis

Special Senses: abnormal vision, amblyopia, conjunctivitis, diplopia, tinnitus

Urogenital/Reproductive: kidney calculus, nocturia, breast engorgement

The following adverse events have been reported rarely in patients given nifedipine in other formulations:

allergic hepatitis, alopecia, anemia, arthritis with ANA (+), depression, arthralgia, fever, gingival hyperplasia, gynecomastia, leukopenia, mood changes, muscle cramps, nervousness, paranoid syndrome, purpura, shakiness, sleep disturbances, syncope, taste perversion, thrombocytopenia, transient blindness of the peak plasma level, tremor and urticaria.

OVERDOSAGE

Experience with nifedipine overdosage is limited. Generally, overdosage with nifedipine leading to pronounced hypotension calls for active cardiovascular support including monitoring of cardiovascular and respiratory function, elevation of extremities, judicious use of calcium infusion, pressor agents and fluids. Clearance of nifedipine would be expected to be prolonged in patients with impaired liver function. Since nifedipine is highly protein bound, dialysis is not likely to be of any benefit; however, plasmapheresis may be beneficial.

There has been one reported case of massive overdosage with tablets of another extended-release formulation of nifedipine. The main effects of ingestion of approximately 4800 mg of nifedipine in a young man attempting suicide as a result of cocaine-induced depression was initial dizziness, palpitations, flushing, and nervousness. Within several hours of ingestion, nausea, vomiting, and generalized edema developed. No significant hypotension was apparent at presentation, 18 hours post ingestion. Blood chemistry abnormalities consisted of a mild, transient elevation of serum creatinine, and modest elevations of LDH and CPK, but normal SGOT. Vital signs remained stable, no electrocardiographic abnormalities were noted and renal function returned to normal within 24 to 48 hours with routine supportive measures alone. No prolonged sequelae were observed.

The effect of a single 900 mg ingestion of nifedipine capsules in a depressed original patient on tricyclic antidepressants was loss of consciousness within 30 minutes of ingestion, and profound hypotension, which responded to calcium infusion, pressor agents, and fluid replacement. A variety of ECG abnormalities were seen in this patient with a history of bundle branch block, including sinus bradycardia and varying degrees of AV block. These dictated the prophylactic placement of a temporary ventricular pacemaker, but otherwise resolved spontaneously. Significant hyperglycemia was seen initially in this patient, but plasma

as a whole/Systemic: cellulitis, chills, facial edema, neck pain, pelvic pain, pain

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Urogenital/Reproductive: kidney calculus, nocturia, breast engorgement

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A young hypertensive patient with advanced renal failure ingested 280 mg of nifedipine capsules at one time, with resulting marked hypotension responding to calcium infusion and fluids. No AV conduction abnormalities, arrhythmias, or pronounced changes in heart rate were noted, nor was there any further deterioration in renal function.

DOSEAGE AND ADMINISTRATION

Dosage should be adjusted according to each patient's needs. It is recommended that Nifedipine Extended-release Tablets be administered orally once daily on an empty stomach. Nifedipine Extended-release Tablets is an extended-release dosage form and tablets should be swallowed whole, not bitten or divided. In general, titration should proceed over a 7 to 14 day period starting with 30 mg once daily. Upward titration should be based on therapeutic efficacy and safety. The usual maintenance dose is 30 mg to 60 mg once daily. Titration to doses above 90 mg daily is not recommended.

If discontinuation of Nifedipine Extended-release Tablets is necessary, sound clinical practice suggests that the dosage should be decreased gradually with close

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If discontinuation of Nifedipine Extended-release Tablets is necessary, sound clinical practice suggests that the dosage should be decreased gradually with close physician supervision. Care should be taken when dispensing Nifedipine Extended-release Tablets to assure that the extended-release dosage form has been prescribed.

HOW SUPPLIED
Nifedipine Extended-release Tablets are supplied as 30 mg, round, brownish red, film coated unscored tablets imprinted with "ELN 30." Nifedipine Extended-release Tablets are supplied in:

Nifedipine Extended-release Tablets are supplied in:	
Bottles of 100	Strength
Bottles of 500	30 mg
	30 mg

The tablets should be protected from light and moisture, and stored at controlled room temperature below 30°C (86°F). Dispense in light, light-resistant containers.

NBC Code
0093-1021-01
0093-1021-05

Rx only



Manufactured By:
Elan Pharma Ltd
Athlone, Co.
Westmeath, Ireland

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75-128

CSO LABELING REVIEW(S)

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

ANDA Number: 75-128 Date of Submission: March 18, 1998

Applicant's Name: Élan Pharmaceutical Research Corporation

Established Name: Nifedipine Extended-release Tablets, 30 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: 100s and 500s
Satisfactory as of June 10, 1998 submission.

Professional Package Insert Labeling:
Satisfactory as of June 10, 1998 submission.

Revisions needed post-approval: "Rx only" changes - PI ADVERSE REACTIONS - second paragraph, first sentence ... tablets are ... When this drug appears on the marketplace pharmacists will not know whether to substitute it for Procardia XL or Adalat CC unless they have access to the Orange Book - Internal discussions within the Agency are leaning towards a statement such as "AB to ___" to clarify this ambiguity. When this is finalized such a statement should appear on the labels/labeling of this drug product.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

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

NDA Number: 20-198

NDA Drug Name: Adalat® CC (Nifedipine) Extended Release Tablets

NDA Firm: Bayer

Date of Approval of NDA Insert and supplement #: The last approved supplement in the system is S-003; approved 7/7/94. I used an insert with a revision date of 2/96 (date stamped as approved 3/29/96) for my review.

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: labels on file

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter? Firm using CC in the name (Proprietary?)		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		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? If yes, complete this subsection.	X		
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present? Proposing Nifedipine CC - includes entire USAN stem COMPANY HAS DROPPED THIS NAME AND GONE WITH USING THE ESTABLISHED NAME .	X		
Has the name been forwarded to the Labeling and Nomenclature Committee? NO - Feeling is that it would be summarily rejected. If so, what were the recommendations? If the name was unacceptable, has the firm been notified? SEE ABOVE COMMENT		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	
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

	Yes	No	N.A.
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	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		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? UNCLEAR - CONTAINER & PI SAY PROTECT FROM LIGHT. If so, is NDA and/or ANDA in a light resistant container? YES - HDPE	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 C _{max} , T _{max} , T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? YES If so, was a food study done? YES	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.			

NOTES/QUESTIONS TO THE CHEMIST:

This drug product is not USP but it has been listed in the PF. I will not ask the firm to put the statement "USP Drug release test pending." in the insert.

FOR THE RECORD:

1. This review was based on Adalat CC - the PI model used was one which has a revision date of 2/96 and is date stamped approved 3/29/96. The latest approved labeling for this drug product in the MIS system is S-003 - approved 7/7/94. There are no open supplements in the system for Adalat CC.
2. The inactives are accurately listed in the DESCRIPTION section. See p. 1 vol B 1.2.
3. Elan is the manufacturer for this drug product.
4. There are no exclusivities for this drug product but there are two patents 5264446 - expires 11/23/10 and 4892741 - expires 6/8/08. Elan claims they are infringing on neither one.
5. The containers (100s and 500s) are made of HDPE and have non CRC caps. The RLD is available in bottles of 100s, 1000s and UD 100s and bulk containers of 5000s.
6. Storage temperature recommendations

RLD - Store below 86°F (30°C)

ANDA - Store below 30°C (86°F).

7. The information in the Pharmacokinetics and Metabolism subsection of the CLINICAL PHARMACOLOGY section in the insert labeling needs to be verified before this drug product can be approved. I have elected to keep the third paragraph of this subsection in. However, the information clearly refers to the innovator product since they are the only ones on the market and no one else has proposed 60 mg or 90 mg extended-release tablets. The paragraph in question:

Two 30 mg nifedipine extended-release tablets may be interchanged with a 60 mg nifedipine extended-release tablet. Three 30 mg nifedipine extended-release tablets, however, result in substantially higher C_{max} values than those after a single 90 mg nifedipine extended-release tablet. Three 30 mg tablets should, therefore, not be considered interchangeable with a 90 mg tablet.

Bio has requested additional dissolution data.

8. This review was done with the red "dup" jackets. Sufficient number of FPL labels/labeling are present in the blue jackets.

Date of Review: 8-12-98 Date of Submission: 3-18-98

Primary Reviewer: Adolph Vezza

Date:

ISI

8/12/98

Team Leader: Charlie Hoppes

Date:

ISI

8/12/98

cc:

ANDA: 75-128

DUP/DIVISION FILE

HFD-613/AVezza/CHoppes (no cc)

aev/8/12/98 | X:\NEW\FIRMSAM\ELAN\LTRS&REV\75128AP.L

Review

APPEARS THIS WAY
ON ORIGINAL

(THIS APPROVAL SUMMARY SUPERSEDES THE ONE PREPARED ON 8/12/98)
APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-128 Date of Submission: August 24, 1999, December 3, 1999 and
January 6, 2000

Applicant's Name: Élan Pharmaceutical Research Corporation

Established Name: Nifedipine Extended-release Tablets, 30 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: December 3 av 3/20/00
100s - Satisfactory as of August 24, 1999 submission.
500s - Satisfactory as of January 6, 2000 submission.

Professional Package Insert Labeling:
Satisfactory as of August 24, 1999 submission.

Revisions needed post-approval: December 3 av 3/20/00

- a. When this drug appears on the marketplace pharmacists will not know whether to substitute it for Procardia XL or Adalat CC unless they have access to the Orange Book.
- b. PACKAGE INSERT LABELING - CLINICAL PHARMACOLOGY (Pharmacokinetics and metabolism)

Separate the "STUDY 1" further from the "STUDY 2" in the table.
- c. The following information is from the previous reviewer.

The information in the Pharmacokinetics and Metabolism subsection of the CLINICAL PHARMACOLOGY section in the insert labeling needs to be verified before this drug product can be approved. I have elected to keep the third paragraph of this subsection in. However, the information clearly refers to the innovator product since they are the only ones on the market and no one else (including the sponsor) has proposed 60 mg or 90 mg extended-release tablets. The paragraph in question:

Two 30 mg nifedipine extended-release tablets may be interchanged with a 60 mg nifedipine extended-release tablet. Three 30 mg nifedipine extended-release tablets, however, result in substantially higher C_{max} values than those after a single 90 mg nifedipine extended-release tablet. Three 30 mg tablets should, therefore, not be considered interchangeable with a 90 mg tablet.

* Assuming the sponsor's 30 mg tablet is bioequivalent to the innovator's 30 mg, this information should be applicable to the generic products as well even though they do not market 60 mg & 90 mg tablets. In this regard, I believe this information should be retained. (This is the opinion of the current reviewer) *

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Adalat[®] CC

NDA Number: 20-198

NDA Drug Name: Adalat[®] CC (Nifedipine) Extended Release Tablets

NDA Firm: Bayer

Date of Approval of NDA Insert and supplement #: The last approved supplement in the system is S-003; approved 7/7/94. I used an insert with a revision date of 2/96 (date stamped as approved 3/29/96) for my review.

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: labels on file

FOR THE RECORD:

1. This review was based on Adalat CC - the PI model used was one which has a revision date of 2/96 and is date stamped approved 3/29/96. The latest approved labeling for this drug product in the MIS system is S-003 - approved 7/7/94. There are no open supplements in the system for Adalat CC.
 2. This drug product is being imprinted at the Athlone manufacturing site as requested by the firm. Therefore, Elan's Athlone site is responsible for the tablet manufacturing including the imprinting process.
 3. The firm has changed the imprinting on the tablets at this new site. The description of the imprinting is accurate in the HOW SUPPLIED section. (See vol.3.1, p.000093)
 4. The inactives are accurately listed in the DESCRIPTION section. See p. 1 vol B 1.2.
 5. There are no exclusivities for this drug product but there are two patents 5264446 - expires 11/23/10 and 4892741 - expires 6/8/08. Elan claims they are infringing on neither one.
 6. The containers (100s and 500s) are made of HDPE and have non CRC caps. The RLD is available in bottles of 100s, 1000s and UD 100s and bulk containers of 5000s.
 7. Storage temperature recommendations

RLD - Store below 86°F (30°C)

ANDA - Store below 30°C (86°F).
 8. This drug product is to be by the new distributor, TEVA Pharmaceuticals, USA.
-
-

Date of Review: 1/7/00

Date of Submission: 8/24/99 & 12/3/99 & 1/6/00

Primary Reviewer: Chan Park

Date:

ISI for C. Park 1/10/00

Team Leader: Charlie Hoppes

Date:

cc:

ANDA: 75-128
DUP/DIVISION FILE
HFD-613/CPark/CHoppes (no cc)
V:\FIRMSAM\ELAN\LTRS&REV\75128AP.L2
Review

ISI 4/10/00
ISI 11/10/2000

+

APPEARS THIS WAY
ON ORIGINAL

guidance.

- c. Revise the "Dispense in" statement to be consistent with the your insert labeling and the innovator:

Dispense in tight, light-resistant containers as defined in USP/NF.

- d. Please include the following statements:
 - i. Protect from light and moisture.
 - ii. Tablets should be swallowed whole, not bitten or divided.

3. BULK CONTAINER

Although we do not approve bulk container labels we have reviewed the labels submitted and have the following comment:

Please include the storage temperature recommendations on this container label.

4. INSERT

a. GENERAL COMMENTS

- i. See GENERAL COMMENT 1(a).
- ii. Hyphenate "immediate-release" and "extended-release".

b. DESCRIPTION

- i. Please improve the readability of the subscripts in the structural formula.
- ii. Revise the first sentence of the third paragraph to read:

Each tablet also contains the following inactive ingredients:

c. CLINICAL PHARMACOLOGY

- i. Pharmacokinetics and Metabolism

A). Second paragraph, first sentence

... release tablets are ... ("are"
rather than '—').

B). Fourth paragraph - penultimate and last sentences

... tablets are ... (rather than "tablet
—").

C). Sixth paragraph, last sentence

... have not ... ("have" rather than
—).

D). We will withhold comment on the pharmacokinetic parameters mentioned in this subsection until completion of the bioequivalence review.

ii. Clinical Studies, penultimate sentence

... tablets were ... (two instances).

iii. Table

A). Delete the blank line/space in the title.

B). "mg" rather than '—'.

d. INDICATIONS AND USAGE

i. "INDICATIONS" rather than ~~INDICATIONS~~

ii. First sentence ... Tablets are indicated ...

iii. Last sentence - They may be ...

e. PRECAUTIONS

Drug Interactions - First sentence

... tablets were well ...

f. ADVERSE REACTIONS

i. "REACTIONS" rather than ~~REACTIONS~~

ii. Second paragraph, first sentence

... tablets was ...

iii. Table - Realign the columns of numbers so that they are centered beneath their respective headings.

iv. Delete the _____, i.e. "1%" rather than "_____".

g. DOSAGE AND ADMINISTRATION

Fourth sentence - Replace _____ with "to".

h. HOW SUPPLIED

i. Please describe your tablets as unscored.

ii. Please describe any imprintings/debossings/embossings on your drug product. We refer you to 21 CFR 206.10 for guidance. If an imprinting ink is used, please include, at a minimum, any dye present in the ink with your listing of inactive ingredients in the DESCRIPTION section.

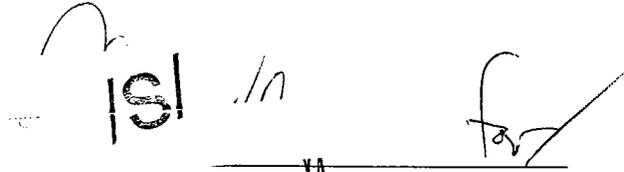
iii. See GENERAL COMMENT 1(b) and comment 2(b).

Please revise your labels and labeling, as instructed above, and submit final print container labels and draft insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

**APPEARS THIS WAY
ON ORIGINAL**

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.

Handwritten initials "JS" and "JA" are positioned above a horizontal line. To the right of the line is a checkmark.

Jerry Phillips
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:

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: Adalat® CC

NDA Number: 20-198

NDA Drug Name: Adalat® CC (Nifedipine) Extended Release Tablets

NDA Firm: Bayer

Date of Approval of NDA Insert and supplement #: The last approved supplement in the system is S-003; approved 7/7/94. I used an insert with a revision date of 2/96 (date stamped as approved 3/29/96) for my review

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: labels on file

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter? Firm using CC in the name (Proprietary?)		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		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? If yes, complete this subsection.	X		

	Yes	No	N.A.
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present? Proposing Nifedipine CC - includes entire USAN stem	X		
Has the name been forwarded to the Labeling and Nomenclature Committee? NO - Feeling is that it would be summarily rejected. If so, what were the recommendations? If the name was unacceptable, has the firm been notified?		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	
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	

	Yes	No	N. A.
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	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed) DON'T KNOW IF TABLET IS IMPRINTED OR NOT			
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? YES If so, are the recommendations supported and is the difference acceptable? NO - SEE COMMENTS IN REVIEW	X		
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? I HAVE ASKED THE CHEMIST THIS 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? YES If so, was a food study done? YES	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.			

NOTE TO THE PROJECT MANAGER

Please ensure that the notes/questions to the chemist are answered before the labeling deficiencies are faxed out.

NOTES/QUESTIONS TO THE CHEMIST:

1. Is this drug product light-sensitive?
2. This drug product is not USP but it has been listed in the PF. I will not ask the firm to put the statement "USP Drug release test pending." in the insert.
3. Does the tablet have any markings on it?
4. I note that the storage recommendations for this ANDA (CRT 20°-25°C) are different than for the innovator (Store below 30°C). I have asked the firm to revise to be the same as the innovator - do you concur?
5. I have noted that the innovator's container labels for the 1000s and 5000s sizes contain the statement "NOTE: Product must be dispensed within 3 months of opening container." I do not have any container labels for smaller container sizes. My feeling is that this statement has to do more with the repeated exposure to moisture that occurs with a

large container size and so I have not asked the applicant to add this statement since their proposed container sizes are 100s and 500s. Do you concur?

FOR THE RECORD:

1. This review was based on Adalat CC - the PI model used was one which has a revision date of 2/96 and is date stamped approved 3/29/96. The latest approved labeling for this drug product in the MIS system is S-003 - approved 7/7/94. There are no open supplements in the system for Adalat CC.
2. The inactives are accurately listed in the DESCRIPTION section. See p. 1 vol B 1.2.
3. Elan is the manufacturer for this drug product.
4. There are no exclusivities for this drug product but there are two patents 5264446 - expires 11/23/10 and 4892741 - expires 6/8/08. Elan claims they are infringing on neither one.
5. The containers (100s and 500s) are made of HDPE and have non CRC caps. The RLD is available in bottles of 100s, 1000s and UD 100s and bulk containers of 5000s.
6. The company has failed to describe the scoring configuration and the markings on their tablet in the HOW SUPPLIED section. See comments to chemist and in the review.
7. Storage temperature recommendations

RLD - Store below 86°F (30°C)

ANDA - Store at CRT 20°-25°C (68°-77°F)

I have asked the firm to revise to be the same as the RLD.

8. The information in the Pharmacokinetics and Metabolism subsection of the CLINICAL PHARMACOLOGY section in the insert labeling needs to be verified before this drug product can be approved. I have elected to keep the third paragraph of this subsection in. However, the information clearly refers to the innovator product since they are the only ones on the market and no one else has proposed 60 mg or 90 mg extended-release tablets. The paragraph in question:

Two 30 mg nifedipine extended-release tablets may be interchanged with a 60 mg nifedipine extended-release

tablet. Three 30 mg nifedipine extended-release tablets, however, result in substantially higher C_{max} values than those after a single 90 mg nifedipine extended-release tablet. Three 30 mg tablets should, therefore, not be considered interchangeable with a 90 mg tablet.

9. This review was done with the red "dup" jackets.

Date of Review: 10-10-97 Date of Submission: 4-30-97

Primary Reviewer: Adolph Vezza Date:

10/15/97

Team Leader: Charlie Hoppes Date:

10/16/97

CC:

ANDA: 75-128
DUP/DIVISION FILE
HFD-613/AVezza/CHoppes (no cc)
aev/10/10/97|X:\NEW\FIRMSAM\ELAN\LTRS&REV\75128NA1.L
Review

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ON ORIGINAL

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75-128

CHEMISTRY REVIEW(S)

15. CHEMICAL NAME AND STRUCTURE
3,5-Pyridinecarboxylic acid, 1,4-dihydro-2,6,-dimethyl-4-(2-nitrophenyl)-dimethyl ester
Molecular weight: 346.34; C₁₇H₁₈N₂O₆.
16. RECORDS AND REPORTS
NA
17. COMMENTS
Chemistry deficiencies have been identified under various sections of the review.
18. CONCLUSIONS AND RECOMMENDATIONS
This application is not approvable in this review cycle. Major amendment is required.
19. REVIEWER: Radhika Rajagopalan, Ph.D. DATE COMPLETED: 10/3/97; 10/30/97

Handwritten signature: [illegible]

Handwritten date: 11/10/97

**APPEARS THIS WAY
ON ORIGINAL**

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1. CHEMIST'S REVIEW NO. 2

2. ANDA # 75-128

3. NAME AND ADDRESS OF APPLICANT

Elan Pharmaceutical Research Group
Attention: Roger Wayne Wiley, R.Ph.
U.S. Agent for: Elan Corporation plc
1300 Gould Drive
Gainsville, GA 30504

4. BASIS FOR SUBMISSION:

The applicant includes Patent expiry information on page 11. The Reference Listed Drug, Adalat® CC is covered by two patents. U.S. Patent No. 4,892,741 expires on June 8, 2008 and 5,264,446 expires on November 23, 2010. The firm has included a non-infringement (Paragraph IV) patent certification on page 14. The RLD is not covered by marketing exclusivity.

5. SUPPLEMENT(s)

NA

6. PROPRIETARY NAME

NA

7. NONPROPRIETARY NAME

Nifedipine Extended-Release
Tablets 30 mg

8. SUPPLEMENT(s) PROVIDE(s) FOR:

NA

9. AMENDMENTS AND OTHER DATES:

Firm

Original Submission	April 30, 1997
New Correspondence	July 30, 1997
New Correspondence	August 22, 1997
New Correspondence	November 13, 1997
Major amendment	March 18, 1998
New Correspondence	June 10, 1998
Fax amendment	July 28, 1998

FDA

Acknowledgment letter	July 2, 1997
Chemistry & labeling def	February 12, 1998
Bio deficiency fax	March 10, 1998
Methods result	June 2, 1998
Phone call by Chemist	July 24, 1998

10. PHARMACOLOGICAL CATEGORY 11. Rx or OTC
Indicated for hypertension Rx
(Calcium channel blocker)

12. RELATED IND/NDA/DMF (s)

NDA #20-198

DMF # _____

DMF # _____

13. DOSAGE FORM 14. POTENCY
Tablets 30 mg

15. CHEMICAL NAME AND STRUCTURE

3,5-Pyridinecarboxylic acid, 1,4-dihydro-2,6,-dimethyl-4-(2-nitrophenyl)-dimethyl ester

Molecular weight: 346.34; C₁₇H₁₈N₂O₆.

16. RECORDS AND REPORTS

NA

17. COMMENTS

Chemistry deficiencies have been identified under various sections of the review.

18. CONCLUSIONS AND RECOMMENDATIONS

This application is not approvable in this review cycle. Major amendment is required.

19. REVIEWER:

Radhika Rajagopalan, Ph.D.

DATE COMPLETED:

7/29/98

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~ 0 0 1 ~

8/31/98

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1. CHEMIST'S REVIEW NO. 3

2. ANDA # 75-128

3. NAME AND ADDRESS OF APPLICANT

Elan Pharmaceutical Research Group
Attention: Roger Wayne Wiley, R.Ph.
U.S. Agent for: Elan Corporation plc
1300 Gould Drive
Gainsville, GA 30504

4. BASIS FOR SUBMISSION:

The applicant includes Patent expiry information on page 11. The Reference Listed Drug, Adalat® CC is covered by two patents. U.S. Patent No. 4,892,741 expires on June 8, 2008 and 5,264,446 expires on November 23, 2010. The firm has included a non-infringement (Paragraph IV) patent certification on page 14. The RLD is not covered by marketing exclusivity.

5. SUPPLEMENT(s)

NA

6. PROPRIETARY NAME

NA

7. NONPROPRIETARY NAME

Nifedipine Extended-Release
Tablets 30 mg

8. SUPPLEMENT(s) PROVIDE(s) FOR:

NA

9. AMENDMENTS AND OTHER DATES:

Firm

Original Submission	April 30, 1997
New Correspondence	July 30, 1997
New Correspondence	August 22, 1997
New Correspondence	November 13, 1997
Major amendment	March 18, 1998
New Correspondence	June 10, 1998
Fax amendment	July 28, 1998
Amendment	October 23, 1998
Telephone amendment	April 12, 1999

FDA

Acknowledgment letter	July 2, 1997
Chemistry & labeling def	February 12, 1998
Bio deficiency fax	March 10, 1998
Methods result	June 2, 1998
Phone call by Chemist	July 24, 1998
Label review acceptable	August 12, 1998
Chemistry def. Fax	September 9, 1998
Dissolution result- lab	October 15, 1998
Bio review acceptable	January 22, 1999
Phone call by Chemist/CSO	March 26 & April 12, 1999

10. PHARMACOLOGICAL CATEGORY 11. Rx or OTC
Indicated for hypertension Rx
(Calcium channel blocker)
12. RELATED IND/NDA/DMF(s)
NDA #20-198
DMF # _____
DMF # _____
13. DOSAGE FORM 14. POTENCY
Tablets 30 mg
15. CHEMICAL NAME AND STRUCTURE
3,5-Pyridinecarboxylic acid, 1,4-dihydro-2,6,-dimethyl-4-(2-nitrophenyl)-dimethyl ester
Molecular weight: 346.34; C₁₇H₁₈N₂O₆.
16. RECORDS AND REPORTS
NA
17. COMMENTS
Chemistry deficiencies have been addressed satisfactorily.
Method validation is completed and found acceptable.
18. CONCLUSIONS AND RECOMMENDATIONS
This application is recommended for approval.
19. REVIEWER: DATE COMPLETED:
Radhika Rajagopalan, Ph.D. 3/8/99 and 4/15/99

151 4/23/99

APPEARS THIS WAY
ON ORIGINAL

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1. CHEMIST'S REVIEW NO. 4

2. ANDA # 75-128

3. NAME AND ADDRESS OF APPLICANT

Elan Pharmaceutical Research Group
Attention: Roger Wayne Wiley, R.Ph.
U.S. Agent for: Elan Corporation plc
1300 Gould Drive
Gainsville, GA 30504

4. BASIS FOR SUBMISSION:

The applicant includes Patent expiry information on page 11. The Reference Listed Drug, Adalat® CC is covered by two patents. U.S. Patent No. 4,892,741 expires on June 8, 2008 and 5,264,446 expires on November 23, 2010. The firm has included a non-infringement (Paragraph IV) patent certification on page 14. The RLD is not covered by marketing exclusivity.

5. SUPPLEMENT(s)

NA

6. PROPRIETARY NAME

NA

7. NONPROPRIETARY NAME

Nifedipine Extended-Release
Tablets 30 mg

8. SUPPLEMENT(s) PROVIDE(s) FOR:

NA

9. AMENDMENTS AND OTHER DATES:

Firm

Original Submission	April 30, 1997
New Correspondence	July 30, 1997
New Correspondence	August 22, 1997
New Correspondence	November 13, 1997
Major amendment	March 18, 1998
New Correspondence	June 10, 1998
Fax amendment	July 28, 1998
Amendment	October 23, 1998
Telephone amendment	April 12, 1999
Amendment	August 24, 1999
Minor amendment	December 3, 1999
Telephone amendment	January 6, and February 4, 2000

FDA

Acknowledgment letter	July 2, 1997
Chemistry & labeling def	February 12, 1998
Bio deficiency fax	March 10, 1998
Methods result	June 2, 1998
Phone call by Chemist	July 24, 1998

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**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75-128

**BIOEQUIVALENCE
REVIEW(S)**

Nifedipine CC
Extended Release Tablets, 30 mg
ANDA # 75-128
Reviewer: Jahnvi S. Kharidia
V:\FIRMSAMELAN\LTRS&REV\75128a.o98

Elan Pharmaceutical Research Corp.
Gainesville, Georgia 30504
Submission Date:
October 23, 1998

Review of Dissolution Data (Amendment)

Introduction

Elan Pharmaceutical submitted four bioequivalence studies and dissolution data on its Nifedipine Extended Release Tablets, 30 mg in April 30, 1997. The Division of Bioequivalence completed its review (Review Date: March 10, 1998, Attachment A) and the following deficiencies were communicated to the firm. In the original application, the firm submitted three bioequivalence studies (Fasting Study, Non-fasting study and Multiple Dose Study) using lot # 6J55895 and one bioequivalence study (Four way cross over study) using lot # DC4601 (Lot # 6J55895 = printed/package version of lot # DC4601). For more details, please see page # 15 of the original review dated March 10, 1998 (Attachment A).

The deficiencies and the firm's comments are summarized below.

Deficiency # 1:

You are advised to conduct dissolution using the following method:

Medium: _____

Apparatus: _____

Time: 1, 2, 4, 6, 8, 10, 12, 16 hours

RSD% for 12 units at each sampling time should be given. Range of % dissolution at each sampling time should also be included.

Firm's Response:

The firm has submitted dissolution data using different pH media. Full details of the media preparation and experimental procedure are also given (page # 125).

Reviewer's Comment:

The firm's response is acceptable. The dissolution data are summarized in Table 1.

Deficiency # 2:

Please submit the dissolution method or methods you plan to use along with the proposed dissolution specification.

Firm's Response:

The dissolution method and specifications we plan to use for the testing and release of Nifedipine 30 mg ER product, both uncoated tablet cores and printed film coated tablets are unchanged from the original ANDA filing. The most recent proposed analytical protocols are provided in Attachment 9 (For more details, please see the original review dated March 10, 1998 & vol. 1.1).

Reviewer's Comment:

The firm proposed the following dissolution method and specifications.

Medium:	_____	
Volume:	_____	
Temperature:	_____	
Apparatus:	_____	
Speed:	_____	
Sample time:	1, 2, 4 and 10 hours	
Specifications;	Time Points	% Released
	1	NMT _____
	2	_____
	4	_____
	10	NLT _____

The firm's response is acceptable.

Deficiency # 3:

Please submit dissolution data on printed/packaged (Lot No: 6J55895) and unprinted/unpackaged (Lot No: DC4601) version of biobatch using the method described in deficiency No: 1. RSD% for 12 units at each sampling time should be given. Range of % dissolution at each sampling time should also be included.

Firm's Response:

The firm has submitted dissolution data on its unprinted/unpackaged and printed/packaged test products.

Reviewer's Comment:

The firm has submitted dissolution data on its unprinted/unpackaged and printed/packaged test product. The data are summarized in Table 1. The dissolution profiles of two test products are comparable in each of the media as shown in Figures 1-4.

The firm's response is acceptable.

Comment:

The firm has addressed all the deficiencies and from the bioequivalence point of view, the application has been found complete.

**APPEARS THIS WAY
ON ORIGINAL**

Dissolution Testing:

Table 1 - In Vitro Dissolution Testing

Drug (Generic Name): Nifedipine
 Dosage Form: Extended Release Tablet
 Dose Strength: 30 mg

I. Conditions for Dissolution Testing:

Apparatus:
 Speed:
 No. Units: 12

II. Results of In Vitro Dissolution Testing:

Time (hours)	Test# Lot # 6J55895			Test# Lot # DC4601			Reference Lot # 8AAN		
	Mean	R.S.D.	Range	Mean	R.S.D.	Range	Mean	R.S.D.	Range
1	4.9	43.6		1.8	85.4		4.9	17.9	
2	12.7	35.8		8.5	41.3		12.0	15.1	
4	30.5	30.9		23.6	31.3		27.3	11.2	
6	48.5	28.5		40.3	30.1		46.1	19.0	
8	65.1	25.7		55.4	24.9		66.6	14.9	
10	77.8	21.7		70.6	18.1		83.9	5.8	
12	89.0	16.3		81.8	12.5		91.9	5.3	

Time (hours)	Test# Lot # 6J55895			Test# Lot # DC4601			Reference Lot # 8AAN		
	Mean	R.S.D.	Range	Mean	R.S.D.	Range	Mean	R.S.D.	Range
1	6.5	27.5		5.8	28.7		6.6	22.1	
2	14.9	25.8		14.4	27.6		16.1	18.4	
4	33.5	22.5		33.5	22.0		35.0	15.2	
6	51.7	22.1		51.8	21.1		65.1	24.5	
8	68.0	22.4		70.2	21.1		82.4	19.1	
10	80.5	17.9		81.6	19.8		93.3	10.9	
12	89.4	12.5		91.9	11.7		99.3	5.7	

pH:	Time (hours)	Test*			Test#			Reference		
		Mean	R.S.D.	Range	Lot # 6J55895	Lot # DC4601	Lot # 8AAN	Mean	R.S.D.	Range
	1	6.2	36.3		6.9	20.2	5.9	13.3		
	2	15.0	33.0		17.4	16.1	18.3	30.6		
	4	35.5	28.3		41.7	20.4	29.4	7.4		
	6	55.5	28.1		62.1	11.7	45.2	9.2		
	8	70.7	23.2		81.0	11.3	68.5	14.5		
	10	84.0	16.1		94.3	5.2	86.7	6.4		
	12	93.5	9.1		99.6	4.4	97.1	2.9		

pH:	Time (hours)	Test*			Test#			Reference		
		Mean	R.S.D.	Range	Lot # 6J55895	Lot # DC4601	Lot # 8AAN	Mean	R.S.D.	Range
	1	1.5	80.9		7.4	28.3	4.8	28.6		
	2	7.7	34.3		17.8	27.5	12.7	19.1		
	4	27.5	21.0		39.3	21.7	29.5	17.8		
	6	46.7	17.4		60.2	21.2	49.9	25.7		
	8	63.6	17.9		77.0	18.2	75.2	20.8		
	10	83.0	13.2		87.3	13.4	91.1	11.8		
	12	92.3	8.7		94.1	8.8	98.9	6.0		

* printed packaged
unprinted/unpackaged

APPEARS THIS WAY
ON ORIGINAL

Recommendation:

1. The *in vivo* bioequivalence study # 0696-005 conducted under fasting and non-fasting conditions by Elan Pharmaceuticals on its Nifedipine Extended Release Tablet, 30 mg, Lot # DC4601, comparing it to Bayer's ADALAT CC®, 30 mg Tablet, Lot # 6AIA, has been found acceptable.
2. The *in vivo* bioequivalence study # 0396-003 conducted under non-fasting conditions by Elan Pharmaceuticals on its Nifedipine Extended Release Tablet, 30 mg, Lot # 6J55895 comparing it to Bayer's ADALAT CC®, 30 mg, Lot # 6AIA, has been found acceptable.
3. The *in vivo* bioequivalence study # 0396-005 conducted at steady state conditions by Elan Pharmaceuticals on its Nifedipine Extended Release Tablet, 30 mg, Lot # 6J55895 comparing it to Bayer's ADALAT CC®, 30 mg, Lot # 6AIA, has been found acceptable.
4. The dissolution testing conducted by Elan Pharmaceuticals on its Nifedipine Extended Release 30 mg Tablet has been found acceptable. The following dissolution testing should be included in to firm's manufacturing and controls. The dissolution testing should be conducted in _____ containing _____, at _____. The test product should meet the following tentative specifications:

<u>Time Points</u>	<u>% Released</u>
1	NMT _____
2	_____
4	_____
10	NLT _____

From the bioequivalence point of view, the application has been found complete.

ISI
 Jahnvi S. Kharida, Ph.D.
 Review Branch III
 The Division of Bioequivalence

RD INITIALED BDAVIT
 FT INITIALED BDAVIT

6mg 1/8/99

ISI

Date 1/14/99

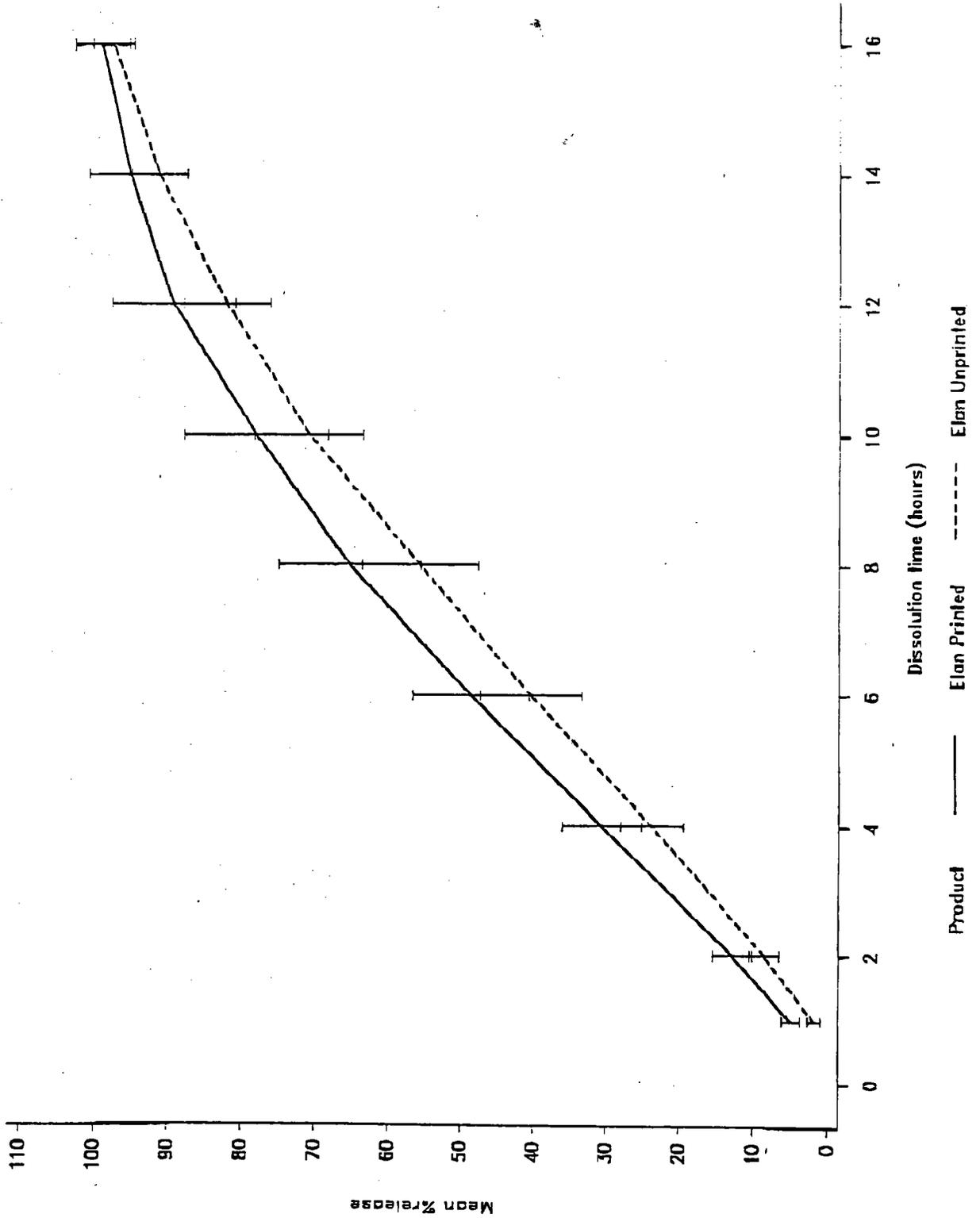
Concur:
 Dale P. Conner, Pharm.D.
 Director
 Division of Bioequivalence

ISI

Date 1/22/99

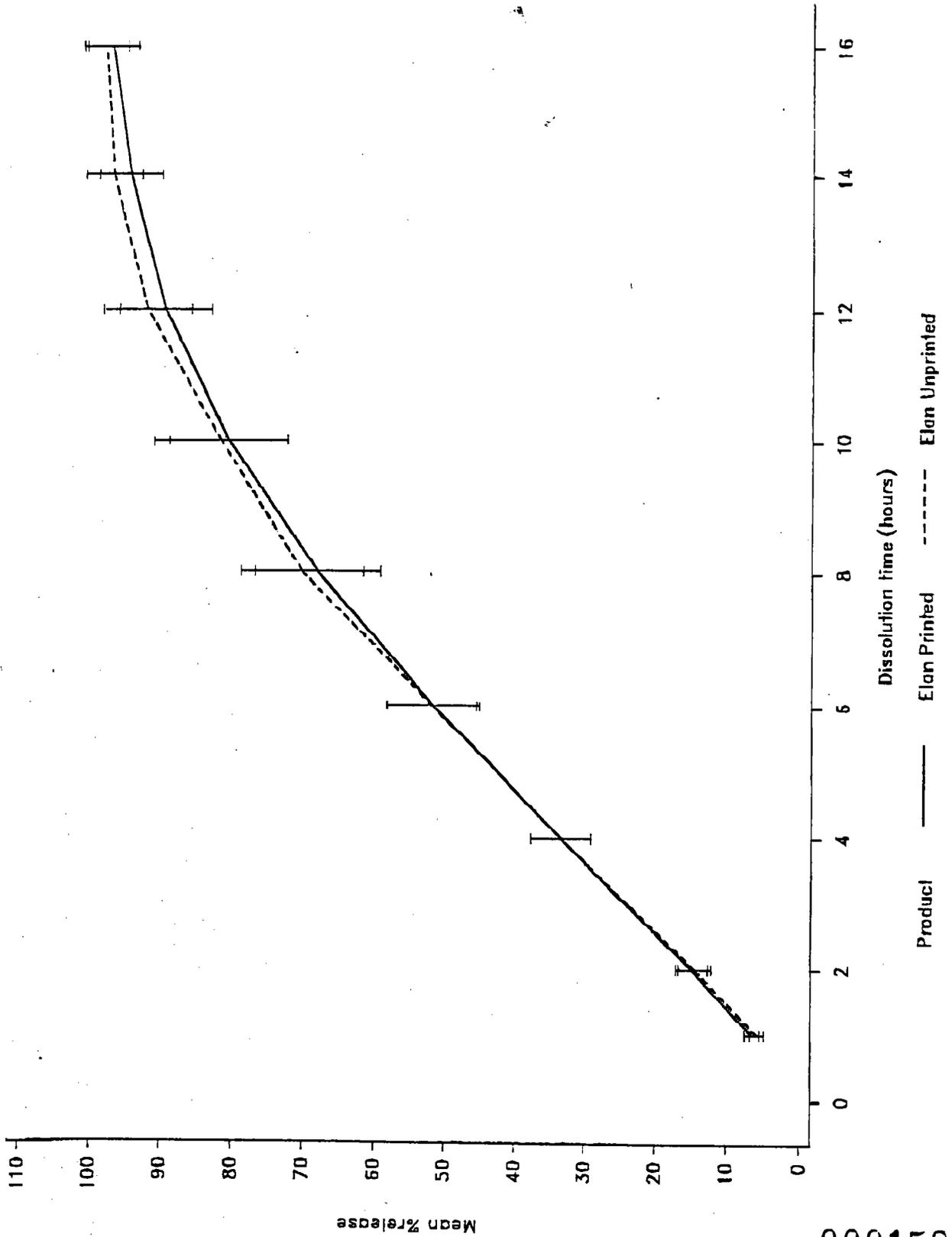
Comparative dissolution profiles of Elan Printed/Packaged Nifedipine 30mg ER & Elan Unprinted Nifedipine 30mg ER in medium: pH 1.2
 n=12 for each profile; 2 Standard Errors each side of mean are indicated

Figure 1



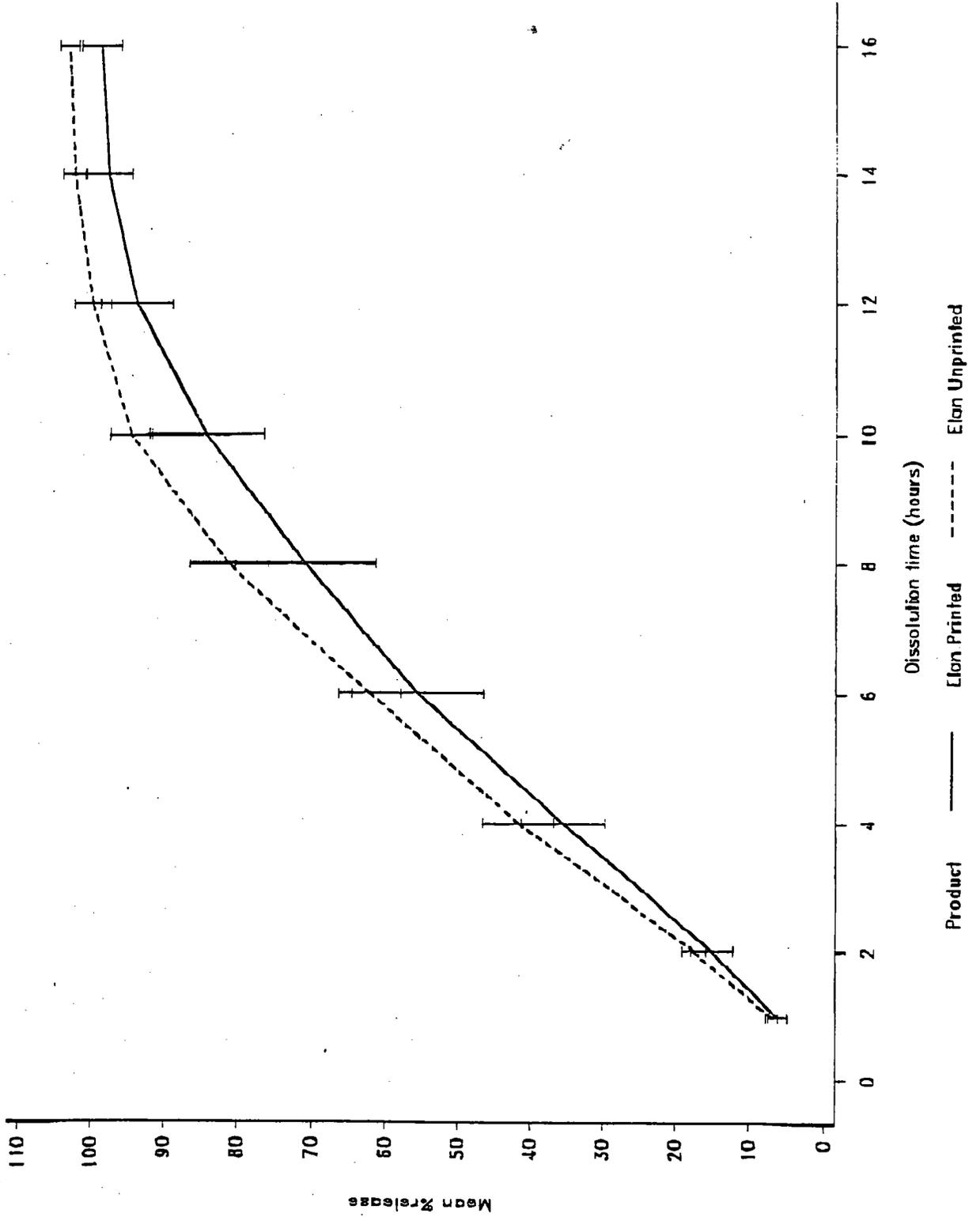
000157

Comparative dissolution profiles of Elan Printed/Packaged Nifedipine 30mg ER & Elan Unprinted Nifedipine 30mg ER in medium: pH4.0
n=12 for each profile; 2 Standard Errors each side of mean are indicated



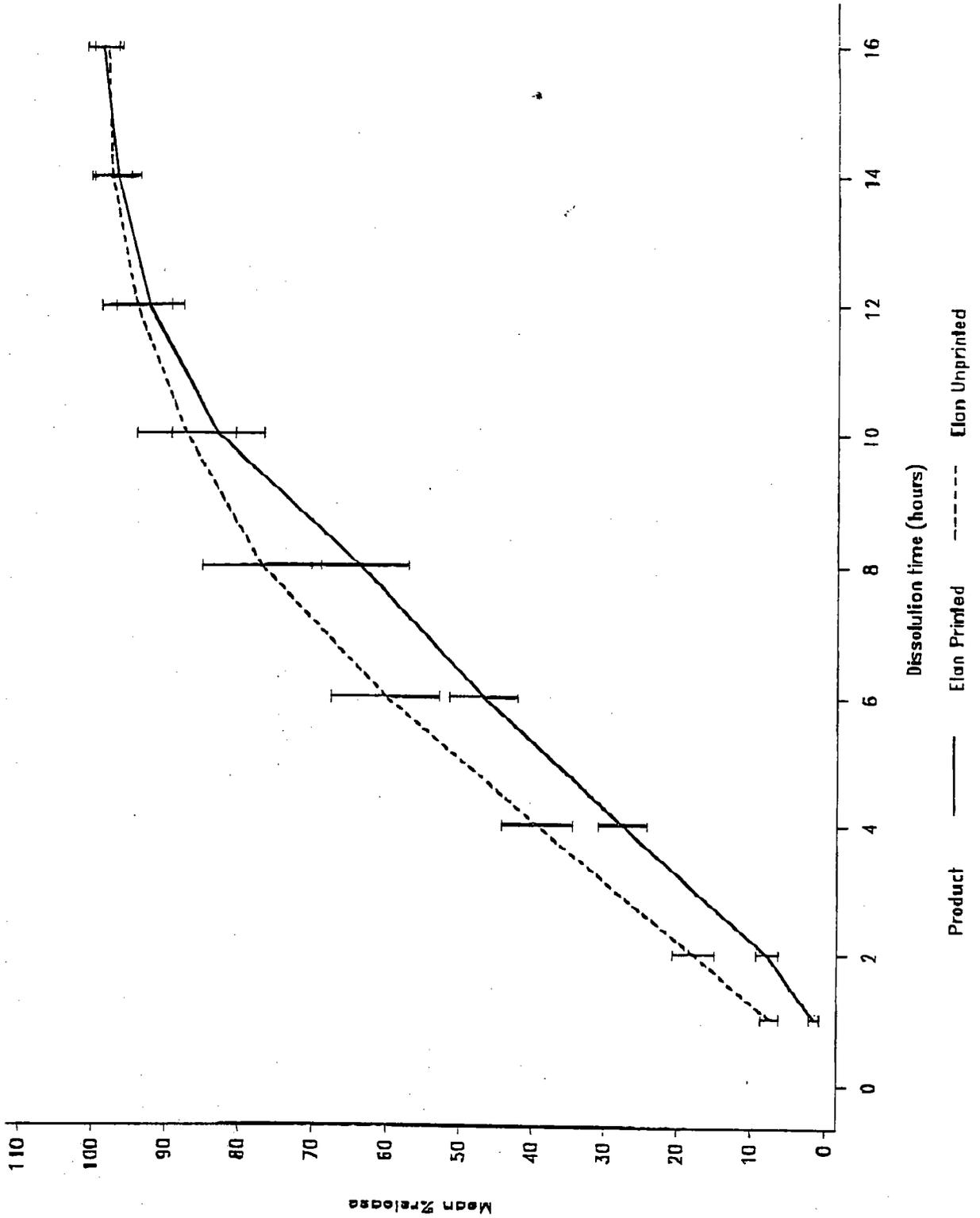
000158

Comparative dissolution profiles of Elan Printed/Packaged Nifedipine 30mg ER & Elan Unprinted Nifedipine 30mg ER in medium: pH6.8
n=12 for each profile; 2 Standard Errors each side of mean are indicated



000159

Figure 4
 Comparative dissolution profiles of Elan Printed/Packaged Nifedipine 30mg ER &
 Elan Unprinted Nifedipine 30mg ER in medium; pH7.2
 n=12 for each profile; 2 Standard Errors each side of mean are indicated



000160

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:75-128

APPLICANT: Elan Pharmaceuticals

DRUG PRODUCT: Nifedipine ER Tablets, 30 mg

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

Your proposal to use ~~_____~~ for your manufacturing controls and stability program is not acceptable. The OGD prefers the use of a ~~_____~~ when it is not necessary to use a higher one ~~_____~~. In addition, the physiological medium such as ~~_____~~ is more preferable than ~~_____~~.

Based on the data submitted, the DBE recommends the following dissolution testing for your stability and quality control programs:

The dissolution testing should be conducted in ~~_____~~ containing ~~_____~~ using ~~_____~~ at ~~_____~~. The test product should meet the following tentative specifications:

<u>Time Points</u>	<u>% Released</u>
1	NMT _____
2	_____
4	_____
10	NLT _____

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

CC: ANDA
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-650/ Reviewer
HFD-658/ B. Davit

Printed in final on 1/8/99

V:\FIRMSAM\ELAN\LTRS&REV\75128a.o98

Endorsements: (Final with Dates)

HFD-658/ J. Kharidia *J. Kharidia* 1/14/99

HFD-655/ B. Davit *Barbara M. Davit* 1/14/99

HFD-650/ D. Conner *DKC* 1/22/99

BIOEQUIVALENCY - ACCEPTABLE submission date: October 23, 1998

5. Study Amendment Strengths: 30 mg

Outcome: AC

~~6. DISSOLUTION DATA (DIS) Strengths: 30~~

~~Outcome: AC~~

Outcome Decisions: AC - Acceptable

WinBio Comments: Dissolution Acceptable
Application approvable

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS

DIVISION OF BIOEQUIVALENCE

ANDA # 75-128 SPONSOR : Elan Pharmaceuticals
DRUG & DOSAGE FORM : Nifedipine ER tablets
STRENGTH(s) : 30 mg
TYPE OF STUDY: X SD X X SDF X MULT X OTHER

STUDY SUMMARY : FAST NG STUDY (30 mg) A
FOOD STUDY (30 mg) A
Multiple STUDY (30 mg) A
Diss luti n data acceptable

PRIMARY REVIEWER : Jahnvi S. Kharidia BRANCH : 3
INITIAL : JS DATE : 1/14/99

Team Leader : Barbara M. Davit BRANCH : 3
INITIAL : BS DATE : 1/14/99

DIRECTOR
DIVISION OF BIOEQUIVALENCE
INITIAL : [Signature] DATE : 1/22/99

DIRECTOR
OFFICE OF GENERIC DRUGS
INITIAL : _____ DATE : _____

APPEARS THIS WAY
ON ORIGINAL

Nifedipine CC
Extended Release Tablets, 30 mg
ANDA # 75-128
Reviewer: Jahnavi S. Kharidia
X:\new\firm\sam\Elan\ltrs&rev\ 75128sd.497

Elan Pharmaceutical Research Corp.
Gainesville, Georgia 30504
Submission Date:
April 30, 1997

Review of Four Bioequivalence Studies and Dissolution Data

Introduction

Nifedipine is a calcium channel blocker which has potent vasodilating properties and is indicated for the management of vasospastic angina and chronic stable angina and hypertension. The usual starting dose is 30 mg given once daily. Nifedipine is currently marketed as 10 and 20 mg soft gelatin capsules (Procardia), and as 30, 60 and 90 mg extended release tablets by Pfizer Pharmaceuticals. It is also available as Adalat CC® (30 mg) by Bayer pharmaceuticals. Both products are listed as reference products in the orange book.

Pharmacokinetics of nifedipine in an extended release formulation are linear over the dose range 30 to 180 mg. The plasma half-life is about 2 hours.

Objective

To compare the relative bioavailability of Elan's Nifedipine Extended Release tablets to the reference drug product, Bayer's Adalat CC® under fasting and non-fasting conditions following a single oral dose and at steady state following multiple doses.

Study #1 - Fasting Study

1. Protocol Number:

#0396-004: A Single-Dose Study In Healthy Male Volunteers To Compare The Bioavailability Of An Elan Nifedipine 30 mg Tablet Formulation Relative To ADALAT CC® 30 mg Tablet (Bayer Pharmaceuticals)

2. Study Sites:

Clinical Facility:

Analytical Facility: _____

3. Investigators:

Principal Investigator: _____

4. Dates:

Study Dates: 1/11/97 - 1/18/97

Assay Dates: 2/3/97 - 2/17/97

5. Study Design:

This was an open-label, randomized, two-way, single-dose crossover bioequivalence study in thirty six normal, healthy, non-smoking male volunteers. The treatment phases were separated by a washout period of at least seven days.

6. Subject Inclusion/Exclusion Criteria:

Inclusion Criteria:

Subjects meeting the following criteria were included in the study.

- a) Non-smoking males between 18 and 40 years of age
- b) At least 60 kg (132 lbs) and within $\pm 10\%$ of the ideal weight
- c) Normal findings in the physical examination, vital signs and ECG prior to the start of the study

Exclusion Criteria:

Subjects meeting the following criteria were excluded from the study.

- a) History of any significant chronic disease, drug/alcohol abuse or presence of acute illness at the time of prescreening or dosing
- b) Participation in a clinical trial with an investigational drug within 90 days preceding this study

- c) Donation of blood or plasma within ninety days previous to study entry
- d) Systolic blood pressure < 110/60 mm Hg or a sitting heart rate of < 50 bpm

7. Drug Treatments:

A. Test Product

Nifedipine Extended Release 30 mg Tablet
Mfg: Elan pharmaceuticals
Lot #: 6J55895

B. Reference Product

Adalat CC® 30 mg
Mfg: Bayer Pharmaceuticals
Lot #: 6AIA
Expiration: 01/01/98

8. Dosing:

1 x 30 mg Tablet

After an overnight fasting of ten hours, each subject randomly received either a test product or a reference product with 240 mL of water. Standard meals were provided at 4 and 9 hours after dosing. Water was not permitted for 2 hours before and 2 hours after dosing in each period.

9. Housing:

The subjects were institutionalized in the clinic on the evening prior to each drug administration until 36 hours after dosing. Subjects returned to the clinic for subsequent blood sampling (48 and 60 hours).

10. Blood Sampling:

During each study phase, twenty blood samples (1X 10 mL each) were collected from each subject at 0 and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 30, 36, 48 and 60 hours after dosing. The blood samples were centrifuged for 15 minutes at 3000 rpm and plasma samples were separated and stored at -20 °C until analyzed. Upon completion of the study, all plasma samples were delivered to the analytical facility.

Redacted _____ | _____

Page(s) of trade

secret and /or

confidential

commercial

information

Results

All of the thirty six healthy volunteers successfully completed the study.

1. Adverse Events

A total of 79 adverse events were reported. All of the adverse events were considered mild or moderate in severity and were resolved without treatment. Headache was the most common adverse event, reported 42 times. Other adverse events were: dizziness, vasodilatation, chest pain, hypesthesia, abdominal pain.

2. Pharmacokinetics/Statistical Analysis

Mean Plasma Concentrations

Table 1: Mean nifedipine levels for test and reference products (N=36)

Time (hour)	Test (ng/mL) (Lot Number: 6J55895)		Reference (ng/mL) (Lot Number: 6AIA)		Ratio T/R
	Mean	STD	Mean	STD	
0	0.00	0.00	0.00	0.00	
0.5	3.71	4.42	3.56	3.83	1.04
1	8.03	4.37	15.22	9.51	0.53
1.5	13.20	7.79	22.98	12.81	0.57
2	17.88	9.01	29.17	15.58	0.61
2.5	24.21	12.89	30.72	19.34	0.79
3	24.90	13.07	31.19	19.03	0.80
4	25.11	15.14	28.57	16.71	0.88
5	26.98	16.55	28.82	13.42	0.94
6	21.69	12.71	24.79	14.75	0.88
8	16.53	9.94	16.50	9.90	1.00
10	12.41	8.07	15.91	8.27	0.78
12	9.46	5.04	13.63	7.21	0.69
16	8.44	4.51	11.41	7.08	0.74
20	7.36	4.68	7.00	5.02	1.05
24	6.56	5.20	6.10	5.13	1.08
30	4.58	5.45	3.59	3.90	1.28
36	2.23	3.58	1.52	2.12	1.47
48	0.29	0.79	0.21	0.71	1.39
60	0.03	0.18	0.08	0.36	0.35

Pharmacokinetic Parameters/Statistical Analysis

Analysis of variance was performed on each pharmacokinetic parameter using SAS GLM procedure. Mean reported pharmacokinetic parameters for Nifedipine are shown in Tables 2 for the 36 subjects who successfully completed both phases of study. The LS means of the non-transformed and log-transformed pharmacokinetic parameters, ratios of these means and the 90% confidence intervals of test product versus reference product are presented in Table 3.

Table 2: Test mean/Reference mean ratios of Nifedipine pharmacokinetic parameters (N=36)

Parameter*	Test Mean	SD	Ref Mean	SD	Ratio
AUCI	394.34	149.35	431.77	195.91	0.91
AUCT	370.26	155.36	416.82	195.97	0.89
C _{MAX}	34.60	17.73	40.21	20.17	0.86
LAUCI	369.59	0.37	398.34	0.40	0.93
LAUCT	342.09	0.41	383.06	0.40	0.89
LC _{MAX}	30.75	0.50	36.10	0.46	0.85
THALF	9.04	7.48	7.68	4.94	1.18
T _{MAX}	4.17	3.02	3.69	1.95	1.13

* AUCT=ng-hr/mL, AUCI= ng-hr/mL, T_{MAX}=hr, C_{MAX}=ng/mL

Table 3: LSMeans and 90% Confidence Intervals for Nifedipine (N=36)

Parameter	LS Mean _{test}	LS Mean _{ref}	Ratio	Low CI	Upp CI
AUCI	391.66	431.77	0.91	84.63	96.79
AUCT	370.26	416.82	0.89	82.81	94.86
C _{MAX}	34.60	40.21	0.86	73.56	98.54
LAUCI	367.76	398.34	0.92	87.21	97.73
LAUCT	342.09	383.06	0.89	84.33	94.57
LC _{MAX}	30.75	36.10	0.85	75.46	96.16

Comment:

1. The mean plasma profiles of nifedipine for the test and reference products are comparable as shown in Figure 1.
2. The 90% confidence intervals for log-transformed AUCT and AUCI are all within 80-125% range. However, the 90% confidence interval for log-transformed C_{max} is outside the acceptable range.

The study is not acceptable.

Study # 2 - Non-fasting Study

1. Protocol Number:

0396-003: A Study In Healthy Male Volunteers To Assess The Effect Of Food On The Bioavailability Of An Elan Nifedipine 30mg Tablet Formulation Relative To ADALAT CC® 30 mg Tablet (Bayer Pharmaceuticals)

2. Study Sites:

Clinical Facility: _____

Analytical Facility: _____

3. Investigators:

Principal Investigator: _____

4. Dates:

Study Dates: 11/30/96 - 1/9/97

Assay Dates: 12/16/96- 1/22/97

5. Study Design:

The study followed a randomized, three-way, single dose, cross-over design in thirty six normal, healthy, male volunteers with a washout period of ten days.

6. Subject Inclusion/Exclusion Criteria:

Inclusion and exclusion criteria were the same as in the fasting study

7. Drug Treatments:

A. Test Product (Fasting condition)

Nifedipine Extended Release Tablet, 30 mg

Mfg: Elan Pharmaceuticals

Lot #: 6J55895

B. Test Product (Non-fasting condition)

Nifedipine Extended Release Tablet, 30 mg
Mfg: Elan Pharmaceuticals
Lot #: 6J55895

C. Reference Product (Non-fasting condition)

Adalat CC® 30 mg tablet
Bayer Pharmaceuticals
Lot#: 6AIA
Expiration: 01/01/98

8. Dosing:

1 X 30 mg Nifedipine Tablet

Treatments B & C :

All subjects fasted 10 hours prior to dosing. Subjects then received a standardized breakfast and exactly 30 minutes after starting breakfast, each subject received either a test product or a reference product with 240 mL of water.

A standard breakfast consists of:

1 egg (fried)	1 serving of hash brown potatoes
1 buttered english muffin	8 fluid ounces of whole milk
1 slice of american cheese	6 fluid ounces of orange juice
1 slice of canadian bacon	

Treatment A:

After an overnight fast of ten hours, each subject received a test product with 240 mL of water.

During each phase of the study, standardized meals were provided to all subjects at 4 and 9 hours following dosing. Water was not permitted for 2 hours before and 2 hours after dosing in each dosing period.

9. Blood Sampling:

During each study phase, a total of 20 blood samples (1X 10 mL each) were collected from each subject at 0.00 and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 36, 48 and 60 hours after dosing. The blood samples were centrifuged and plasma samples were separated and stored at -20 °C until analyzed.

10. Safety Monitoring:

Blood pressure and heart rate were measured at 0 and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 30, 36, 48 and 60 hours after dosing.

Analytical Method

Results:

1. Adverse Events

A total of 71 adverse events were reported during the study (TRT A-15, TRT B-28, TRT C-28). Headache was reported a total of 57 times. Eight of these headache episodes required therapy (paracetamol®). Other adverse events such as dizziness, neck rigidity, infection, dyspepsia, ECG abnormal were mild in nature and resolved without any treatment.

2. Pharmacokinetic/Statistical Analysis

Mean Plasma Levels

Table 4: Mean nifedipine levels (ng/mL) for test and reference product (N=36)

Time (hour)	Test _{Fast} - A (Lot Number: 6J55895)		Test _{Non-fasting} - B (Lot Number: 6J55895)		Reference _{Non-fasting} - C (Lot Number: 6A1A)		B/C
	Mean	Std	Mean	Std	Mean	Std	
0	0.00	0.00	0.00	0.00	0.00	0.00	.
0.5	3.23	2.86	3.26	8.44	1.18	3.67	2.76
1	11.50	7.75	11.74	17.02	6.31	13.18	1.86
1.5	20.25	14.76	22.75	22.48	15.20	19.60	1.50
2	24.96	17.99	31.45	32.77	23.46	22.56	1.34
2.5	27.80	19.21	31.44	31.37	32.00	22.52	0.98
3	31.11	24.52	44.90	44.57	37.65	25.19	1.19
4	33.32	26.95	49.48	36.90	50.78	36.42	0.97
5	33.07	24.85	55.10	38.38	57.96	32.95	0.95
6	25.84	17.58	54.24	37.34	58.63	31.24	0.93
8	16.89	11.07	31.99	20.53	50.49	37.96	0.63
10	16.08	10.22	23.36	19.23	28.36	19.65	0.82
12	13.17	6.22	15.35	12.29	16.94	11.85	0.91
16	12.29	7.38	7.52	6.37	7.88	6.53	0.95
20	8.72	5.85	4.33	5.82	4.49	4.08	0.96
24	8.24	6.48	3.02	5.29	2.87	4.07	1.05
30	5.15	4.24	1.60	3.74	0.99	1.62	1.61
36	2.41	2.70	0.60	1.58	0.39	0.71	1.53
48	0.33	0.80	0.00	0.00	0.00	0.00	.
60	0.04	0.27	0.00	0.00	0.00	0.00	.

Pharmacokinetic Parameters

Mean reported pharmacokinetic parameters for nifedipine are shown in Table 5. AUCT, AUCI and Cmax mean values for the test product to that of the reference product administered under non-fasting conditions (Ratio B/C) differ no more than 20% for nifedipine.

Table 5: Mean pharmacokinetic parameters and relative ratio of test (non-fasting) vs. reference (non-fasting) for nifedipine (N=36)

Parameter*	Test (Fasting) A	Std	Test (Non-fasting) B	Std	Reference (Non-fasting) C	Std	B/C
AUCI	489.26	228.73	511.55	271.91	551.30	251.52	0.93
AUCT	459.79	233.72	504.14	270.03	545.83	252.65	0.92
CMAx	43.64	28.09	84.47	44.48	84.66	38.72	1.00
KE	0.10	0.05	0.18	0.08	0.19	0.08	0.94
LAUCI	443.43	0.45	449.25	0.52	497.53	0.47	0.90
LAUCT	408.95	0.49	441.86	0.52	491.07	0.47	0.90
LCMAx	37.16	0.56	73.88	0.53	75.43	0.51	0.98
THALF	9.65	7.63	4.82	2.33	4.41	2.13	1.09
TMAx	3.57	1.67	4.60	2.12	5.29	1.86	0.87

*AUCT=ng-hr/mL, AUCI= ng-hr/mL, TMAx=hr, CMAx=ng/mL

Comment:

1. Under non-fasting condition, the ratios of the test mean to the reference mean are within the acceptable range of 0.80-1.20 for AUCT, AUCI and Cmax.
2. Administration of test product under non-fasting conditions resulted in an increase in the rate of absorption (Cmax) but had no effect on the extent of absorption (as estimated by AUC).

The study is acceptable.

Study # 3 - Multiple Dose Study

1. Protocol Number:

#0396-005: A Study In Healthy Male Volunteers To Compare The Steady State Bioavailability Of An Nifedipine 30 mg Tablet Formulation To ADALAT CC® (Bayer Pharmaceuticals)

2. Study Sites:

Clinical Facility:

Analytical Facility:

3. Investigators:

Principal Investigator:

4. Dates:

Study Dates: 12/5/96 - 12/24/96

5. Study Design:

This was a multiple-dose, two-way crossover, randomized study in forty one healthy adult male subjects, to evaluate the bioequivalence of two nifedipine formulations under steady state conditions.

6. Subject Inclusion/Exclusion Criteria:

Inclusion criteria and exclusion criteria were the same as in the fasting study.

7. Drug Treatments:

A. Test Product

Nifedipine Extended Release Tablet, 30 mg
Mfg: Elan Pharmaceuticals
Lot #: 6J55895

B. Reference Product
Adalat CC® 30 mg tablet
Bayer Pharmaceuticals
Lot#: 6AIA
Expiration: 01/01/98

The same lots of test and reference products were used in the single-dose fasting and multiple-dose fasting studies.

8. Dosing:
1 X 30 mg Nifedipine tablet
once a day, 5 days

In each period, on each day of dosing all subjects fasted for a period 10 hours prior and for four hours after dosing. Each subject received either a test product or a reference product with 240 mL of water. Standard meals were provided at 4 and 9 hours after dosing. Water was not permitted for 1 hour before and 1 hour after dosing.

9. Housing:

The subjects were institutionalized in the clinic on the evening prior to each drug administration until 36 hours after the last dose of medication on day 5. Subjects returned to the clinic for subsequent blood sampling (48 and 60 hours).

10. Blood Sampling:

A total of 24 blood samples (1X 10 mL each) were collected from each subject at the following times.

Day 1 to 4: 0 hours

Day 5: 0 hours and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 36, 48 and 60 hours after dosing.

The blood samples were centrifuged and plasma samples were separated and stored at -20 °C until analyzed.

Analytical Method

Results:

Forty one subjects were enrolled in this study, 5 subjects (#4, #5, #105, #29, #36) dropped out and thirty six subjects successfully completed the study.

#4 - wished to discontinue from the study after receiving four doses in period 1

#5 - develop tachycardia following first dose in period 1 (Test Product)

#105, #29, #36 - did not check in for period 2

1. Adverse Events

A total of 97 drug related adverse events were reported during the study (Trt A-44, Trt B-53). All the adverse events were considered either mild or moderate. The most common adverse event was headache, with 28 and 36 episodes after Trt A and Trt B, respectively. Other events were dizziness, rash, nausea, vomiting, myalgia and tachycardia.

2. Pharmacokinetic/Statistical Analysis

Mean Plasma Levels

The mean plasma levels of nifedipine after test and reference products are shown in Table 6 and Figure 3, respectively.

Table 6: Mean nifedipine levels (ng/mL) for test and reference products (N=36)

Time (hour)	Test A (Lot Number:6J55895)		Reference B (Lot Number:6A1A)		RatioA/B
	Mean	CV%	Mean	CV%	
96	7.06	4.17	5.99	3.67	1.18
96.5	10.57	6.23	9.60	6.01	1.10
97	18.10	10.88	21.67	9.30	0.84
97.5	22.40	11.86	30.17	15.02	0.74
98	25.31	12.16	33.92	17.96	0.75
98.5	31.02	17.41	38.01	19.77	0.82
99	31.51	15.04	38.85	18.83	0.81
100	35.30	18.95	39.63	24.56	0.89
101	38.81	19.04	42.03	22.74	0.92
102	31.37	13.63	32.64	20.41	0.96
104	20.35	9.73	23.72	16.26	0.86
106	18.07	9.97	23.71	13.28	0.76
108	15.97	8.29	19.38	9.76	0.82
112	13.65	7.51	12.47	7.97	1.09
116	8.86	4.91	7.56	6.50	1.17
120	7.40	5.34	5.87	6.10	1.26
126	3.47	2.95	2.49	2.28	1.39
132	1.68	1.90	1.06	1.77	1.58
144	0.17	0.73	0.10	0.35	1.70
156	0.23	1.18	0.16	0.67	1.44

Pharmacokinetic Parameters

Analysis of variance was performed on each pharmacokinetic parameter using SAS GLM procedure. Mean reported pharmacokinetic parameters for nifedipine are shown in Table 7, for the 36 subjects who successfully completed both phases of study. The LS means of the non-transformed and log-transformed pharmacokinetic parameters, ratios of these means and the 90% confidence intervals of test product versus reference product are presented in Tables 8.

Table 7: Mean pharmacokinetic parameters and relative ratio of test vs. reference for nifedipine (N=36)

Parameter*	Test Mean	SD	Ref Mean	SD	Ratio
AUCTss (0-24h)	428.09	169.38	472.79	226.63	0.91
CMAxss	45.77	19.08	51.94	24.86	0.88
TMAX	4.74	2.84	3.46	1.46	1.37
CMIN	5.23	3.46	4.32	3.20	1.21
DF#	10.75	7.51	14.47	11.07	0.74
CAV	17.84	7.06	19.70	9.44	0.91

*AUCT=ng-hr/mL, TMAX=hr, CMAX=ng/mL, CMIN=ng/mL

DF= ((Cmax-Cmin)/Cmin)*100

Table 8: LSMeans and 90% Confidence Intervals for nifedipine (N=36)

Parameter*	LS Mean _{test}	LS Mean _{ref}	Ratio (test/ref)	Low CI	Upp CI
LCMAX ss	42.43	46.93	0.90	81.54	100.24
LAUCT ss	399.54	431.01	0.93	87.02	98.75

*AUCT=ng-hr/mL, CMAX=ng/mL

Comment:

1. At steady state, the mean plasma profiles of nifedipine for the test and reference products are comparable as shown in Figure 3.
2. The 90% confidence intervals for log-transformed AUCTss and LCMAXss are within 80-125% range. These results showed that the Elan nifedipine 30 mg tablet formulation achieved bioequivalence at steady state with the reference product, Adalat CC® 30 mg tablet.

The study is acceptable.

Study #4- Additional Study

Background for Submitting Study #4

- The firm has submitted an additional study (protocol number #0696-005, Four way cross over study), which was performed on the **unprinted/unpackaged version (lot#DC4601)** of the biobatch. The single dose study (# 0696-005) performed using the unprinted/unpackaged lot#DC4601 concluded that the Elan formulation was bioequivalent to ADALAT CC® in terms of Cmax and AUC comparisons. This study also showed that food had a similar effect on the pharmacokinetics of both formulations.
- The earlier reported studies (Fasting Study, Non-fasting Study and Multiple Dose Study) were performed using **lot#6J55895, which is a printed/packaged version of the biobatch (Lot# 6J55895=printed/packaged version of lot # DC4601)**. As reported earlier under the fasting study (study #1), the single dose study using the printed/packaged Lot# 6J55895 showed bioequivalence in terms of AUC but not in terms of Cmax. Although Lot# 6J55895 is the printed/packaged version of lot # DC4601, both studies gave different results. The firm's explanation for the different results was the inherent intersubject variability of nifedipine.
- The firm is trying to provide evidence for single dose bioequivalence in terms of Cmax and AUCI by submitting this additional study. The details of the study are as follow:

1. Protocol Number:

#0696-005: A Single Dose Study In Healthy Volunteers To Assess The Bioequivalence Of An Elan Nifedipine 30 mg Tablet Formulation And ADALAT CC® 30 mg (Bayer Pharmaceuticals) Administered Under Fasting Condition And To Assess The Effect Of Food On Both Formulations.

2. Study Sites:

Clinical Facility:

Analytical Facility:

3. Investigators:

Principal Investigator: _____

Analytical Investigator: _____

4. Dates:

Study Dates: 8/7/96 - 8/28/96

Assay Dates: 8/22/96 - 9/17/96

5. Study Design:

This was an open-label, four treatment, four period, randomized crossover study in twenty four normal, healthy, non-smoking male volunteers. The treatment phases were separated by a washout period of at least seven days.

6. Subject Inclusion/Exclusion Criteria:

Inclusion and exclusion criteria were the same as in the fasting study.

7. Drug Treatments:

A. Test Product

Nifedipine Extended Release 30 mg Tablet, **Fasting Condition**
Mfg: Elan pharmaceuticals
Lot #: DC4061

B. Test Product

Nifedipine Extended Release 30 mg Tablet, **Non-fasting Condition**
Mfg: Elan pharmaceuticals
Lot #: DC4061

C. Reference Product

Adalat CC® 30 mg, **Fasting Condition**
Mfg: Bayer Pharmaceuticals
Lot #: 6AIA
Expiration: 01/01/98

D. Reference Product

Adalat CC® 30 mg, **Non-fasting Condition**
Mfg: Bayer Pharmaceuticals
Lot #: 6A1A
Expiration: 01/01/98

8. Dosing:

1 x 30 mg Tablet

Treatments A & C

After an overnight fasting of ten hours, each subject randomly received either a test product or a reference product with 240 mL of water. Standard meals were provided at 4 and 9 hours after dosing. Water was not permitted for 2 hours before and 2 hours after dosing in each dosing period.

Treatments B & D

All subjects fasted 10 hours prior to dosing. Subjects then received a standardized breakfast and exactly 30 minutes after starting breakfast, each subject received either a test product or a reference product with 240 mL of water.

A standard breakfast consists of:

1 egg (fried)	1 serving of hash brown potatoes
1 buttered english muffin	8 fluid ounces of whole milk
1 slice of american cheese	6 fluid ounces of orange juice
1 slice of canadian bacon	

9. Housing:

The subjects were institutionalized in the clinic on the evening prior to each drug administration until 36 hours after dosing. Subjects returned to the clinic for subsequent blood sampling (48 and 60 hours).

10. Blood Sampling:

During each study phase, twenty blood samples (1 X 10 mL each) were collected from each subject at 0 and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 30, 36, 48 and 60 hours after dosing. The blood samples were centrifuged for 15 minutes at 3000 rpm and plasma samples were separated and stored at -20 °C until analyzed.

Analytical Method

1. Pre Study Assay Validation:



2. Precision and accuracy data are shown below in Table 1.



Results:

1. Adverse Events

A total of 22 drug related adverse events were reported; all of the events were classified as mild or moderate.

Treatment A - 6 Events, Treatment B - 8 Events

Treatment C - 4 Events, Treatment D - 4 Events

The most common adverse event was headache, which was reported 18 times. The other events included nausea, abdominal pain, diarrhoea etc.

2. Pharmacokinetic/Statistical Analysis

Mean Plasma Levels and Pharmacokinetic Parameters

The mean plasma levels of nifedipine after four treatments are shown in Table 9 and Figure 4, respectively. Analysis of variance was performed on each pharmacokinetic parameter using SAS GLM procedure. Mean reported pharmacokinetic parameters for nifedipine are shown in Table 10 for the 24 subjects who successfully completed all four phases of study. The LS means of the non-transformed and log-transformed pharmacokinetic parameters, ratios of these means and the 90% confidence intervals of test product versus reference product are presented in Table 11.

Table 11. Mean Plasma concentration for nifedipine after four treatments (N=24)

TIME HR	Trit A		Trit B		Trit C		Trit D		Ratio A/C	Ratio B/D
	Mean	Std	Mean	Std	Mean	Std	Mean	Std		
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00		
0.5	3.23	3.18	0.22	0.81	5.51	7.30	1.09	2.71		0.20
1	10.85	6.00	4.04	5.44	18.40	10.79	6.80	9.00	0.59	0.59
1.5	18.09	10.74	11.55	11.45	27.55	12.25	16.51	20.81	0.59	0.70
2	20.94	10.70	20.21	16.20	31.88	13.01	22.37	24.26	0.66	0.90
2.5	22.97	10.24	30.89	27.95	32.85	14.00	28.24	22.09	0.66	1.09
3	26.04	14.04	39.28	31.63	32.89	15.69	34.19	24.95	0.70	1.15
4	26.84	17.09	56.77	34.09	30.89	19.11	40.80	22.60	0.79	1.39
5	37.78	27.77	65.09	34.66	32.12	21.28	63.43	31.24	0.87	1.03
6	34.59	35.07	53.09	28.04	25.13	17.28	52.27	33.85	1.18	1.02
8	17.91	10.07	31.99	16.32	21.56	15.65	41.32	23.42	1.38	0.77
10	15.57	8.43	21.73	12.29	21.72	11.53	23.03	9.78	0.83	0.94
12	13.55	7.06	13.33	7.03	18.47	8.29	14.81	7.13	0.72	0.90
16	11.17	5.69	6.91	6.00	14.04	7.37	8.19	6.95	0.73	0.84
20	6.84	3.46	4.21	3.88	8.00	4.79	4.40	4.00	0.80	0.96
24	6.15	3.35	2.42	2.41	6.83	5.09	2.52	2.45	0.85	0.96
30	2.76	1.96	0.74	1.01	3.10	2.76	1.15	3.11	0.90	0.64
36	1.22	1.18	0.00	0.00	1.19	1.48	0.77	3.20	0.89	0.00
48	0.13	0.46	0.00	0.00	0.06	0.29	0.18	0.89	1.03	0.00
60	0.06	0.31	0.00	0.00	0.00	0.00	0.00	0.00	2.15	

Trit A = Elan's Nifedipine Tablet, 30 mg, Lot DC4601, Fasting Condition
Trit B = Elan's Nifedipine Tablet, 30 mg, Lot DC4601, Non-fasting Condition
Trit C = Reference Product, ADALAT CC® 30 mg tablet, Fasting Condition
Trit D = Reference Product, ADALAT CC® 30 mg tablet, Non-fasting Condition

Table 10: Mean pharmacokinetic parameters for Nifedipine (N=24)

Parameter	Trt A		Trt B		Trt C		Trt D		Ratio	Ratio
	Mean	Std	Mean	Std	Mean	Std	Mean	Std	A/C	B/D
AUCI	426.78	181.83	479.56	180.44	488.47	185.62	504.04	160.86	0.87	0.95
AUCT	413.96	186.93	472.85	178.12	477.72	189.40	497.89	158.95	0.87	0.95
C _{MAX}	46.91	36.35	80.42	33.72	41.33	19.82	78.58	33.72	1.13	1.02
KE	0.11	0.04	0.18	0.08	0.12	0.03	0.17	0.06	0.95	1.04
LAUCI	392.70	0.42	447.15	0.39	454.77	0.39	477.49	0.35	0.86	0.94
LAUCT	377.00	0.44	440.67	0.39	441.51	0.41	471.52	0.35	0.85	0.93
LC _{MAX}	37.91	0.64	73.82	0.43	37.75	0.42	71.91	0.44	1.00	1.03
THALF	7.22	3.44	4.44	1.40	6.51	2.40	4.48	1.53	1.11	0.99
T _{MAX}	4.35	1.51	4.40	1.34	3.65	2.92	5.23	2.86	1.19	0.84

Trt A = Elan's Nifedipine Tablet, 30 mg, Lot DC4601, Fasting Condition
 Trt B = Elan's Nifedipine Tablet, 30 mg, Lot DC4601, Non-fasting Condition
 Trt C = Reference Product, ADALAT CC® 30 mg tablet, Fasting Condition
 Trt D = Reference Product, ADALAT CC® 30 mg tablet, Non-fasting Condition

Table 11: LS_{Mean} and 90% Confidence Interval for Nifedipine (N=24)

Parameter	LS _{Mean}		LS _{Mean}		LS _{Mean}		LS _{Mean}		Ratio	Ratio	Trt A vs. Trt C		Trt B vs. Trt D	
	A	B	C	D	C	D	C	D	B/D	A/C	Upp CI	Low CI	Upp CI	Low CI
AUCI	426.78	479.56	488.47	504.04	488.47	504.04	488.47	504.04	0.87	0.87	79.96	94.78	87.96	102.33
AUCT	413.96	472.85	477.72	497.89	477.72	497.89	477.72	497.89	0.87	0.87	78.96	94.34	87.60	102.35
C _{MAX}	46.91	80.42	41.33	78.58	41.33	78.58	41.33	78.58	1.13	1.13	82.83	144.15	86.21	118.47
LAUCI	392.70	447.15	454.77	477.49	454.77	477.49	454.77	477.49	0.86	0.86	80.83	92.25	87.66	100.04
LAUCT	377.00	440.67	441.51	471.52	441.51	471.52	441.51	471.52	0.85	0.85	79.69	91.50	87.22	100.14
LC _{MAX}	37.91	73.82	37.75	71.91	37.75	71.91	37.75	71.91	1.00	1.00	85.02	118.64	86.90	121.26

Trt A = Elan's Nifedipine Tablet, 30 mg, Lot DC4601, Fasting Condition
 Trt B = Elan's Nifedipine Tablet, 30 mg, Lot DC4601, Non-fasting Condition
 Trt C = Reference Product, ADALAT CC® 30 mg tablet, Fasting Condition
 Trt D = Reference Product, ADALAT CC® 30 mg tablet, Non-fasting Condition

Comment:

The firm has also performed ANOVA on pooled data (combining data from the two studies: fasting study (study #1) and (study #4)). The results of the pooled analysis are summarized in Table 12. The two studies (Study #1 and Study #4) were conducted at different sites and plasma samples were also analyzed by different analytical laboratories. Therefore, in reviewer's opinion, pooled analysis on combined data are not acceptable.

The reviewer discussed the results of all four studies with the division's deputy director and it was agreed that the results of the study # 4 could be accepted in support of the ANDA based on the following comments.

1. The test product displayed slower and less extent of absorption as compare to the reference product (Table 11, Ratio A/C for AUCI-0.86, AUCT-0.85)
2. The 90% confidence intervals for log-transformed AUCT, AUCI and Cmax are within 80-125% range, however, it should be noted that the test product very marginally passes the 90% confidence intervals for AUCT (Table 11).
3. In terms of Cmax, the test/reference ratios is 1.00 which suggest that rate of absorption is similar in both test and reference products (Table 11).
4. The results of the study # 4 also showed that the ratios of the test mean to the reference mean are within the acceptable range of 0.80-1.20 for AUCT, AUCI and Cmax under non-fasting condition (Table 11, Ratio B/D).
5. In addition, the earlier reported studies (Study # 2 - Non-fasting study and Study # 3 - Steady state study) showed that the Elan nifedipine 30 mg tablet formulation is bioequivalent to Adalat CC® 30 mg tablet. The 90% confidence intervals for log-transformed pharmacokinetic parameters are within 80-125% range.

Based on the results from all four studies, it can be concluded that Elan's Nifedipine extended release tablet is bioequivalent to ADALAT CC® 30 mg (Bayer Pharmaceuticals) under fasting, non-fasting and steady state condition.

Dissolution Testing:

The dissolution testing was carried out according to the procedure described in the OGD guidance for Extended Release tablets. General conditions were as follows:

Table 13 - In Vitro Dissolution Testing					
Drug (Generic Name): Nifedipine					
Dosage Form: Extended Release Tablet					
Dose Strength: 30 mg					
I. Conditions for Dissolution Testing: (Company's Method)					
Apparatus: _____					
Speed: _____					
No. Units: 12 Tablets					
Medium: _____					
Volume: _____					
Sampling Time: 1, 2, 4, 6, 8, 10, 12 and 16 hours					
II. Results of In Vitro Dissolution Testing:					
pH: 1.2			pH: 6.2		
Time (hours)	Test Lot # DC4601	Reference Lot # 6AIA	Time (hours)	Test Lot # DC4601	Reference Lot # 6AIA
1	8.5 ± 0	9.4 ± 0.7	1	11.5 ± 2.3	8.5 ± 0.9
2	19.9 ± 4.9	20.8 ± 1.6	2	25.3 ± 4.3	19.2 ± 1.7
4	44.0 ± 8.7	43.0 ± 3.11	4	51.2 ± 7.6	40.6 ± 3.1
6	66.7 ± 13.0	77.7 ± 13.3	6	73.6 ± 9.2	70.4 ± 11.1
8	87.1 ± 11.3	102.3 ± 3.2	8	93.8 ± 6.6	98.8 ± 4.6
10	99.6 ± 5.7	108.5 ± 2.2	10	101.4 ± 3.1	105.7 ± 2.4
12	104.1 ± 2.4	111.1 ± 11.8	12	103.0 ± 1.1	108.2 ± 1.3
16	105.0 ± 1.8	111.7 ± 1.8	16	103.8 ± 0.9	109.0 ± 1.0
pH: 4.0			pH: 7.2		
Time (hours)	Test Lot # DC4601	Reference Lot # 6AIA	Time (hours)	Test Lot # DC4601	Reference Lot # 6AIA
1	11.3 ± 1.7	8.2 ± 0.7	1	11.1 ± 1.4	8.0 ± 1.2
2	25.2 ± 3.1	18.6 ± 1.4	2	24.6 ± 2.9	18.0 ± 2.0
4	51.6 ± 5.6	39.5 ± 2.4	4	51.9 ± 5.7	38.7 ± 3.4
6	74.2 ± 6.3	60.3 ± 6.3	6	76.6 ± 7.8	61.2 ± 12.5
8	94.8 ± 3.7	91.4 ± 12.5	8	96.2 ± 4.1	89.7 ± 14.1
10	102.6 ± 1.6	104.2 ± 3.3	10	102.9 ± 2.7	104.1 ± 5.2
12	103.3 ± 1.4	107.8 ± 2.1	12	104.4 ± 2.2	109.0 ± 2.1
16	103.8 ± 1.5	108.9 ± 1.4	16	105.7 ± 2.5	111.4 ± 1.5

Comment:

- The firm has used _____ as a medium. It is recommended that the firm conduct dissolution using following method:

Medium: _____

Apparatus: _____ Speed: _____
 Time: 1, 2, 4, 6, 8, 10, 12, 16 hours

2. The dissolution method or methods the firm plans to use along with the proposed dissolution specification should be submitted in detail.
3. The firm has submitted mean dissolution data comparing lot#DC4601 and Lot# 6J55895 (Table 14), however, the firm did not specify dissolution condition. For lot #6J55895 tablets, the firm should conduct dissolution according to the method described under comment #1.

Table 14: Mean Dissolution data of lot#DC4601 and lot#6J55895

Time (h)	Lot# DC4601: Unprinted/Un packaged	Lot# 6J55895: Printed/Packaged
1	12.5 ± 1.7	13.6 ± 2.8
2	26.8 ± 2.8	28.7 ± 4.4
4	53.6 ± 3.7	56.2 ± 6.5
6	77.8 ± 6.5	80.3 ± 8.1
8	96.0 ± 3.6	98.2 ± 5.3
12	101.5 ± 1.1	104.3 ± 1.4
22	102.7 ± 1.4	105.3 ± 1.5

Dissolution data submitted by the firm are incomplete.

Composition of Nifedipine 30 mg Extended-Release Tablet (Not To Be Released Under FOI)

Table 15 shows composition of nifedipine 30 mg Extended Release Tablet.

Deficiencies:

1. The firm should conduct dissolution using the following method:

Medium: _____

Apparatus: _____ Speed: _____

Time: 1, 2, 4, 6, 8, 10, 12, 16 hours

RSD% for 12 units at each sampling time should be given. Range of % dissolution at each sampling time should also be included.

2. The dissolution method or methods the firm plans to use along with the proposed dissolution specification should be submitted in detail.
3. The firm should also submit dissolution data on printed/packaged (Lot# 6J55895) and unprinted/unpackaged (Lot# DC4601) version of biobatch using the method described in deficiency #1. RSD% for 12 units at each

sampling time should be given. Range of % dissolution at each sampling time should also be included.

Recommendation:

1. The *in vivo* bioequivalence study # 0696-005 conducted under fasting and non-fasting conditions by Elan Pharmaceuticals on its Nifedipine Extended Release Tablet, 30 mg, Lot # DC4601, comparing it to Bayer's ADALAT CC®, 30 mg Tablet, Lot # 6AIA, has been found acceptable.
2. The *in vivo* bioequivalence study # 0396-003 conducted under non-fasting conditions by Elan Pharmaceuticals on its Nifedipine Extended Release Tablet, 30 mg, Lot # 6J55895 comparing it to Bayer's ADALAT CC®, 30 mg, Lot # 6AIA, has been found acceptable.
3. The *in vivo* bioequivalence study # 0396-005 conducted at steady state conditions by Elan Pharmaceuticals on its Nifedipine Extended Release Tablet, 30 mg, Lot # 6J55895 comparing it to Bayer's ADALAT CC®, 30 mg, Lot # 6AIA, has been found acceptable.
4. The dissolution testing conducted by Elan Pharmaceuticals on its Nifedipine Extended Release 30 mg Tablet has been found **incomplete** by the Division of Bioequivalence for the deficiencies cited above (1-3).

/s/

Jahnvi S. Kharidia, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED MMAKARY
FT INITIALED MMAKARY
Moheb H. Makary, Ph.D.
Acting Team Leader, Branch III
Division of Bioequivalence

/s/

Concur:

/s/ Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence

Date: 3/10/98

cc: ANDA # 75-128 (original, duplicate), Kharidia, HFD-630, Drug File, Division File

Table 12: Pooled Analysis
(Study # 1 & Study #4)

Parameter	Elan 30mg nifedipine	Adalat CC® 30mg	90% Confidence intervals
C _{max}	39.52 ± 27.18	40.66 ± 19.87	80.36 - 114.06
AUC(0-60)	387.74 ± 168.54	441.18 ± 194.09	82.94 - 92.84
AUC(0-inf)	407.53 ± 162.62	454.45 ± 192.31	84.84 - 94.51
Log ₁₀ C _{max}	33.44 (1.75)	36.75 (1.56)	82.27 - 100.65
Log ₁₀ AUC(0-60)	355.66 (1.52)	405.45 (1.51)	83.98 - 91.63
Log ₁₀ AUC(0-inf)	378.84 (1.47)	420.02 (1.49)	86.46 - 94.10

APPEARS THIS WAY
ON ORIGINAL

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Table 15 :

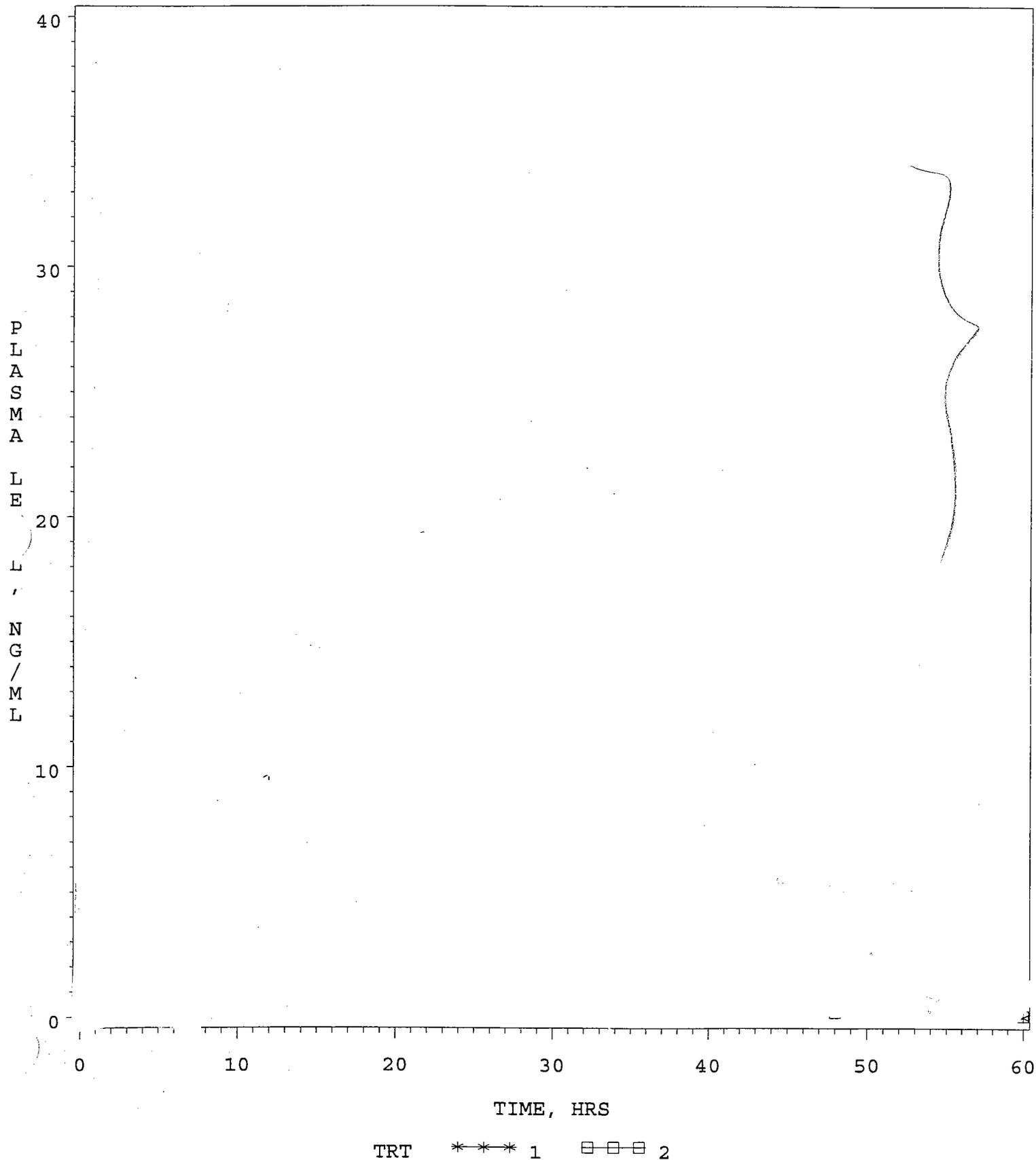
NOT TO BE
RELEASED UNDER
FOI "

Qualitative and Quantitative Composition (Mg/Tablet)

INGREDIENTS	ANDA BATCH (mg/TABLET)	SCALE-UP BATCH (mg/TABLET)
Nifedipine	30.00	30.00
Hydroxypropyl Methylcellulose	—	—
Microcrystalline Cellulose	—	—
Colloidal Silicon Dioxide	—	—
Magnesium Stearate	—	—
Hydroxypropyl Methylcellulose	—	—
Polyethylene Glycol	—	—
Titanium Dioxide	—	—
Iron Oxide	—	—

FIGURE - 1. PLASMA NIFEDIPINE LEVELS

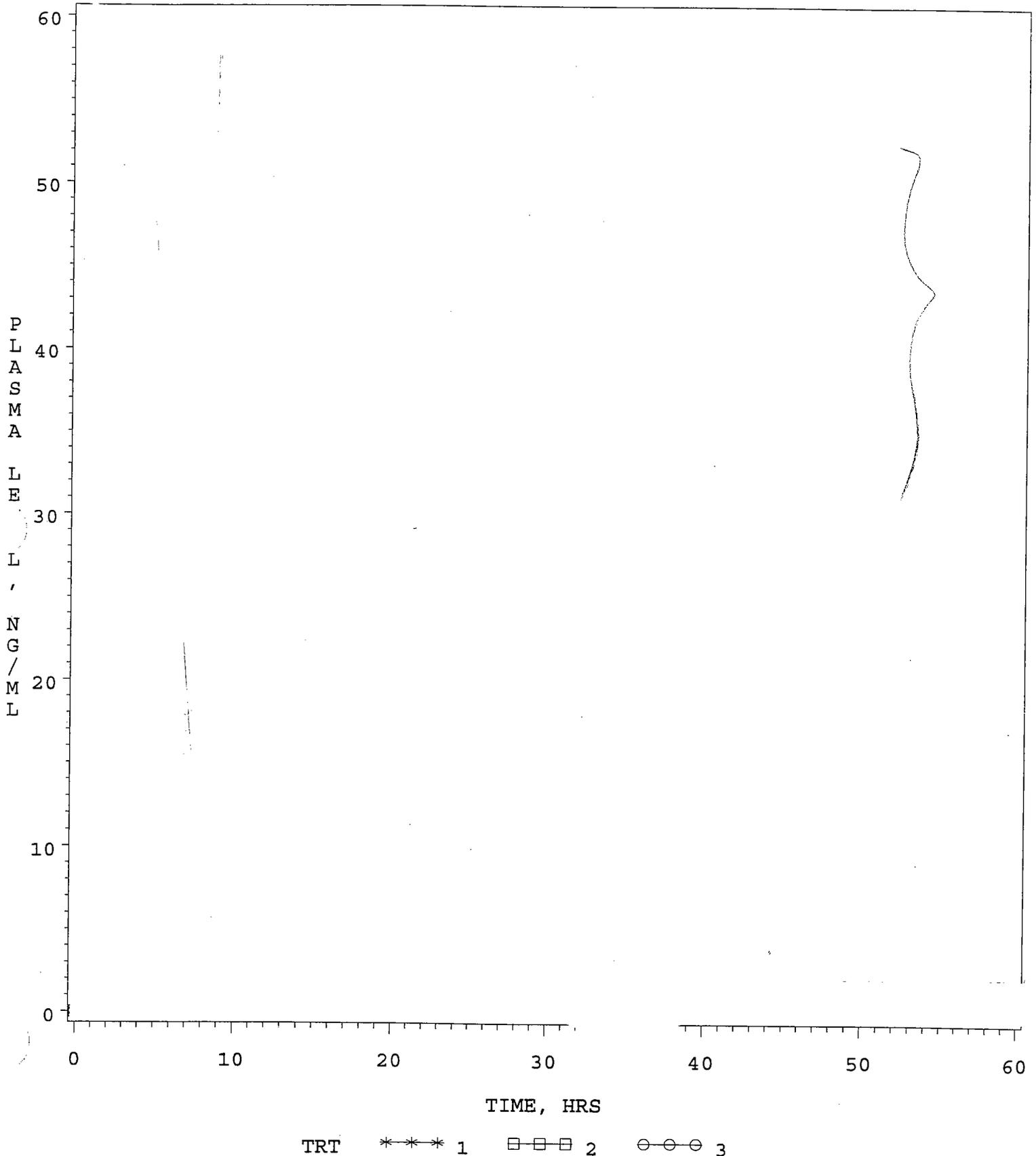
NIFEDIPINE ER TABLETS, 30 MG, ANDA #75-128
UNDER FASTING CONDITIONS
DOSE=1 X 30 MG



1=TEST PRODUCT (ELAN PHARMACEUTICALS) 2=REFERENCE PRODUCT (BAYER)

FIG 2. PLASMA NIFEDIPINE LEVELS

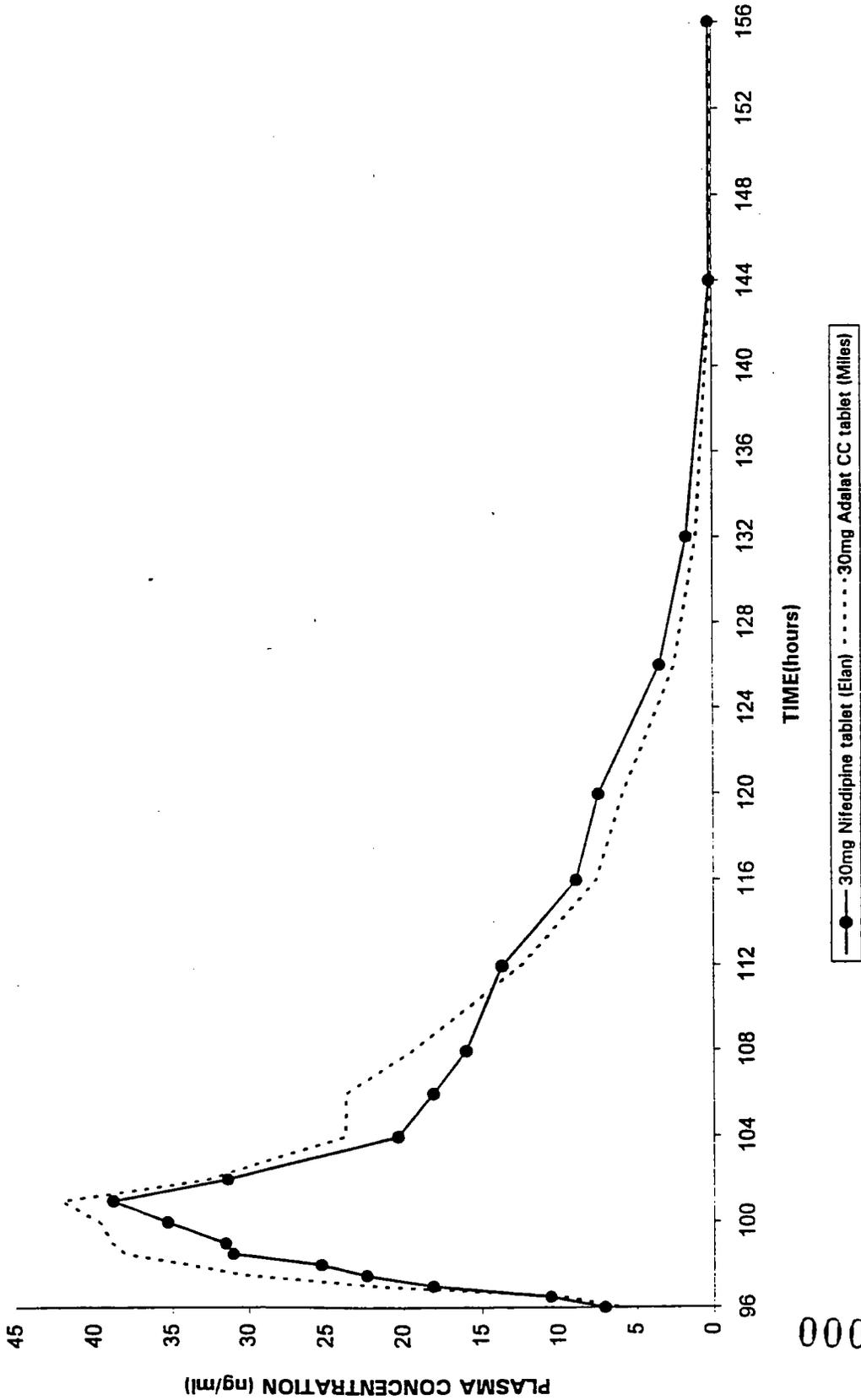
NIFEDIPINE EXTENDED RELEASE TABLETS, 30 MG, ANDA #75-128
UNDER NONFASTING CONDITIONS
DOSE=1 X 30 MG



1=TEST-FAST (ELAN) 2=TEST-NONFASTING (ELAN) 3=REF-NONFASTING (BAYER)

Figure 3: Plasma Nifedipine Levels at steady state

Plasma nifedipine concentration versus time
Protocol# 0396005
Mean Data



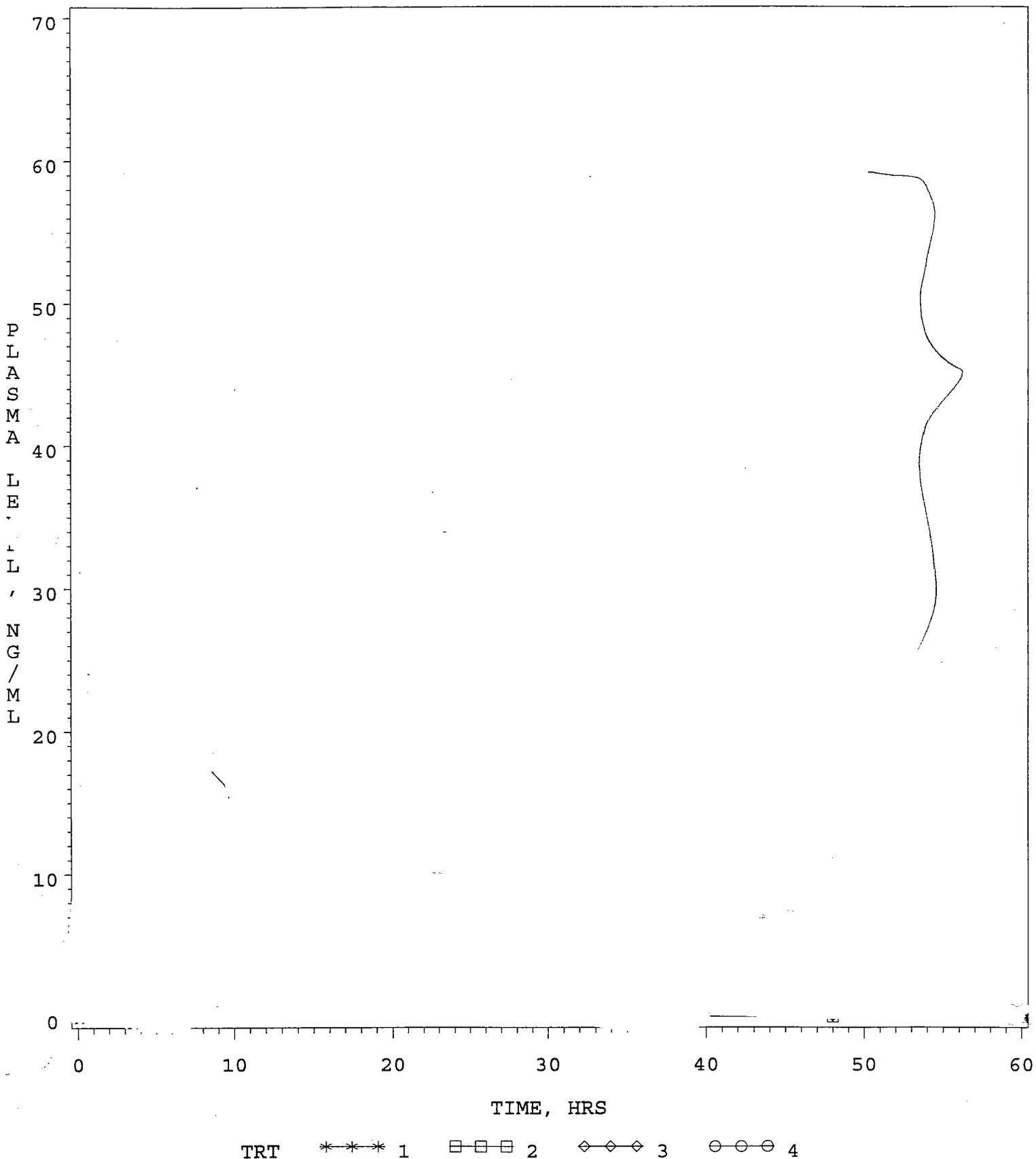
000314

FIGURE 4. PLASMA NIFEDIPINE LEVELS

NIFEDIPINE EXTENDED RELEASE TABLETS, 30 MG, ANDA #75-128

DOSE=1 X 30 MG

&TITLE6



~~TEST PRODUCT (HELANE)~~ ~~REFERENCE PRODUCT (BAYER)~~

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75-128

**ADMINISTRATIVE
DOCUMENTS**

JUSTIFICATION OF APPROVAL

This application is a first generic for the extended release formulation. The drug substance has a USP Monograph. AWD (source) has been supplying several immediate release manufacturers. The drug product has a PF proposal in Volume 23, Number 2. The firm has provided a comparison of how their methods and proposed specifications measure up to the PF proposals. The dissolution method and specifications have been reviewed by the Division of Bioequivalence and accepted. The stability data are satisfactory for the proposed bulk, and other container/closure systems (100 and 500 count bottles).

Radhika Rajagopalan, Ph.D.

**APPEARS THIS WAY
ON ORIGINAL**

Printed by Robert West
Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 27-May-1999 05:32pm
From: David Read
READD
Dept: HFD-007 WOC2 3047
Tel No: 301-594-2041 FAX 301-827-5562

TO: See Below

Subject: Re: FWD: TENTATIVE APPROVAL OF ANDA 75-128 FOR NIFEDIPINE EXTENDE

Cec-

Just FYI - there are no pending nifedipine citizen petitions in our shop (the last of these was closed about a year ago). I assume that the controlled correspondence 97-201 mentioned in the forwarded e-mail is referring to something other than a CP.

Dave

=====

FYI,

Tentative approval for generic version of Adalat CC.

Cecelia

Distribution:

TO: Cecelia Parise	(OC)	(PARISEC)
T ELIZABETH H DICKINSON	(OC)	(EDICKINS@OC.FDA.GOV)
BARBARA J STRADLING	(OC)	(BSTRADLI@OC.FDA.GOV)
TU. Jane Axelrad		(AXELRADJ)
CC: Robert West		(WESTR)
CC: Leanne Cusumano		(CUSUMANOL)
CC: Wayne Mitchell		(MITCHELLW)

E L E C T R O N I C M A I L M E S S A G E

Date: 12-Mar-1999 09:31am EST
From: Kassandra Sherrod
SHERRODK
Dept: HFD-617 MPN2 113
Tel No: 301-827-5849 FAX 301-594-3839

TO: Ted Sherwood

(SHERWOODT)

CC: Pat Beers-Block

(BEERSBLOCKP)

Subject: Nifedipine CC

Ted,

A TA package for ANDA 75-128, Elan's Nifedipine CC Extended release tablets is being prepared.

Kassandra

DIVISION APPROVAL SUMMARY

ANDA: 75-128

DRUG PRODUCT: Nifedipine Extended-release tablets, 30 mg

FIRM: Elan Pharmaceutical Research Corporation

DOSAGE: Extended-release Tablets

STRENGTH: 30 mg

CGMP STATEMENT/EIR UPDATE STATUS:

CGMP: Statement provided on page 173.

EIR: EER acceptable 3/22/99

METHODS VALIDATION:

Validation has been performed by the Philadelphia field labs. Assay and dissolution methods yielded satisfactory results. Results filed in volume 2.1.

STABILITY (Conditions, containers and methods)

Bio batch stability data are provided.

Test	Specification
Description	Round tablets with convex faces and uniform in appearance. Brick red color with 'WC 179' printed on one face
Identification	<hr/>
Weight variation	98.3-102.4% of mean tablet weight
Dissolution in at	1 Hr. NMT — dissolved 2 Hrs. — % dissolved 4 Hrs. — % dissolved 10 Hrs. NLT — dissolved

**ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application: **ANDA 75128/000**
 Stamp: **02-MAY-1997** Regulatory Due:
 Applicant: **ELAN PHARM**
1300 GOULD DR
GAINESVILLE, GA 30504

Priority:
 Action Goal:
 Brand Name:
 Established Name: **NIFEDIPINE**
 Generic Name:
 Dosage Form: **EXT (EXTENDED-RELEASE TABLET)**
 Strength: **30MG**

Org Code: **600**
 District Goal: **02-JUL-1998**

FDA Contacts: **T. AMES (HFD-640) 301-827-5849 , Project Manager**
S. BASARAN (HFD-647) 301-827-5849 , Team Leader

Overall Recommendation:

ACCEPTABLE on 05-OCT-1999 by S. FERGUSON (HFD-324) 301-827-0062
ACCEPTABLE on 22-MAR-1999 by M. EGAS (HFD-322) 301-594-0095
ACCEPTABLE on 12-DEC-1997 by M. EGAS (HFD-322) 301-594-0095

Establishment: _____ DMF No: _____
 _____ AADA No: _____

Profile: **CSN** OAI Status: **NONE**
 Last Milestone: **OC RECOMMENDATION**
 Milestone Date: **19-MAR-1999**
 Decision: **ACCEPTABLE**
 Reason: **BASED ON PROFILE**

Responsibilities: _____

Establishment: _____ DMF No: _____
 _____ AADA No: _____

Profile: **TTR** OAI Status: **NONE**
 Last Milestone: **OC RECOMMENDATION**
 Milestone Date: **19-MAR-1999**
 Decision: **ACCEPTABLE**
 Reason: **BASED ON PROFILE**

Responsibilities: _____

Establishment: **9611013** DMF No:
ELAN CORP PLC AADA No:

WESTMEATH COUNTY, ATHLONE,]

Profile: **TTR** OAI Status: **NONE**
 Last Milestone: **OC RECOMMENDATION**
 Milestone Date: **22-MAR-1999**

Responsibilities: **FINISHED DOSAGE
MANUFACTURER**

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: **1035761** DMF No:
ELAN PHARMACEUTICAL RESEARC AADA No:
1300 GOULD DR
GAINESVILLE, GA 30504

Profile: **TTR** OAI Status: **NONE** Responsibilities: **FINISHED DOSAGE PACKAGER**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **05-OCT-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

**APPEARS THIS WAY
ON ORIGINAL**

Printed by Pat Beers-Block
Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 17-Feb-2000 02:44pm

From: Pat Beers-Block
BEERSBLOCKP

Dept: HFD-640 MPN2 E260

Tel No: 301-827-5849 FAX 301-443-3839

TO: DSI Bioequivalence

(DSIBE)

CC: Robert West

(WESTR)

CC: Jennifer Fan

(FANJE)

CC: Dale Conner

(CONNERD)

Subject: Inspection status

We are reviewing ANDA 75-128 (Nifedipine Ext-rel tablets; 30mg strength) in anticipation of approval. A request for inspection of one of the clinical sites-
- and one of the analytical sites- ' was sent in March, 1999. Have these inspections been accomplished?

If not, do you have inspectional history for either of these facilities?

Along with these sites, the application also made reference to a single dose non-fasting study conducted by
study by and analytical work done for this Do you have any inspectional history for these sites?

Your help is greatly appreciated. pb2

APPEARS THIS WAY
ON ORIGINAL

CC: Pat Beers-Block
CC: C.T. Viswanathan
CC: Martin Yau
CC: Michael Skelly
CC: Jacqueline O'Shaughnessy

(BEERSBLOCKP)
(VISWANATHANC)
(YAUM)
(SKELLYM)
(OSHAUGHNESSY)

**APPEARS THIS WAY
ON ORIGINAL**

ANDA 75-128



OFFICE OF GENERIC DRUGS

Food and Drug Administration
HFD-600, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Fax: (301-594-0180)

FAX TRANSMISSION COVER SHEET

TO: APPLICANT: Elan Pharmaceutical Research
Corporation

PHONE: 770-⁵³⁸~~531~~-6360

ATTN: Roger Wayne Wiley

FAX: 770-531-0835

FROM: Mark Anderson

PROJECT MANAGER (301) 827-5849

Dear Sir:

This facsimile is in reference to your abbreviated new drug application for Nifedipine Extended-release Tablets, 30 mg.

We are pleased to inform you that this application is APPROVED!

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address..

X:\new\ogdadmin\macros\faxapp.frm

DATE: 3/16/99

TO: C.T. Vishwanathan, Ph.D.
Associate Director, Division of Scientific Investigations, HFD-340, MPN I

THROUGH: Dale P. Conner, Pharm. D. Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence, HFD-650

FROM: DBE/DBIB Liaison
Division of Bioequivalenc, Office of Generic Drugs. HFD-617, MPN II

SUBJECT: Biopharmaceutics Compliance Program 73-48.001
Request for Inspection

Clinical Laboratory: _____

Analytical Laboratory: _____

References:

ANDA# 75-128
Product Nifedipine ER Tabs
Sponsor Elan Pharm.
Submission Date 4/30/97

1. Bio-study attachment Content

single dose study multi-dose study fasting study food study

- _____ protocol
- _____ medical records/case reports
- _____ clinical records
- _____ analytical method validation data
- _____ sample chromatogram
- _____ raw data
- _____ study summary
- _____ other:

2. Facilities and Principal Investigators

Clinical Laboratory _____
Principal Investigator _____
Analytical Laboratory _____
Principal Investigator _____
Analytical Method _____

3. Areas of Inspection Requested

- Data audit of clinical report
- Data audit of analytical report
- Visual examination of test and reference samples retained at study site
- Other specific instruction

4. Reason for Inspection Request

- Routine data audit
- For Cause

COMMENTS:

FIRST GENERIC

5. Bio-study Status

- Study under review
- Study review completed
 - study incomplete pending additional information from sponsor
 - study unacceptable with questionable data pending inspection verification
 - study acceptable pending satisfactory inspection results
- Other:

CC: HFD-600 (OGD)
HFD-640 (Hare)
HFD-617 (DBE/GBIB Liaison)
HFD-344 (Vishwanathan)
HFD-65_ (Bio Reviewer) J. Kharidia
HFD-630 (ANDA# _____) 75-128

B 97-115

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 : May 12 1997

TO : Director
Division of Bioequivalence (HFD-650)

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

|S| 5/12/97

SUBJECT: Examination of the bioequivalence study submitted with an ANDA for Nifedipine Extended-release Tablets, 30 mg to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to USC 355(4) (B) (iv).

Elan Pharmaceutical Research Corp. has submitted ANDA 75-128 for Nifedipine Extended-release Tablets, 30 mg. The ANDA contains a certification pursuant to 21 USC 355(j) (2) (A) (vii) (iv) stating that a patent expiring November 23, 2010 will not be infringed by the manufacture or sale of the proposed product. In order to accept an ANDA for filing that contains such a patent certification, the Agency must formally 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 Elan on April 30, 1997 for its Nifedipine product satisfies the statutory requirements of "completeness" so that the ANDA may be filed and that a period of six months of market exclusivity can be granted to the applicant who submitted the first substantially complete ANDA under 21 USC 355(j) (4) (B) (iv).

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".

CDER Establishment Evaluation Report
for June 05, 1997

Page 1 of 1

Application: ANDA 75128/000
Stamp: 02-MAY-1997 Regulatory Due:
Applicant: ELAN PHARM
1300 GOULD DR
GAINESVILLE, GA 30504

Priority:
Action Goal:
Brand Name:
Established Name: NIFEDIPINE
Generic Name:
Dosage Form: TAB (TABLET)
Strength: 30MG

Org Code: 600

District Goal: 02-JUL-1998

FDA Contacts: T. AMES (HFD-617)
S. BASARAN (HFD-647)

301-827-5849 , Project Manager
301-827-5849 , Team Leader

Overall Recommendation:

Establishment:

DMF No:

Profile: CSN OAI Status: NONE
Last Milestone: SUBMITTED TO OC 05-JUN-1997

Responsibilities:

Establishment:

DMF No:

Profile: TCT OAI Status: NONE
Last Milestone: SUBMITTED TO OC 05-JUN-1997

Responsibilities:

FINISHED DOSAGE PACKAGER

Establishment: 9611013
ELAN CORP PLC
MONKSLAND IND ESTATE
WESTMEATH COUNTY, ATHLONE,

DMF No:
Profile: TCT OAI Status: NONE
Last Milestone: SUBMITTED TO OC 05-JUN-1997

Responsibilities:

FINISHED DOSAGE MANUFACTURER

APPEARS THIS WAY
ON ORIGINAL

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75-128

CORRESPONDENCE



February 4, 2000

élan pharmaceutical research corp.

1300 Gould Drive
Gainesville, Georgia 30504, USA
Telephone (770) 534-8239
Fax (770) 534-8247

VIA TELEFAX (301) 443-3839

Mr. Douglas Sporn, Director
Office of Generic Drugs (HFD-615)
CDER Food and Drug Administration
Document Control Room, Room 150
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Desk Copy: Ms. Cassandra Sherrod

NDA ORIG AMENDMENT
N/AM

RE: ANDA 75-128: Nifedipine Extended-release Tablets 30 mg
Telefax Response: Revision to Nifedipine Substance OVI Specification

Dear Mr. Sporn:

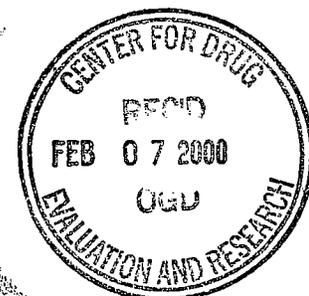
Reference is made to our Abbreviated New Drug Application for Nifedipine Extended-release Tablets 30mg (ANDA 75-128). In addition, reference is made to the telephone call from Ms. Cassandra Sherrod to Dr. Sharon Hamm on Wednesday, February 2, 2000, requesting that we revise the OVI specification in the Nifedipine drug substance analytical protocol (PRA01571) to state "*Meets the requirements of the current USP*" and submit immediately as a Telefax Response.

In accordance with this request we are amending our ANDA application with the analytical protocol revised as requested and have provided a copy in Attachment 1.

In the event you have any questions, please feel free to contact me at telephone (770) 538-6360 or telefax (770) 531-0835.

Sincerely,


Roger Wayne Wiley, R.Ph.
Director, North America Regulatory Affairs





Labeling review
drafted 1/7/00
/S/

élan pharmaceutical research corp.

1300 Gould Drive
Gainesville, Georgia 30504, USA
Telephone (770) 534-8239
Fax (770) 534-8247

January 6, 2000

MINOR TELEPHONE AMENDMENT
(500 Count TEVA Label)

Mr. Douglas Sporn, Director
Office of Generic Drugs (HFD-615)
CDER Food and Drug Administration
Document Control Room, Room 150
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

NDA ORIG AMENDMENT

N/A

**RE: ANDA 75-128: Nifedipine Extended-release Tablets 30 mg
500 Count (TEVA) Label**

Dear Mr. Sporn:

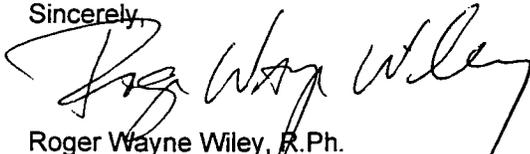
Reference is made to our Abbreviated New Drug Application for Nifedipine Extended-release Tablets 30mg (ANDA 75-128). Also, reference is also made to the submission of our amendment on December 3, 1999 requesting conversion of our "Tentative Approval" to a "Final Approval". In addition, reference is made to the telephone conversation between Chan Park, Adolph Vezza and Wayne Wiley on Tuesday, January 4, 2000 regarding the request for copies of the TEVA 500 count label.

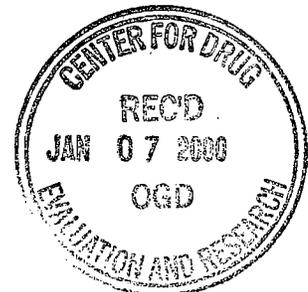
Per our discussion, final printed labels were reviewed and approved via the May 28, 1999 "Tentative Approval Letter", however since that time our distributor has changed from ~~_____~~ to TEVA. We included copies of FPL for the package insert and 100 count label showing TEVA as the distributor for information purposes only.

As requested, we are now providing 12 copies (Attachment 1) of the Final Printed Label for the 500 count (TEVA) label in order that the current labeling package at OGD (for final approval) can be complete.

In the event you have any questions, please feel free to contact me at telephone (770) 538-6360 or telefax (770) 531-0835.

Sincerely,


Roger Wayne Wiley, R.Ph.
Director, North America Regulatory Affairs



done 1/9/00
OK 4/26/99

1. Updated Analytical Protocols

The following Analytical Protocols have been updated mainly to provide clarification/revision to instructions for the analyst and are provided in Attachments 4-9. Details of the update for each individual protocol is provided in a cover sheet in the front of the Attachment:

<u>Analytical Protocol</u>	<u>Elan Code</u>
Attachment 4: Nifedipine	(PRA01571/6)
Attachment 5: Nifedipine ER 30mg Tablets (DC-ADA)	(4000093/2)
Attachment 6: Film Coated Nifedipine ER 30 mg Tablets	(5000041/1)
Attachment 7: Bulk Printed Film Coated 30mg Nifedipine ER Tablets	(5000042/3)
Attachment 8: Printed/Packaged FC Nifedipine ER 30mg Tablets (100's)	(5000043/2)
Attachment 9: Printed/Packaged FC Nifedipine ER 30mg Tablets (500's)	(5000044/2)

2. Updated Master Batch Record

The following Master Batch records have been updated mainly to provide clarification/revision to instructions for the operators and are provided in Attachments 10 & 11. Details of the update for each individual record is provided in a cover sheet in the front of the Attachment:

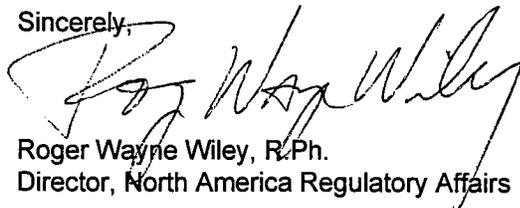
<u>Master Batch Record</u>	<u>Elan Code</u>
Attachment 10: Nifedipine 30mg ER Tablets (DC-ADA)	(4000093/6)
Attachment 11: Film-Coated Nifedipine 30mg ER Tablets	(5000041/5)

3. Final Printed Labeling

Copies of the current 100 count label and package outserts are provided in Attachments 12 & 13. Although final printed labeling (labels & outserts) were previously submitted and approved per the May 28, 1999 Tentative Approval letter, the distributor is now TEVA Pharmaceuticals, USA. Therefore, we are providing the agency copies of labeling with the TEVA logo/color scheme for information purposes only. Please note that the TEVA bottle label format required the addition of a "KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN" statement on the side panel.

In the event you have any questions, please feel free to contact me at telephone (770) 538-6360 or telefax (770) 531-0835.

Sincerely,



Roger Wayne Wiley, R.Ph.
Director, North America Regulatory Affairs



élan pharmaceutical research corp.

1300 Gould Drive
Gainesville, Georgia 30504, USA
Telephone (770) 534-8239
Fax (770) 534-8247

NOA ORIG AMENDMENT

AA

August 24, 1999

Mr. Douglas Sporn
Office of Generic Drugs (HFD-615)
CDER Food and Drug Administration
Document Control Room, Room 150
7500 Standish Place
Rockville, MD 20855-2773

**RE: ANDA 75-128: Nifedipine Extended-release Tablets 30 mg
Amendment:**

Dear Mr. Sporn:

Reference is made to our Abbreviated New Drug Application for Nifedipine Extended-Release Tablets 30mg. Reference is also made to the tentative approval letter issued by your Division on May 28, 1999 for this application. With this correspondence we are requesting an amendment to our application to allow for _____ facilities beyond those identified within the original application. Rather than await the future "tentative approval" amendment (requesting final approval of the application), we felt it appropriate to amend the application at this stage, so as to provide as much lead time for review as possible. Furthermore, an unexpected situation has recently occurred creating the urgency for this request.

As outlined in our pending application, tablet manufacturing occurs at our Athlone Ireland facility. We had however identified _____ as a contractor to perform the _____ of the trade configurations.

On July 25, 1999, _____ announced the acquisition of the parent corporation for _____. As _____ is a competitor in this arena, having recently received their own "tentative approval" for the first generic for nifedipine extended release 60 mg, we are compelled to identify _____ locations. More specific detail on these operations follows:



Tablet Identification Imprinting

Within the current ANDA, tablets are manufactured at our Athlone Ireland facility and sent to _____ We would like to request approval for Elan's Athlone manufacturing site to serve as an alternate imprinter within this application. As Elan's Athlone facility is responsible for tablet manufacture, the imprinting operation would enable the entire process to be completed at the one facility, in lieu of shipping tablets off site to _____ for _____

Packaging

In the current ANDA application bulk tablets are shipped from Elan's Athlone Ireland facility to _____ into _____. We would like to request that Elan's Gainesville, GA facility serve as an alternate packaging site for this application as well. The bulk finished/imprinted Nifedipine Extended Release 30 mg tablets could then be shipped directly from Elan's Athlone Ireland facility to the Elan Gainesville, GA facility for packaging, labelling and final Quality Control Release.

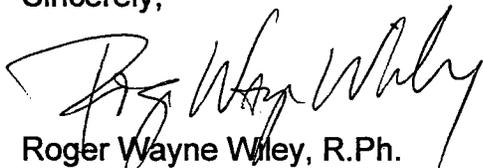
Elan's Gainesville, GA facility was recently approved to package 8 of Elan's products under NDA's 19,614, 20,943 and NDA 20,397 as follows:

NDA 19,614 Verelan 120mg, 180mg, 240mg, 360mg
NDA 20,943 Verelan PM 100mg, 200mg, 300mg
NDA 20,397 Zanaflex 4mg

For ease of the reviewer, copies of the approval letters associated with these recent packaging supplement approvals are included in Attachment 1 herein.

Given the unusual and unexpected potential business challenge of continuing to rely on _____ as a sole provider for _____ under this application, we would greatly appreciate your expedited review of this request, in advance of the submission of our future amendment requesting final approval of this application. Should you have need for any further information or background in this regard, please do not hesitate to contact me. Thank you in advance for your assistance.

Sincerely,



Roger Wayne Wiley, R.Ph.
Director, North America Regulatory Affairs

RWW/bh



élan pharmaceutical research corp.

1300 Gould Drive
Gainesville, Georgia 30504, USA
Telephone (770) 534-8239
Fax (770) 534-8247

April 12, 1999

FOR DRUG AMENDMENT

AC

Mr. Douglas Sporn
Office of Generic Drugs (HFD-615)
CDER Food and Drug Administration
Document Control Room, Room 150
7500 Standish Place
Rockville, MD 20855-2773

75-128

RE: ²75-138: Nifedipine Extended-release Tablets 30 mg (Minor Telephone Amendment)
Response to Telephone Request

Dear Mr. Sporn:

Reference is made to our Abbreviated New Drug Application for Nifedipine Extended-release Tablets (ANDA 75-128) dated April 30, 1997. In addition, reference is made to the telephone call from Radhika Rajagopalan (CMC Reviewer) requesting that Elan submit a Minor Telephone Amendment to revise the following:

1. Drug Substance: Nifedipine impurities need to be reduced from _____
2. Drug Product: Impurities (known and unknown) should be reduced from _____
_____ on both the drug product release and stability specifications.

Revised analytical protocols reflecting these changes are provided under Attachment 1 (Drug Substance) and Attachment 2 (Drug Product).

In the event you have any questions, please feel free to contact me at telephone (770) 538-6360 or telefax (770) 531-0835.

Sincerely,

Roger Wayne Wiley, R.Ph.
Director, North America Regulatory Affairs

RECEIVED

APR 13 1999

GENERIC DRUGS



élan pharmaceutical research corp.

1300 Gould Drive
Gainesville, Georgia 30504, USA
Telephone (770) 534-8239
Fax (770) 534-8247

October 23, 1998

MAJOR AMENDMENT

Mr. Douglas Sporn
Office of Generic Drugs (HFD-615)
CDER Food and Drug Administration
Document Control Room, Room 150
7500 Standish Place
Rockville, MD 20855-2773

NDA ORIG AMENDMENT
N/AC

**RE: 75-128: Nifedipine Extended-release Tablets 30 mg
Response to Chemistry & Bioequivalency FDA Deficiency Telefaxes**

Dear Mr. Sporn:

Reference is made to our Abbreviated New Drug Application for Nifedipine Extended-release Tablets (ANDA 75-128) dated April 30, 1997. In addition, reference is also made to the Chemistry, Manufacturing & Control Deficiency Telefax dated September 9, 1998 and the Bioequivalence Deficiency Telefax dated March 10, 1998. Copies of both telefaxes are provided in Attachment 1. We have responded to each of the deficiencies cited in the telefaxes in a question/answer format with FDA questions in bold and Elan's responses in standard type.

Please direct any written communications regarding this ANDA to the undersigned or Roger Wayne Wiley at the above address. If you need to call or fax me, my numbers are (770) 534-8239 (phone) and (770) 531-0835 (fax).

Sincerely,

Helen M. Ryan M.Sc.
Manager, Regulatory Affairs

Enclosures

K:\Wjcc30-98\Subm\fdarep1098.doc

RECEIVED
OCT 26 1998
GENERIC DRUGS



élan pharmaceutical research corp.

1300 Gould Drive
Gainesville, Georgia 30504, USA
Telephone (770) 534-8239
Fax (770) 534-8247

July 28, 1998

NDA ORIG AMENDMENT
AC

Mr. Douglas Sporn
Office of Generic Drugs (HFD-615)
CDER Food and Drug Administration
Document Control Room, Room 150
7500 Standish Place
Rockville, MD 20855-2773

**RE: ANDA 75-128: Nifedipine Extended-release Tablets 30 mg
Hard Copy of Telefaxed Submission of July 28, 1998**

Dear Mr. Sporn

Enclosed please find the hard-copy of the faxed submission forwarded to the attention of Ms. Radhika Rajagopalan today.

If you have any further questions please feel free to contact me at 770-538-6345.

Sincerely,


Helen Ryan, M.Sc
Manager, Regulatory Affairs

cc: Radhika Rajagopalan

RECEIVED
JUL 29 1998
GENERIC DRUGS



élan pharmaceutical research corp.

1300 Gould Drive
Gainesville, Georgia 30504, USA
Telephone (770) 534-8239

VIA TELEFAX (1) 301-443-3839 (770) 534-8247

July 28, 1998

Ms. Radhika Rajagopalan
Office of Generic Drugs
CDER Food and Drug Administration
Document Control Room, Room 150
7500 Standish Place
Rockville, MD 20855-2773

**RE: ANDA 75-128: Nifedipine Extended-release Tablets 30 mg
Current Finished Product Protocols**

Dear Ms. Rajagopalan

Following on from our telephone conversation this morning, attached please find the following documentation you requested:

1. Current Analytical Protocol
2. Sample of the ~~_____~~ for the dissolution standard

Based on our discussions this morning I understand that there is some confusion regarding our proposed analytical methods.

The automated *in vitro* dissolution test procedure described in the ANDA (Appendix 4, Volume 4 of ANDA) was initially developed and validated for the in-process and finished product release testing and utilized a detection ~~_____~~. The stability laboratory did not at that time have the equipment to perform automated dissolution and hence a manual dissolution was required. This method was developed using a standard ~~_____~~ which resulted in sample response readings falling out of the linear range of the ~~_____~~. It is for this reason that the manual method uses a ~~_____~~.

The use of the manual dissolution method has since been discontinued. The original automated dissolution procedure has been modified to detect over the ~~_____~~ to remove potential excipient interference. This procedure has been validated (see Appendix 5, Volume 1.4 of ANDA) and will be used for routine QC release and stability testing of scale up production batches.

The methods described in the finished product protocol provided in the Methods Validation Packaged submitted to the FDA November 12, 1998 are those proposed for release and stability purposes for scale-up.

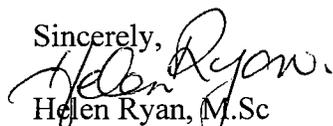
In our March 18, 1998 submission to the Office of Generic Drugs, responding to the February 12, 1998 Chemistry Telefax, the analytical protocols were modified to address comments raised by the reviewer. None of the changes have any impact on the dissolution methods described in the November 1997 methods validation package, sent to the attention of Mr. Nicholas Falcone at the Philadelphia District Office.

Therefore you are advised of the following:

1. The methods described in the attached protocol, previously submitted as Attachment 11 to our March 18, 1998 correspondence, will be utilized for both QC release and for monitoring stability.
2. In response to the problems regarding preparation of the dissolution reference standard I have organised for a sample of the reference standard currently being used at our Irish facility to be couriered to my attention. Once you have had an opportunity to review the attached protocol I will then arrange for a teleconference with our Director of Analytical Services to help explore the problem further.

A hard copy of this correspondence is to follow by courier. If you have any further questions please feel free to contact me at 770-538-6345.

Sincerely,



Helen Ryan, M.Sc
Manager, Regulatory Affairs



élan pharmaceutical research corp.

1300 Gould Drive
Gainesville, Georgia 30504, USA
Telephone (770) 534-8239
Fax (770) 534-8247

July 22, 1998

Mr. Douglas Sporn
Office of Generic Drugs (HFD-615)
CDER Food and Drug Administration
Document Control Room, Room 150
7500 Standish Place
Rockville, MD 20855-2773

NEW BUSINESS

NRY
131
7/22/98

**RE: ANDA 75-128: Nifedipine Extended-release Tablets 30 mg
Acknowledgement of Receipt of Bioequivalency Deficiency Telefax**

Dear Mr. Sporn:

Reference is made to your Bioequivalency Deficiency telefax correspondence to us dated March 10, 1998. In accordance with the provisions of 21 CFR 314.120, I wish to confirm in writing our intention to amend the application, responding in full to the deficiencies as listed.

Presently we are conducting dissolution testing as requested in the deficiency telefax and as soon as the data becomes available we will submit our complete response.

If you have any further questions please feel free to contact the undersigned or Helen Ryan at 770-534-8239.

Sincerely,

A handwritten signature in cursive script that reads "Roger Wayne Wiley".

Roger Wayne Wiley, R.Ph.
Director, North America Regulatory Affairs

CC: Nancy Chamberlin – Project Manager

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JUL 23 1998

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élan pharmaceutical research corp.

1300 Gould Drive
Gainesville, Georgia 30504, USA
Telephone (770) 534-8239
Fax (770) 534-8247

March 18, 1998

Mr. Douglas Sporn
Office of Generic Drugs (HFD-615)
CDER Food and Drug Administration
Document Control Room, Room 150
7500 Standish Place
Rockville, MD 20855-2773

ANDA ORIG AMENDMENT ^{FPL}
N/AC

**RE: 75-128: Nifedipine Extended-release Tablets 30 mg (MAJOR AMENDMENT)
Response to Chemistry and Labeling Deficiencies**

Dear Mr. Sporn:

Reference is made to our Abbreviated New Drug Application for Nifedipine Extended-release Tablets (ANDA 75-128) dated April 30, 1997. In addition, reference is also made to the deficiency letters for chemistry and labeling dated February 12, 1998. A copy of this correspondence is provided in Attachment 1. We have responded to each of the chemistry deficiencies cited in the aforementioned letter in a question/answer format with FDA questions in bold and Elan's responses in standard type.

In response to the attached labeling deficiencies, twelve sets of final printed labels and labeling (Note: combination label and package insert in "fix-a-form" design) are provided in Attachment 15. In addition, a side-by-side comparison of the original Elan labeling compared to the revised labeling including the Agency's recommendations is also provided as requested in Attachment 14.

Please direct any written communications regarding this ANDA to the undersigned or Helen Ryan at the above address. If you need to call or fax me, my numbers are (770) 534-8239 (phone) and (770) 531-0835 (fax).

Sincerely,


Roger Wayne Wiley, R.Ph.
Director, North America Regulatory Affairs

7/23/98
called re:
distribution

Enclosures

K:\Nif-1998\Subm\Response 0216.doc

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MAR 19 1998
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élan pharmaceutical research corp.

1300 Gould Drive
Gainesville, Georgia 30504, USA
Telephone (770) 534-8239
Fax (770) 534-8247

NEW CORRESP
NC

M.E. 2/25/98
J.S.

February 20, 1998

VIA TELEFAX 301-443-3839
& FEDERAL EXPRESS

Ms. Kassandra Sherrod, Project Manager
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

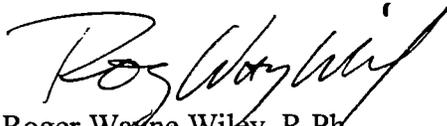
RE: ANDA 75-128 Nifedipine Extended-release Tablets 30mg

Dear Ms. Sherrod:

Reference is made to your telefax correspondence to us dated February 12, 1998 (telefaxed February 13, 1998) detailing deficiencies in the form of a major amendment to this application.

In accordance with the provisions of 21 CFR 314.120, I wish to confirm in writing our intentions to respond in full to the deficiencies as listed. We understand that our response will constitute a Major Amendment and should be designated as such.

Sincerely,


Roger Wayne Wiley, R.Ph.
Director, North America Regulatory Affairs

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FEB 22 1998
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élan pharmaceutical research corp.

1300 Gould Drive
Gainesville, Georgia 30504, USA
Telephone (770) 534-8239
Fax (770) 534-8247

NEW CORRESP
WC

November 13, 1997

Mr. Douglas Sporn
Office of Generic Drugs (HFD-615)
CDER Food and Drug Administration
Document Control Room, Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: Nifedipine CC Extended Release Tablets 30 mg (ANDA #75-128).

Dear Mr. Sporn:

Reference is made to our Abbreviated New Drug Application for Nifedipine CC Extended Release Tablets 30 mg (ANDA #75-128). In addition, reference is made to the letter from Mr. Nicholas Falcone dated October 28, 1997 requesting methods validation samples for evaluation. A copy of this letter follows.

In addition, please find enclosed for your information, a copy of the information submitted with the methods validation samples for evaluation in response to the October 28, 1997 letter.

Sincerely,

A handwritten signature in cursive script that reads 'Darlene Conrad'.

Darlene Conrad
Manager, Regulatory Affairs

Enclosures

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NOV 14 1997

GENERIC DRUGS



DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Laboratory Branch
U.S. Customhouse/Rm 900
2nd and Chestnut Streets
Philadelphia, PA 19106-2973

ANDA METHOD VALIDATION LETTER

DATE: October 28, 1997

ADDRESS: Mr. Roger Wayne Wiley,

Dear Mr. Wiley,

The Food and Drug Administration (FDA) will be performing method validation studies on Nifepidine CC Extended Release Tablets 30mg, in connection with ANDA 75-128.

With your cooperation we can promptly complete this portion of our evaluation of your application.

In order to perform the necessary testing, please provide us with a sample from the reserve portion of the lot used to establish the bioequivalence or bioavailability of your product. Ideally, this sample should be within the proposed expiration date. If it is beyond this date and there is another pre-approval batch within expiration, send that instead. If, however, a batch not in the ANDA is used, the batch record and Certificate of Analysis must be submitted as an unsolicited amendment to the application.

The sample should consist of the following:

- Nifepidine - Reference Standard- 500mg
- Product- Nifepidine E.R. Tablets 30mg-
- Related Substances- Reference Standards-
- a) _____
- b) _____

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NOV 14 1997

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The worksheet for the analysis of the same lot with calculations, results, associated

- Non-compendial reference standards that are needed to test the sample, including impurity and related compound standards. A non-compendial reference standard is one that is not available from the USP.

- For new or unusual chemical compounds, safety or handling information that would be important in their laboratory use information.

Please send us the CFN number of the manufacturer site. (registration number)

Please forward these materials within ten days of receipt via express or overnight mail to:

Nicholas Falcone
Food and Drug Administration
U.S. Customs House/Rm 900
2nd and Chestnut Sts.
Philadelphia, PA 19106-2973

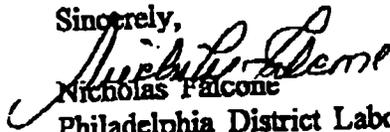
Important:

In addition, in connection with other work that needs to be completed regarding your application, please include in your sample package a letter indicating whether an in-vivo or in-vitro bioequivalence study was performed. If so, please provide the facility name and address. If no study was done, include a letter so stating nevertheless.

Thank you in advance for your cooperation. Please do not hesitate to call or FAX if you have any questions. You may contact me directly by telephone (215-597-4390 ext 4627) or by FAX (215-597-6649)

Also if any change was made in the methods, after the submission please send us the new method(s), if not, indicate with a statement that no change was made.

Sincerely,


Nicholas Falcone
Philadelphia District Laboratory
NDA/ANDA Coordinator



November 12, 1997

élan pharmaceutical research corp.

1300 Gould Drive
Gainesville, Georgia 30504, USA
Telephone (770) 534-8239
Fax (770) 534-8247

Mr. Nicholas Falcone
Food and Drug Administration
U.S. Customs House/Rm 900
2nd and Chestnut Sts.
Philadelphia, PA. 19106-2973

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RE: Nifedipine CC Extended Release Tablets 30 mg. NOV 14 1997
ANDA #75,128: Methods Validation Samples

GENERIC DRUGS

Dear Mr. Falcone

Reference is made to our pending Abbreviated New Drug Application for Nifedipine CC Extended Release Tablets 30mg, (ANDA 75,128). In addition reference is made to the letter from your office dated October 28, 1997 requesting methods validation samples for evaluation.

In response to your request the following samples/information are enclosed for this evaluation:

- 1) The in-vivo bioequivalence studies for this application were conducted at ~~_____~~
~~_____~~. The studies conducted for this ANDA were a Single dose (0396004), Food Effect (0396003) Steady State(0396005) and Food Effect ((0696005)
- 2) *Samples*
 - i) Nifedipine CC Extended Release Tablets 30mg (200 tablets) lot #BN 6I55895.
 - ii) Nifedipine Standard Batch No. C09910
 - iii) ~~_____~~ Analog ~~_____~~ USP Standard Cat # 46360 (2 bottles) Lot J
 - iv) ~~_____~~ Analog ~~_____~~ JSP Standard Cat #46370 (2 bottles) Lot J, Lot I

- 3) Attachment 1: Analytical protocols revised since submission of original ANDA and Methods Validation package.
- 4) Attachment 2: Laboratory Analysis Report.
- 5)
 - Appendix 1: Appearance and identification*
 - Appendix 2: Weight variation*
 - Appendix 3: Assay and related substances*
 - Appendix 4: Dissolution*
 - Appendix 5: Content uniformity*
 - Appendix 6: Friability, hardness and moisture*
- 6) Attachment 3: MSDS documents for above samples.

Should you have any questions regarding the contents of this submission, please do not hesitate to contact me at (770) 538-6356 phone and/or telefax at (770) 531-0835.

Sincerely,



Darlene Conrad
Manager, Regulatory Affairs

LAW OFFICES

CONNOLLY, BOVE, LODGE & HUTZ

1220 MARKET STREET

P.O. Box 2207

WILMINGTON, DELAWARE 19899

TELEPHONE (302) 658-9141

FACSIMILE (302) 658-5614

August 22, 1997

NAT

*litigation
filed against
Elan
9/10/97
NEW CORRESP
NC*

JAMES M. MULLIGAN, JR.
ARTHUR G. CONNOLLY, JR.
RUDOLF E. HUTZ
ROLD PEZZNER
WIN D. FAIRCHILD (MI. BAR)
CHARL M. BECK (D.C. BAR)
PAUL E. CRAWFORD
STANLEY C. MACEL, III
THOMAS M. MESHBESHER
HENRY E. GALLAGHER, JR.
GEORGE PAZUNIAK
N. RICHARD POWERS
RICHARD DAVID LEVIN
JOHN A. CLARK, III
JEFFREY B. BOVE
JAMES J. WOODS, JR.
COLLINS J. SEITZ, JR.
EDWARD F. EATON
CHARLES J. DURANTE
PATRICIA SMINK ROGOWSKI
MARY W. BOURKE
ROBERT G. MCMORROW, JR. (PA. BAR)
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ARTHUR G. CONNOLLY, III

ARTHUR G. CONNOLLY
PARTNER EMERITUS
WERNER H. HUTZ
1944-1970
JANUAR D. BOVE, JR.
1949-1991
COUNSEL
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ANNE L. BARNETT
GERARD M. O'ROURKE
KAREN C. BIFFERATO
OLEH V. BILYNSKY (PA. BAR)
PATRICIA L. KELLY (PA. BAR)
JULIE S. DVORAK

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
5600 Fishers Lane
Rockville, MD 20857

Re: ANDA 75-128
Notice of Filing Legal Action for Patent Infringement

We represent Bayer AG and Bayer Corporation who have brought suit against Elan Pharmaceutical Research Corp. for infringement of US Patent Nos. 5,264,446 and 4,892,741 by the submission of the above-referenced ANDA.

Pursuant to CFR § 314.107(f)(2), Bayer AG provides notification as follows:

- (i) The ANDA number is 75-128.
- (ii) The name of the abbreviated new drug applicant is Elan Pharmaceutical Research Corp.
- (iii) The notice from Elan Pharmaceutical Research Corp. to Bayer about the ANDA filing did not provide an established name for the ANDA drug product. However, it is referred to as a "... once-daily formulation of nifedipine" and "an extended release table dosage form containing 30 mg. of nifedipine".
- (iv) We certify that the above-referenced patent infringement suit was filed under Civil Action No. 2:97 - CV-0143-WCO in the United States District Court for the Northern District of Georgia on August 22, 1997. A copy of the summons and complaint are enclosed.

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AUG 26 1997

GENERIC DRUGS

Office of Generic Drugs

Page 2

August 22, 1997

Bayer AG received notice dated July 8, 1997, pursuant to § 505(j)(2)(B) of the Food, Drug and Cosmetic Act (the "Act") of submission of the above-referenced ANDA. Accordingly, pursuant to § 505(j)(4)(B)(iii) of the Act, approval of the above-referenced ANDA may not be made effective until the expiration of the 30-month period beginning from Bayer AG's receipt of such notice, i.e., until January 8, 2000, or such shorter or longer period as the court may order pursuant to said section of the Act.

Respectfully submitted,



Stanley G. Mace, III

SCM,III/saw
Enclosures

cc (w/enc.): Janet Woodcock, Director
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-001
Room 6027
Woodmont Office Complex 2
1451 Rockville Pike
Rockville, MD 20852

Jane Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-005
Woodmont Office Complex 2
1451 Rockville Pike
Rockville, MD 20852

Margaret Jane Porter, Esquire
Chief Counsel
Food and Drug Administration
CGF-1
Room 657
Parklawn Bldg.
5600 Fishers Lane
Rockville, MD 20857



April 30, 1997

élan pharmaceutical research corp.

1300 Gould Drive
Gainesville, Georgia 30504, USA
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Fax (770) 534-8247

Mr. Douglas Sporn
Office of Generic Drugs
CDER, Food and Drug Administration
Metro Park North II
Document Control Room, Room 150
7500 Standish Place
Rockville, MD 20855-2773

505 (1)(2)(a) (ok)
151
6/5/97

**RE: NIFEDIPINE CC Extended Release Tablets 30 mg
Original ANDA Submission**

Dear Mr. Sporn:

Élan Pharmaceutical Research Corporation is enclosing herein an original Abbreviated New Drug Application (ANDA) for a 30mg Nifedipine Extended-Release Tablet that is bioequivalent to the listed drug, ADALAT CC®, manufactured by Bayer pursuant to NDA #20,198. This application is being submitted on behalf of Élan Corporation, plc of Athlone, Ireland.

This ANDA consists of thirteen volumes. The archival copy (blue jacket) contains all the information required in the ANDA and a technical review copy (red jacket) which contains all of the information in the archival copy with the exception of the Bioequivalence section (VI). The Bioequivalence section (VI) is provided in orange jackets. Required diskettes containing analytical statistical files are provided within volume 1 of the pharmacokinetic (orange volume) review copy under Section VI (Attachment 1). Additional copies (4) of the Methods Validation Package are also included and identified accordingly.

Furthermore, this letter certifies that concurrent with the filing of this ANDA, a true Field Inspection Copy of the chemistry/technical section of the ANDA (including a copy of the 356h form and a certification that the contents are a true copy of those filed with the Office of Generic Drugs) is included with the submission to be held at the Agency's Documentation Management Branch until requested. The manufacture of NIFEDIPINE CC Extended Release Tablets 30 mg will be at Élan's Athlone, Ireland facility.

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MAY 02 1997

GENERIC DRUGS



Please direct any written communications regarding this ANDA to the undersigned or Helen Ryan at the above address. If you need to call or fax me, my numbers are (770) 534-8239 (phone) and (770) 531-0835 (fax).

Sincerely yours,

Roger Wayne Wiley, R. Ph.
Director, North America Regulatory Affairs

K:\nifcc30\fd43097.doc/hr/hr