CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

75-269

Generic Name: Nifedipine Extended-release Tablets USP, 30 mg and 60 mg

Sponsor: Keller and Heckman

Approval Dates: December 4, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
75-269

CONTENTS

Reviews / Information Included in this ANDA Review.	
Approval Letter	X
Tentative Approval Letter	X
ANDAs	
Approvable Letter	
Final Printed Labeling	X
Medical Review(s)	
Chemistry Review(s)	X
EA/FONSI	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology & Biopharmaceutics Reviews	
Bioequivalence Review(s)	X
Administrative Document(s)	X
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-269

APPROVAL LETTER

ANDA 75-269

DEC 4 2000

Keller and Heckman
U.S. Agent for Biovail Laboratories, Incorporated
Attention: John B. Dubeck
1001 G Street N.W., Suite 500 West
Washington, D.C. 20001

Dear Sir:

This is in reference to your abbreviated new drug application dated December 9, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Nifedipine Extended-release Tablets USP, 30 mg and 60 mg.

Reference is also made to the Tentative Approval letter issued June 29, 1999 and to your amendments dated November 9, 22, and 27, 2000.

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 [the '741 patent]) and on November 23, 2010, (U.S. Patent No. 5,264,446 [the '446 patent]). Your application contains Paragraph IV Certifications to both patents 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 these patents or that the patents are otherwise invalid. You further informed the Agency that the patent and NDA holder initiated a patent infringement suit against you (for the '446 patent) in the United States District Court for the District of Puerto Rico (Bayer AG, Bayer Corporation v. Biovail Laboratories Incorporated and Biovail Corporation International, Civil Actions No. 98-1282RLA and 98-1768HL. An additional suit (for the '446 patent) against Biovail is also pending in the United States District Court for the District of Columbia (Civil Action No. 1:98CV01681).

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 USP, 30 mg and 60 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 900 mL of 0.5% sodium lauryl sulfate in simulated gastric fluid (SGF), pH 1.2 using USP XXIV apparatus II (paddle) at 100 rpm.

The 30-mg tablets of the test product should meet the following tentative specifications previously proposed by the Agency:

Time (hour)	Specifications
1	[redacted]
4	[redacted]
12	NLT [redacted]

The 60-mg strength of the test product should meet the following tentative specifications currently proposed by the Agency:

Time (hour)	Specifications
1	[redacted]
4	[redacted]
12	NLT [redacted]

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.

We note that with respect to the 60 mg strength only of this drug product, Biovail Laboratories Incorporated (Biovail) was the first applicant to submit a substantially complete ANDA with

a Paragraph IV Certification. Therefore, Biovail is eligible for 180-days of market exclusivity for the 60 mg strength. Such exclusivity will begin to run either from the date Biovail begins commercial marketing of the 60 mg strength, or from the date of a decision of a court finding the patent invalid or not infringed, whichever event occurs earlier [Section 505(j)(5)(B)(iv)]. A court decision that can trigger the beginning of exclusivity is a decision of a court from which no appeal may be taken (which might not be the one from the district court). With respect to the "first commercial marketing" trigger for the commencement of exclusivity, please refer to 21 CFR 314.107(c)(4). The Agency expects that you will begin commercial marketing of the 60 mg strength of this drug product in a prompt manner.

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

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

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

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.

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,

/S/ 12/4/00

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

cc: ANDA 75-269
Division File
Field Copy
HFD-610/R. West
HFD-210/B. Poole
HFD-330
HFD-205
HFD-617/B.McNeal

/S/ 12/4/00

Endorsements:
HFD-647/M.Selvam/ /S/ 11/29/00
HFD-647/U.Venkataram/ /S/ 11/29/00
HFD-617/B.McNeal/ /S/ 11/29/00
HFD-613/A.Vezza/ /S/ 11/29/00
HFD-613/C.Hoppes/ /S/ 11/29/00

Filename:V:\FIRMSAM\BIOVAIL\LTRS&REV\75269AP+180exc.doc

F/T by

APPROVAL
PACT

cmc satisfactory
/S/ 11/30/00

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-269

TENTATIVE APPROVAL LETTER

ANDA 75-269

JUN 29 1999

Keller and Heckman
Attention: John Dubeck
U.S. Agent for : Biovail Laboratories, Inc.
Suite 500 West
1001 G Street, N.W.
Washington, DC 20001

Dear Sir:

This is in reference to your abbreviated new drug application dated December 9, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Nifedipine Extended-release Tablets, 30 mg and 60 mg.

Reference is also made to your amendments dated April 6, April 15, June 17, July 7, July 9, July 28, September 18, September 24, and November 10, 1998; and April 22, June 9, and June 14, 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 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 (the '741 patent)] and November 23, 2010 [U.S. Patent No. 5,264,446 (the '446 patent)]. 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 these 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 Biovail Laboratories, Inc. (Biovail) 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 involving the '446 patent against Biovail in the United States District Court for the District of Puerto Rico (Bayer AG, Bayer Corporation v. Biovail Laboratories Incorporated, and Biovail Corporation International, Civil Actions No. 98-1282RLA and 98-1768HL). An additional suit against Biovail is also pending in the United States district Court for the District of Columbia (Civil Action No. 1:98CV01681). 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 judgment of that court from which no appeal can be or has been taken, or,

   c. the '446 patent has 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. This amendment must also provide:

1. a copy of a final order or judgment 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 significant change in the conditions outlined in this abbreviated application or the status of the manufacturing and testing facilities' compliance with current good manufacturing procedures (CGMPs) are subject to Agency review before final approval of the application will be made.

In addition to, or instead of, the amendment referred to above, the Agency may, at any time prior to the date of final date, request that you submit an additional amendment containing the same information.

Failure to submit either or both amendments will prompt a review of the application which may result in rescission of this tentative approval letter, or a 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 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 (the "Orange Book").

Prior to submitting an amendment, please contact Timothy Ames, Project Manager, at (301) 827-5849, for further instructions.

Sincerely yours,

/S/ 6/29/99

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-269

Final Printed Labeling

Approval
labeling
12/4/00

75-269

DOSAGE: See accompanying prescribing information.
Dispense in tight, light resistant containers (USP).
RECOMMENDED STORAGE: STORE BELOW 30°C (86°F)
PROTECT FROM LIGHT.
PROTECT FROM MOISTURE.
KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

LL-0189-00/Iss. 6/99

Printed in U.S.A.

Manufactured By:
Biovail Corporation International
Manufacturing Division
Steinbach, Manitoba
Canada ROA 2T3

NDC 0093-1022-10

NIFEDIPINE
Extended-release
Tablets
60 mg

Each tablet contains:
Nifedipine 60 mg
Tablets should be swallowed whole, not bitten or divided.

Product must be dispensed within 3 months of opening container

℞ **only**

1000 TABLETS

TEVA

NDC 0093-1022-55

NIFEDIPINE
Extended-release
Tablets
60 mg

APPROVED

Each tablet contains:
Nifedipine 60 mg
Tablets should be swallowed whole, not bitten or divided.

℞ **only**

TEVA

Printed in U.S.A.

DOSAGE: See accompanying prescribing information.
Dispense in tight, light resistant containers (USP).
RECOMMENDED STORAGE: STORE BELOW 30°C (86°F)
PROTECT FROM LIGHT.
PROTECT FROM MOISTURE.
KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

LL-0188-00/Iss. 6/99

Manufactured By:
Biovail Corporation International
Manufacturing Division
Steinbach, Manitoba
Canada ROA 2T3

NDC 0093-1022-01

NIFEDIPINE
Extended-release
Tablets
60 mg

Each tablet contains:
Nifedipine 60 mg
Tablets should be swallowed whole, not bitten or divided.

℞ **only**

TEVA

Printed in U.S.A.

DOSAGE: See accompanying prescribing information.
Dispense in tight, light resistant containers (USP).
RECOMMENDED STORAGE: STORE BELOW 30°C (86°F)
PROTECT FROM LIGHT.
PROTECT FROM MOISTURE.
KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

LL-0187-00/Iss. 6/99

Manufactured By:
Biovail Corporation International
Manufacturing Division
Steinbach, Manitoba
Canada ROA 2T3

Nifedipine
Extended-release Tablets

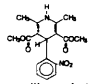
Rx only

For Oral use

DESCRIPTION

Nifedipine extended-release tablets are an extended release tablet dosage form of the calcium channel blocker nifedipine. Nifedipine is dimethyl 1,4-dihydro-2, 6-dimethyl-4-(*o*-nitrophenyl)-3,5-pyridinedicarboxylate.

The molecular formula is $C_{17}H_{18}N_2O_6$ and the structural formula is:



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 60 mg of nifedipine for once-a-day oral administration.

In addition, each tablet contains the following inactive ingredients: anhydrous lactose, ethylcellulose N-100, polyacrylic dispersion (copolymer of ethyl acrylate and methyl methacrylate), hydroxyethyl cellulose, hydroxypropylmethyl cellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol 600, silicon dioxide, sodium lauryl sulphate, talc, titanium dioxide and yellow 10 ferric oxide.

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 vascular smooth muscle. The binding of nifedipine to voltage-dependent and possibly receptor-operated 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 vasodilation 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 tablet relative to immediate release nifedipine is in the range of 84% to 89%. After ingestion of nifedipine extended-release tablets under fasting conditions, plasma concentrations peak at about 2.5 to 5 hours with a second small peak or shoulder evident at approximately 6 to 12 hours post dose. The elimination half-life of nifedipine administered as nifedipine extended-release tablet 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 tablet is 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 t.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 tablet is 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 tablet is 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 tablet is 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 0.1% of the dose) of the

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 t.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 tablet is 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 tablet is 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 tablet is 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 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 tablet has 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% to 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 tablet was given as monotherapy and in the second study, nifedipine extended-release tablet was 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 DOSE	N	MEAN TROUGH REDUCTION*
30 mg	60	5.3/2.9
60 mg	57	8.0/4.1
90 mg	55	12.5/8.1
	STUDY 2	
NIFEDIPINE EXTENDED-RELEASE DOSE	N	MEAN TROUGH REDUCTION*
30 mg	58	7.6/3.8
60 mg	63	10.1/5.3
90 mg	62	10.2/5.8

* Placebo response subtracted

The trough/peak ratios estimated from 24 hour blood pressure monitoring ranged from 41% to 78% for diastolic and 46% to 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 to 10 mmHg 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 patients with normal conduction systems, nifedipine administered as the immediate release capsule has had no tendency to prolong atrioventricular conduction or sinus node recovery time, or to slow sinus rate.

INDICATIONS AND USAGE

Nifedipine extended-release tablet is indicated for the treatment of hypertension. It 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

shown some increase in ejection fraction and reduction in left ventricular filling pressure.

3

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 patients with normal conduction systems, nifedipine administered as the immediate release capsule has had no tendency to prolong atrioventricular conduction or sinus node recovery time, or to slow sinus rate.

INDICATIONS AND USAGE

Nifedipine extended-release tablet is indicated for the treatment of hypertension. It 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 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 tight 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% at 30 mg, 12% at 60 mg and 19% at 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 are an extended release tablet and 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 tablet was 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

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% at 30 mg, 12% at 60 mg and 19% at 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 are an extended release tablet and 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 tablet was 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 tablet, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing nifedipine extended-release tablet 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 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, placentotoxic and fetotoxic effects, inducing 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 phalangeal 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 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 tablet was peripheral edema. This was dose related and the frequency was 18% on nifedipine extended-release tablet 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
Fatigue/asthenia	4	4
Nausea	2	1
Constipation	1	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 1.0% 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 angiectases
Central Nervous System: anxiety, confusion, decreased libido, depression, hypertonia, insomnia, somnofence
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
Respiratory: dyspnea, increase 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: allergenic hepatitis, alopecia, anemia, arthritis with ANA (+), depression, erythromelalagia, exfoliative dermatitis, fever, gingival hyperplasia, gynecomastia, leukopenia, mood changes, muscle cramps, nervousness, paranoid syndrome, purpura, shakiness, sleep disturbances, syncope, taste perversion, thrombocytopenia, transient blindness at the peak plasma level, tremor and urticaria.

There have been rare reports of exfoliative or bullous skin adverse events (such as erythema multiforme, Stevens-Johnson Syndrome, and toxic epidermal necrolysis) and photosensitivity reactions.

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

taste perversion, thrombocytopenia, transient blindness at the peak plasma level, tremor and urticaria.

There have been rare reports of exfoliative or bullous skin adverse events (such as erythema multiforme, Stevens-Johnson Syndrome, and toxic epidermal necrolysis) and photosensitivity reactions.

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 anginal 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 glucose levels rapidly normalized without further treatment.

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.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to each patient's needs. It is recommended that nifedipine extended-release tablet be administered orally once daily on an empty stomach. Nifedipine extended-release tablet is an extended release dosage form and tablets should be swallowed whole, not bitten or divided. In general, titration should proceed over a 7-14 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 tablet 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 tablet to assure that the extended release dosage form has been prescribed.

HOW SUPPLIED

Nifedipine extended-release tablets are supplied as 60 mg round film coated tablets as follows:

Strength	Color	Markings
60 mg	Mustard yellow	60 mg unscored, round film coated tablets, engraved with "B" on one side and "60" on the other side.

Nifedipine Extended-release Tablets are supplied in:

	Strength	NDC Code
Bottles of 100	60 mg	0093-1022-01
Bottles of 300	60 mg	0093-1022-55
Bottles of 1000	60 mg	0093-1022-10

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

Manufactured by:
Biovail Corporation
Mississauga, ON, CANADA
L5L1J9

Manufactured for:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

LB-0010-00/Iss. 6/99

Approve labeling
12/4/00

DOSAGE: See accompanying prescribing information.
Dispense in tight, light resistant containers (USP).
RECOMMENDED STORAGE: STORE BELOW 30°C (86°F)
PROTECT FROM LIGHT.
PROTECT FROM MOISTURE.
KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Manufactured By:
Biovail Corporation International
Manufacturing Division
Steinbach, Manitoba
Canada ROA 2T3

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

LL-0186-00/Iss. 6/99

Printed in U.S.A.

NDC 0093-1021-10

NIFEDIPINE
Extended-release
Tablets
30 mg

DEC 4 2000
APPROVED

Each tablet contains:
Nifedipine 30 mg
Tablets should be swallowed whole, not bitten or divided.

Product must be dispensed within 3 months of opening container

℞ only

1000 TABLETS

TEVA

NDC 0093-1021-55

NIFEDIPINE
Extended-release
Tablets
30 mg

APPROVED

Each tablet contains:
Nifedipine 30 mg
Tablets should be swallowed whole, not bitten or divided.

℞ only

500 TABLETS

TEVA

Printed in U.S.A.

DOSAGE: See accompanying prescribing information.
Dispense in tight, light resistant containers (USP).
RECOMMENDED STORAGE: STORE BELOW 30°C (86°F)
PROTECT FROM LIGHT.
PROTECT FROM MOISTURE.
KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Manufactured By:
Biovail Corporation International
Manufacturing Division
Steinbach, Manitoba
Canada ROA 2T3

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

LL-0185-00/Iss. 6/99

NDC 0093-1021-01

APPROVED

NIFEDIPINE
Extended-release
Tablets
30 mg

Each tablet contains:
Nifedipine 30 mg
Tablets should be swallowed whole, not bitten or divided.

℞ only

Printed in U.S.A.

DOSAGE: See accompanying prescribing information.
Dispense in tight, light resistant containers (USP).
RECOMMENDED STORAGE: STORE BELOW 30°C (86°F).
PROTECT FROM LIGHT.
PROTECT FROM MOISTURE.
KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Manufactured By:
Biovail Corporation International
Manufacturing Division
Steinbach, Manitoba
Canada ROA 2T3

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

LL-0184-00/Iss. 6/99

Nifedipine
Extended-release Tablets

Rx only

For Oral use
LB-0008-00

Rev.09/00

DEC -4 2000

APPROVED

DESCRIPTION

Nifedipine extended-release tablets are an extended release tablet dosage form of the calcium channel blocker nifedipine. Nifedipine is dimethyl 1,4-dihydro-2, 6-dimethyl-4-(*o*-nitrophenyl)-3,5-pyridinedicarboxylate.

The molecular formula is $C_{17}H_{18}N_2O_6$ and the structural formula is:

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.

In addition, each tablet contains the following inactive ingredients: anhydrous lactose, ethylcellulose N-100, polyacrylic dispersion (copolymer of ethyl acrylate and methyl methacrylate), hydroxyethyl cellulose, hydroxypropylmethyl cellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol 600, silicon dioxide, sodium lauryl sulphate, talc, titanium dioxide and yellow 10 ferric oxide.

The USP Drug Release Test number is pending.

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 vascular smooth muscle. The binding of nifedipine to voltage-dependent and possibly receptor-operated 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 vasodilation 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 tablet relative to immediate release nifedipine is in the range of 84% to 89%. After ingestion of nifedipine extended-release tablets under fasting conditions, plasma concentrations peak at about 2.5 to 5 hours with a second small peak or shoulder evident at approximately 6 to 12 hours post dose. The elimination half-life of nifedipine administered as nifedipine extended-release tablet 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 tablet is 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 t.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 tablet is 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 tablet is 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 tablet is 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 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 alter-

fasting conditions, is concentration of nifedipine when compared to t.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 tablet is 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 tablet is 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 tablet is 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 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 tablet has 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% to 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 tablet was given as monotherapy and in the second study, nifedipine extended-release tablet was 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 N	MEAN TROUGH REDUCTION*
NIFEDIPINE EXTENDED-RELEASE DOSE		
30 mg	60	5.3/2.9
60 mg	57	8.0/4.1
90 mg	55	12.5/8.1
	STUDY 2 N	MEAN TROUGH REDUCTION*
NIFEDIPINE EXTENDED-RELEASE DOSE		
30 mg	58	7.6/3.8
60 mg	63	10.1/5.3
90 mg	62	10.2/5.8

* Placebo response subtracted

The trough/peak ratios estimated from 24 hour blood pressure monitoring ranged from 41% to 78% for diastolic and 46% to 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 to 10 mmHg 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 patients with normal conduction systems, nifedipine administered as the immediate release capsule has had no tendency to prolong atrioventricular conduction or sinus node recovery time, or to slow sinus rate.

INDICATIONS AND USAGE

Nifedipine extended-release tablet is indicated for the treatment of hypertension. It 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 fen-

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 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 tight 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% at 30 mg, 12% at 60 mg and 19% at 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 are an extended release tablet and 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 tablet was 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 tablet, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing nifedipine extended-release tablet 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 two years and was

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% at 30 mg, 12% at 60 mg and 19% at 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 are an extended release tablet and 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 tablet was 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 tablet, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing nifedipine extended-release tablet 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 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, placentotoxic and fetotoxic effects, inducing 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 phalangeal 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 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 tablet was peripheral edema. This was dose related and the frequency was 18% on nifedipine extended-release tablet 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
Fatigue/asthenia	4	4
Nausea	2	1
Constipation	1	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 1.0% 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 angiectases
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
Respiratory: dyspnea, increase 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: allergenic hepatitis, alopecia, anemia, arthritis with ANA (+), depression, erythromelalagia, exfoliative dermatitis, fever, gingival hyperplasia, gynecomastia, leukopenia, mood changes, muscle cramps, nervousness, paranoid syndrome, purpura, shakiness, sleep disturbances, syncope, taste perversion, thrombocytopenia, transient blindness at the peak plasma level, tremor and urticaria.

There have been rare reports of exfoliative or bullous skin adverse events (such as erythema multiforme, Stevens-Johnson Syndrome, and toxic epidermal necrolysis) and photosensitivity reactions.

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

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 anginal 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 glucose levels rapidly normalized without further treatment.

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.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to each patient's needs. It is recommended that nifedipine extended-release tablet be administered orally once daily on an empty stomach. Nifedipine extended-release tablet is an extended release dosage form and tablets should be swallowed whole, not bitten or divided. In general, titration should proceed over a 7-14 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 tablet 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 tablet to assure that the extended release dosage form has been prescribed.

HOW SUPPLIED

Nifedipine extended-release tablets are supplied as 30 mg round film coated tablets as follows:

Strength	Color	Markings
30 mg	Mustard yellow	30 mg unscored, round film coated tablets, engraved with "B" on one side and "30" on the other side.

Nifedipine Extended-release Tablets are supplied in:

	Strength	NDC Code
Bottles of 100	30 mg	0093-1021-01
Bottles of 300	30 mg	0093-1021-55
Bottles of 1000	30 mg	0093-1021-10

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

Manufactured by:
Biovail Corporation
Mississauga, ON, CANADA
L5L1J9

Manufactured for:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

LB-0008-00

Rev 09/00

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-269

CHEMISTRY REVIEW(S)

DJ

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Chemistry Division II - Branch VI
Abbreviated New Drug Application Review

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 75-269

3. NAME AND ADDRESS OF APPLICANT
Biovail Laboratories Incorporated
#34 Iturregui Avenue
Carolina, Puerto Rico USA 00983

4. LEGAL BASIS FOR SUBMISSION
Adalat® CC Tablets, 30 mg
Bayer Corporation
100 Bayer Road
Pittsburgh, PA 15205-5774

The firm filed Paragraph IV Certification, February 2, 1998, with respect to Patents 4,892,741 and 5,264,446 for the innovator product, and submitted evidence of notification April 6, 1998. In response to notification of Biovail's Paragraph IV patent certification, Bayer Corporation brought action against Biovail on March 19, 1998 for patent infringement.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Nifedipine USP

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

9. AMENDMENTS AND OTHER DATES:
Firm:
12/9/97 Original Submission
4/6/98 Amendment - Paragraph IV Notification

FDA:
1/9/98 Receipt Acknowledged - Paragraph IV Notice Request

10. PHARMACOLOGICAL CATEGORY
Calcium Channel Blocker

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

NDA
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF

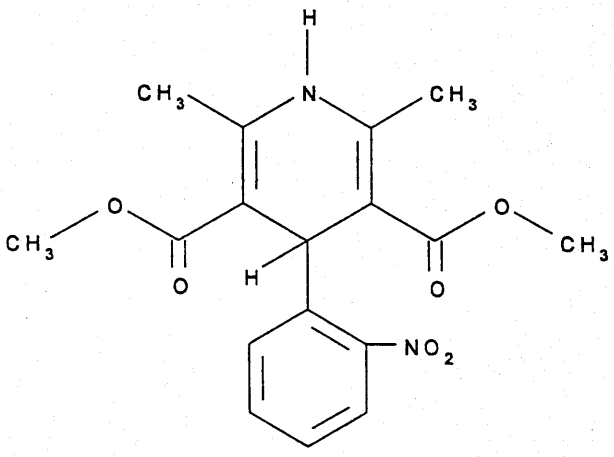
13. DOSAGE FORM
Coated tablet for oral administration

14. POTENCIES
30 mg

15. CHEMICAL NAME AND STRUCTURE

Nifedipine USP

$C_{17}H_{18}N_2O_6$; M.W. = 346.34



Dimethyl 1,4-dihydro-2,6-dimethyl-4-(o-nitrophenyl)-3,5-pyridinedicarboxylate. CAS [21829-25-4]

Yellow crystals, mp 172 - 174°. Easily sol in acetone, chloroform; less sol in ethanol. Practically insol in water. Very light sensitive in soln. LD_{50} in mice, rats (mg/kg): 494, 1022 orally; 4.2, 15.5 i.v.

16. RECORDS AND REPORTS
None

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS
The application should be considered Not Approvable - Major Amendment.

19. REVIEWER: Glen Jon Smith

DATE COMPLETED: 29 May 1998

Redacted 28

pages of trade secret and/or confidential commercial information

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Chemistry Division II - Branch VI
Abbreviated New Drug Application Review

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 75-269

3. NAME AND ADDRESS OF APPLICANT
Biovail Laboratories Incorporated
#34 Iturregui Avenue
Carolina, Puerto Rico USA 00983

4. LEGAL BASIS FOR SUBMISSION
Adalat® CC Tablets, 30 mg and 60 mg
Bayer Corporation
100 Bayer Road
Pittsburgh, PA 15205-5774

The firm filed Paragraph IV Certification, May 22, 1998, with respect to Patents 4,892,741 and 5,264,446 for the innovator product, and submitted evidence of notification July 9, 1998. In response to notification of Biovail's Paragraph IV patent certification, Bayer Corporation brought action against Biovail on July 2, 1998 for patent infringement. The notification from Bayer was updated November 10, 1998 to include the 60 mg tablet after ANDA 75-359 (60 mg tablet) was collapsed into ANDA 75-269 (30 mg tablet)

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Nifedipine USP

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

9. AMENDMENTS AND OTHER DATES:
Firm:
12/9/97 Original Submission
4/6/98 Amendment - Paragraph IV Notification
9/24/98 Response to Agency's letter of 6/30/98.

FDA:
1/9/98 Receipt Acknowledged - Paragraph IV Notice Request
6/30/98 Issuance of Not Approvable Letter.
10/7/98 Notification, Combining of ANDA'a.

10. PHARMACOLOGICAL CATEGORY
Calcium Channel Blocker

11. Rx or OTC
Rx

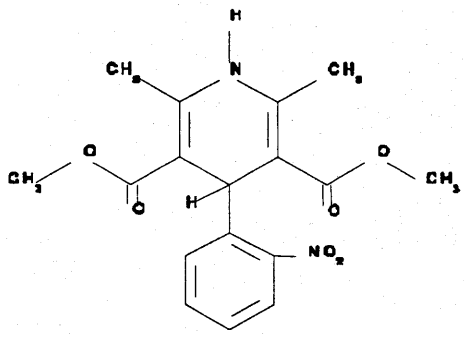
12. RELATED IND/NDA/DMF(s)
NDA
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF

13. DOSAGE FORM
Coated tablet for oral administration

14. POTENCIES
30 mg, 60 mg

15. CHEMICAL NAME AND STRUCTURE

Nifedipine USP
$C_{17}H_{18}N_2O_6$; M.W. = 346.3



Dimethyl 1,4-dihydro-2,6-dimethyl-4-(*o*-nitrophenyl)-3,5-pyridinedicarboxylate. CAS [21829-25-4]

Yellow crystals, mp 172 - 174 . Easily sol in acetone, chloroform; less sol in ethanol. Practically insol in water. Very light sensitive in soln. LD_{50} in mice, rats (mg/kg): 494, 1022 orally; 4.2, 15.5 i.v.

16. RECORDS AND REPORTS
6/2/98 - Chemistry review, G.J. Smith.
11/6/98 - Bioequivalence, S. Pradhan.
11/20/98 - Labeling review, A. Vezza.

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS
The application remains Not Approvable - Facsimile Amendment

19. REVIEWER: Glen Jon Smith
DATE COMPLETED: March 30, 1999

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Redacted 20

pages of trade secret and/or confidential commercial information

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 75-269

3. NAME AND ADDRESS OF APPLICANT
Biovail Laboratories Incorporated
#34 Iturregui Avenue
Carolina, Puerto Rico USA 00983

4. LEGAL BASIS FOR SUBMISSION
Adalat® CC Tablets, 30 mg and 60 mg
Bayer Corporation
100 Bayer Road
Pittsburgh, PA 15205-5774

The firm filed Paragraph IV Certification, May 22, 1998, with respect to Patents 4,892,741 and 5,264,446 for the innovator product, and submitted evidence of notification July 9, 1998. In response to notification of Biovail's Paragraph IV patent certification, Bayer Corporation brought action against Biovail on July 2, 1998 for patent infringement. The notification from Bayer was updated November 10, 1998 to include the 60 mg tablet after ANDA 75-359 (60 mg tablet) was collapsed into ANDA 75-269 (30 mg tablet)

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Nifedipine USP

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

9. AMENDMENTS AND OTHER DATES:
Firm:

12/9/97	Original Submission
4/6/98	Amendment - Paragraph IV Notification
9/24/98	Response to Agency's letter of 6/30/98.
4/22/99	**Amendment - Response to Agency's facsimile of 4/15/99.**

FDA:

1/9/98	Receipt Acknowledged - Paragraph IV Notice Request
6/30/98	Issuance of Not Approvable Letter.
10/7/98	Notification, Combining of ANDA'a.
4/15/99	Issuance of Not Approvable Facsimile.

10. PHARMACOLOGICAL CATEGORY
Calcium Channel Blocker

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

NDA #20-198 - Bayer

DMF [redacted]

DMF [redacted]

DMF [redacted]

DMF [redacted]

DMF [redacted]

DMF [redacted]

DMF [redacted]

DMF [redacted]

DMF [redacted]

DMF [redacted]

DMF [redacted]

DMF [redacted]

DMF [redacted]

DMF [redacted]

DMF [redacted]

DMF [redacted]

13. DOSAGE FORM

Coated tablet for oral administration

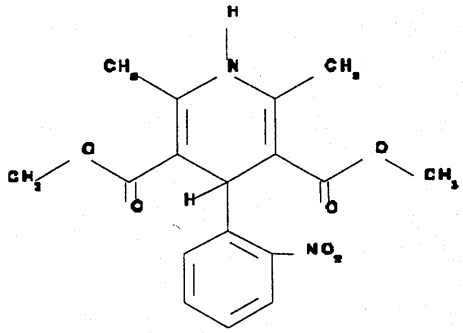
14. POTENCIES

30 mg, 60 mg

15. CHEMICAL NAME AND STRUCTURE

Nifedipine USP

$C_{17}H_{18}N_2O_6$; M.W. = 346.3



Dimethyl 1,4-dihydro-2,6-dimethyl-4-(*o*-nitrophenyl)-3,5-pyridinedicarboxylate. CAS [21829-25-4]

Yellow crystals, mp 172 - 174 . Easily sol in acetone, chloroform; less sol in ethanol. Practically insol in water. Very light sensitive in soln. LD_{50} in mice, rats (mg/kg): 494, 1022 orally; 4.2, 15.5 i.v.

16. RECORDS AND REPORTS
6/2/98 - Chemistry review #1, G.J. Smith.
11/6/98 - Bioequivalence, S. Pradhan.
11/20/98 - Labeling review, A. Vezza.
3/30/99 - Chemistry review #2, G.J. Smith.

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS
The application may receive Tentative Approval.

19. REVIEWER: Glen Jon Smith

DATE COMPLETED: May 11, 1999.

APPEARS THIS WAY ON ORIGINAL

Redacted 12

pages of trade secret and/or confidential commercial information

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Chemistry Division II - Branch VIII
Abbreviated New Drug Application Review

1. **CHEMISTRY REVIEW NO:** 4

2. **ANDA # 75-269**

3. **NAME AND ADDRESS OF APPLICANT:**
Biovail Laboratories Incorporated
Chelston Park, Building 2
Collymore Rock
St. Michael, BHI
Barbados, WI

U.S. Agent: John Dubeck
Keller and Heckman
1001 G St., N.W., Suite 500 West
Washington, DC 20001

4. **LEGAL BASIS FOR SUBMISSION:**
Adalat® CC Tablets, 30 mg and 60 mg
Bayer Corporation
100 Bayer Road
Pittsburgh, PA 15205-5774

The firm filed Paragraph IV Certification, May 22, 1998, with respect to Patents 4,892,741 and 5,264,446 for the innovator product, and submitted evidence of notification July 9, 1998. In response to notification of Biovail's Paragraph IV patent certification, Bayer Corporation brought action against Biovail on July 2, 1998 for patent infringement. The notification from Bayer was updated November 10, 1998 to include the 60 mg tablet after ANDA 75-359 (60 mg tablet) was collapsed into ANDA 75-269 (30 mg tablet)

5. **SUPPLEMENT(s):**
N/A

6. **PROPRIETARY NAME:**
N/A

7. **NONPROPRIETARY NAME:**
Nifedipine ER Tablets, USP

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

9. **AMENDMENTS AND OTHER DATES:**

Firm:

12/09/97	Original Submission
04/06/98	Amendment - Paragraph IV Notification
9/24/98	Response to Agency's letter of 6/30/98.
04/22/99	Amendment - Response to Agency's facsimile of 4/15/99.
06/30/00	Minor Amendment to Tentative approval
10/04/00	Tel Amendment

FDA:

01/09/98	Receipt Acknowledged - Paragraph IV Notice Request
6/30/98	Issuance of Not Approvable Letter.
10/7/98	Notification, Combining of ANDA'a.
04/15/99	Issuance of Not Approvable Facsimile.
6/29/99	Tentative Approval Letter
08/21/00	Bio Approval
09/06/00	Teleconference
10/26/00	Teleconferece

10. **PHARMACOLOGICAL CATEGORY:**
Calcium Channel Blocker

11. **Rx or OTC:**
Rx

12. **RELATED IND/NDA/DMF(s):**
NDA #20-198 - Bayer
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]

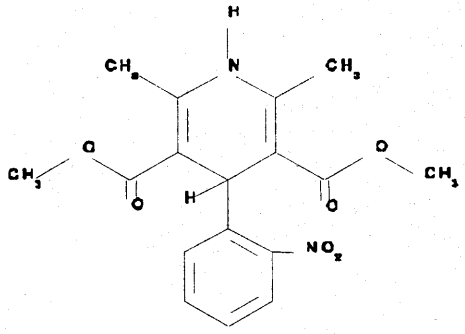
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF

13. **DOSAGE FORM:**
Coated tablet for oral administration

14. **POTENCIES:**
30 mg and 60 mg

15. **CHEMICAL NAME AND STRUCTURE:**

Nifedipine USP
$C_{17}H_{18}N_2O_6$; M.W. = 346.3



Dimethyl 1,4-dihydro-2,6-dimethyl-4-(*o*-nitrophenyl)-3,5-pyridinedicarboxylate. CAS [21829-25-4]

Yellow crystals, mp 172°C - 174°C. Easily soluble in acetone, chloroform; less soluble in ethanol, insoluble in water. Very light sensitive in solution

LD_{50} in mice, rats (mg/kg): 494, 1022 orally; 4.2, 15.5 i.v.

16. RECORDS AND REPORTS:

12/09/97	Original Submission
04/06/98	Amendment - Paragraph IV Notification
9/24/98	Response to Agency's letter of 6/30/98.
6/30/98	Issuance of Not Approvable Letter.
10/7/98	Notification, Combining of ANDA'a.
04/15/99	Issuance of Not Approvable Facsimile.
04/22/99	Amendment - Response to Agency's facsimile of 4/15/99.
6/29/99	Tentative Approval Letter
06/30/00	Minor Amendment to Tentative approval
08/21/00	Bio Approval
09/6/00	Teleconference
10/04/00	Tel Amendment
10/06/00	Teleconference

17. COMMENTS:

[redacted]

The recent submission (Tel Amendment) of Specifications, didn't incorporate the recent dissolution specifications, as recommended by the Bioequivalence Division. At present the Application is not considered for full Approval (See Element #38).

18. **CONCLUSIONS AND RECOMMENDATIONS:**
Biovail has not made any changes to the Chemistry, Manufacturing and control terms of the Application since the time of the tentative approval. This Application is not Approved (Full). (See Element #38)

19. **REVIEWER:** Mouna P. Selvam, Ph.D., **DATE COMPLETED:** 10/26/2000

APPEARS THIS WAY
ON ORIGINAL

Redacted 1

pages of trade secret and/or confidential commercial information

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Chemistry Division II - Branch VIII

Abbreviated New Drug Application Review

1. **CHEMISTRY REVIEW NO:** 5

2. **ANDA # 75-269**

3. **NAME AND ADDRESS OF APPLICANT:**
Biovail Laboratories Incorporated
Chelston Park, Building 2
Collymore Rock
St. Michael, BHI
Barbados, WI

U.S. Agent: John Dubeck
Keller and Heckman
1001 G St., N.W., Suite 500 West
Washington, DC 20001

4. **LEGAL BASIS FOR SUBMISSION:**
Adalat® CC Tablets, 30 mg and 60 mg
Bayer Corporation
100 Bayer Road
Pittsburgh, PA 15205-5774

The firm filed Paragraph IV Certification, May 22, 1998, with respect to Patents 4,892,741 and 5,264,446 for the innovator product, and submitted evidence of notification July 9, 1998. In response to notification of Biovail's Paragraph IV patent certification, Bayer Corporation brought action against Biovail on July 2, 1998 for patent infringement. The notification from Bayer was updated November 10, 1998 to include the 60 mg tablet after ANDA _____ was collapsed into ANDA 75-269 (30 mg tablet)

5. **SUPPLEMENT(s):**
N/A

6. **PROPRIETARY NAME:**
N/A

7. **NONPROPRIETARY NAME:**
Nifedipine ER Tablets, USP

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

9. **AMENDMENTS AND OTHER DATES:**

Firm:

12/09/97	Original Submission
04/06/98	Amendment - Paragraph IV Notification
09/24/98	Response to Agency's letter of 6/30/98.
04/22/99	Amendment - Response to Agency's facsimile of 4/15/99.
06/30/00	Minor Amendment to Tentative approval
10/04/00	Tel Amendment
11/09/00	FAX Amendment
11/~~28~~27/00	FAX Amendment

11/22/00 Fax Amendment B.Jac

B.Jac

FDA:

01/09/98	Receipt Acknowledged - Paragraph IV Notice Request
6/30/98	Issuance of Not Approvable Letter.
10/7/98	Notification, Combining of ANDA'a.
04/15/99	Issuance of Not Approvable Facsimile.
6/29/99	Tentative Approval Letter
08/21/00	Bio Approval
08/25/00	Labeling Approval
09/06/00	Teleconference
10/26/00	Teleconferece
11/27/00	Teleconferece
11/27/00	Final Labeling Approval
11/28/00	FAX Amendment

10. **PHARMACOLOGICAL CATEGORY:**
Calcium Channel Blocker

11. **Rx or OTC:**
Rx

12. **RELATED IND/NDA/DMF(s):**

NDA #20-198 - Bayer

DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]

13. DOSAGE FORM:

Coated tablet for oral administration

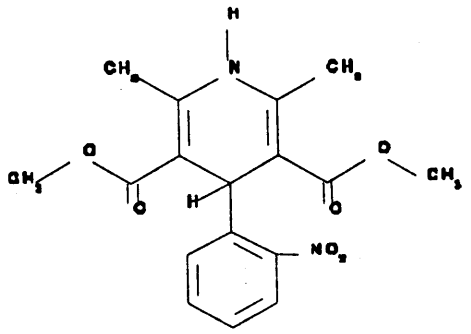
14. POTENCIES:

30 mg and 60 mg

15. CHEMICAL NAME AND STRUCTURE:

Nifedipine USP

$C_{17}H_{18}N_2O_6$; M.W. = 346.3



Dimethyl 1,4-dihydro-2,6-dimethyl-4-(*o*-nitrophenyl)-3,5-pyridinedicarboxylate. CAS [21829-25-4]

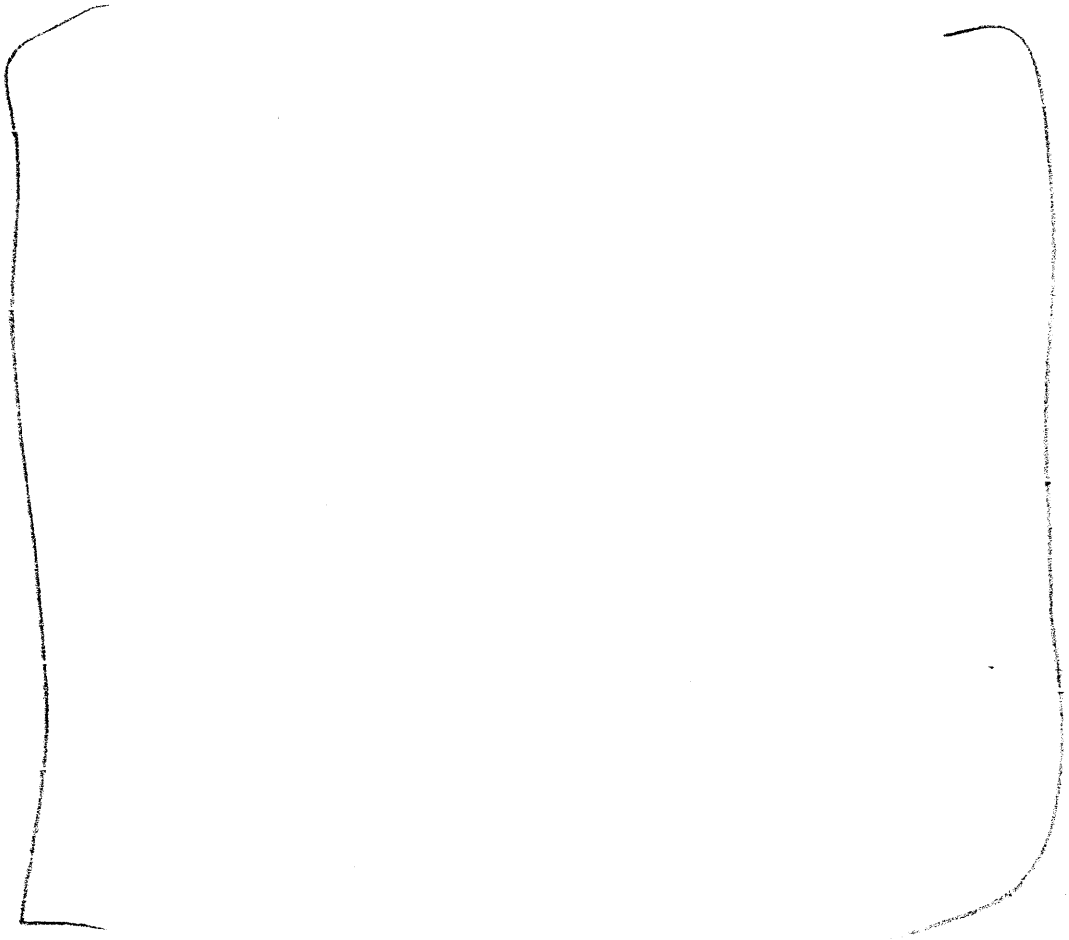
Yellow crystals, mp 172°C - 174°C. Easily soluble in acetone, chloroform; less soluble in ethanol, insoluble in water. Very light sensitive in solution LD_{50} in mice, rats (mg/kg): 494, 1022 orally; 4.2, 15.5 i.v.

16. RECORDS AND REPORTS:

12/09/97	Original Submission
04/06/98	Amendment - Paragraph IV Notification
09/24/98	Response to Agency's letter of 6/30/98.
06/30/98	Issuance of Not Approvable Letter.
10/07/98	Notification, Combining of ANDA'a.
04/15/99	Issuance of Not Approvable Facsimile.
04/22/99	Amendment - Response to Agency's facsimile of 4/15/99.
6/29/99	Tentative Approval Letter
06/30/00	Minor Amendment to Tentative approval
08/21/00	Bio Approval
08/25/00	Labeling Approval
09/6/00	Teleconference
10/04/00	Tel Amendment
10/26/00	Teleconference
11/09/00	FAX Amendment
11/27/00	Final Labeling Approval
11/27/00	Teleconference
11/28/00	FAX Amendment

17. COMMENTS:

[ ]



18. **CONCLUSIONS AND RECOMMENDATIONS:**
Biovail has not made any changes to the Chemistry, Manufacturing and control terms of the Application since the time of the tentative approval. This Application is Approved for both 30 mg and 60 mg(Full).

19. **REVIEWER:** Mouna P. Selvam, Ph.D., **DATE COMPLETED:** 11/28/2000

Redacted 8

pages of trade secret and/or confidential commercial information

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-269

BIOEQUIVALENCE REVIEW

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

#8

ANDA #: 75-269 SPONSOR: Biovail

DRUG AND DOSAGE FORM: Nifedipine ER Tablets

STRENGTH(S): 30 mg & 60 mg

TYPES OF STUDIES: Amendment to Dissolution

CLINICAL STUDY SITE(S): N/A

ANALYTICAL SITE(S): N/A

STUDY SUMMARY: please see Review

DISSOLUTION:

DSI INSPECTION STATUS

Inspection needed: YES / (NO)	Inspection status:	Inspection results:
First Generic NC	Inspection requested: (date)	
New facility ____	Inspection completed: (date)	
For cause ____		
other ____		

PRIMARY REVIEWER: (NAME) BRANCH:

INITIAL: /S/ DATE: 7/31/00

TEAM LEADER: (NAME) BRANCH:

INITIAL: /S/ DATE: 7/31/2000

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

INITIAL: /S/ DATE: 8/24/00

V:\division\bio\signoff.doc

3.1
Selvam

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-269 APPLICANT: Biovail Lab., Inc.
DRUG PRODUCT:Nifedipine ER Tablets, 30 mg and 60 mg

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

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of 0.5% sodium lauryl sulphate in simulated gastric fluid (SGF), pH 1.2 using USP XXIV apparatus II (paddle) at 100 rpm.

The 60-mg strength of the test product should meet the following tentative specifications currently proposed by the Agency:

Time (hour)	Specifications
1	[redacted]
4	[redacted]
12	NLT [redacted]

The 30-mg strength of the test product should meet the following tentative specifications previously proposed by the Agency:

Time (hour)	Specifications
1	[redacted]
4	[redacted]
12	NLT [redacted]

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,

/S/

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

Nifedipine 30 & 60 mg ER Tablets
ANDA # 75-269
Reviewer: Sikta Pradhan
File #75269AD.600

Biovail Laboratories, Inc.
Mississauga, Ontario, Canada
Submission Date:
June 30, 2000

REVIEW OF AN AMENDMENT TO A BIOEQUIVALENCE STUDY

Background:

- The firm had conducted single dose bioequivalence studies, under fasting and fed conditions, and the multiple dose study under fasting condition on the test product, Nifedipine ER Tablets, 30 mg and 60 mg, comparing them with the reference product, Adalat[R] CC (Bayer Corporation), 30-mg and 60-mg tablets, respectively. These studies were found to be acceptable (submission dated July 28, 1998) by the Division of Bioequivalence.

- The firm had conducted acceptable in vitro dissolution testing on its Nifedipine ER 30 mg tablets (submission dated 12/09/97) and proposed the following tentative specifications:

Time (hour)	Specifications
1	[redacted]
4	[redacted]
12	NLT [redacted]

- The firm had also conducted acceptable in vitro dissolution testing on its Nifedipine ER 60 mg tablets (submission dated 4/15/98) and proposed the following tentative specifications:

Time (hour)	Specifications
1	[redacted]
4	[redacted]
12	NLT [redacted]

- Based on these data, the Division of Bioequivalence proposed the following tentative specifications for both strengths of the test product:

Time (hour)	Specifications
1	[redacted]
4	[redacted]
12	NLT [redacted]

In the current minor amendment, the applicant has informed the Agency that the firm would like to change the dissolution specifications only for its 60-mg strength as the 30-

mg strength is subject to unexpired "first-to-file" market exclusivity. Since the time of the tentative approval, the firm has manufactured three validation batches at commercial scale. Based on the results from these validation lots, Biovail is requesting a revision to the tentatively approved dissolution specifications. **Specifically, the applicant wishes to revise the dissolution specifications at the 1-hour time-point from [redacted] to NMT [redacted] and at the 4-hour time-point from [redacted]**

In support of these new dissolution specifications the applicant has included the dissolution data from the three commercial scale validation batches. Other than the proposed revision to the dissolution specifications, the applicant has not made any changes to the Chemistry, Manufacturing and Controls terms of the application since the time of the tentative approval.

Dissolution Data:

Lot Number	Time (hr.)	Number of Tabs.	Mean(%)	Range(%): low - high
Lot #00D089	1	12	19	[redacted]
	4	12	52	[redacted]
	12	12	104	[redacted]
Lot #00D090	1	12	14	[redacted]
	4	12	45	[redacted]
	12	12	105	[redacted]
Lot #00D092	1	Not provided	21.0	[redacted]
	4	"	56.0	[redacted]
	12	"	107.0	[redacted]

Agency's Comments on the Dissolution Specifications for 60 mg :

1. On the basis of the dissolution data provided by the firm on its 60-mg tablets (lot #00D089, lot #00D090 and lot #00D092), the firm's currently proposed specifications for 1-hour time - point should be modified and replaced by a specified range. Hence the Agency proposed dissolution specifications for 60-mg tablets are the following:

Time (hour)	Specifications
1	[redacted]
4	[redacted]
12	NLT [redacted]

2. The dissolution specifications for Biovail's 30-mg tablets remain unchanged. The dissolution specifications for 30-mg tablets are the following:

Time (hour)	Specifications
1	[redacted]
4	[redacted]
12	NLT [redacted]

Recommendation:

1. The single dose bioequivalence studies (under fasting and fed conditions) and the multiple dose study (under fasting condition) conducted on the test product, Biovail's Nifedipine ER 30 mg and 60 mg Tablets, comparing them with the reference products, Adalat^{R} CC, 30 mg and 60 mg tablets, respectively, of Bayer Corporation have been found acceptable by the Division of Bioequivalence. These studies demonstrate that Nifedipine ER 30 mg and 60 mg Tablets of Biovail Laboratories, Inc. are bioequivalent to the reference products, Adalat^{R} CC, 30 mg and 60 mg tablets, respectively, manufactured by Bayer Corporation.

2. The in vitro dissolution testing conducted by Biovail Laboratories, Inc. on its Nifedipine ER 30 mg tablets (lot #97E003 & lot #97D042) and 60 mg tablets (lot #97E004 & lot #97D052), comparing them to the reference products, Adalat^{R} CC, 30 mg and 60 mg tablets, respectively, of Bayer Corporation is acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program.

3. The dissolution testing should be conducted in 900 mL of 0.5% sodium lauryl sulphate in simulated gastric fluid (SGF), pH 1.2 using USP XXIV apparatus II (paddle) at 100 rpm. The test product, 60-mg tablets should meet the following specifications proposed by the Agency:

Time (hour)	Specifications
1	[redacted]
4	[redacted]
12	NLT [redacted]

4. The 30-mg tablets of the test product should meet the following tentative specifications previously proposed by the Agency:

Time (hour)	Specifications
1	[redacted]
4	[redacted]
12	NLT [redacted]

/S/

Sikta Pradhan, Ph. D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG /S/ 7/31/2000
FT INITIALED YCHUANG

Concur. /S/ Date: 8/21/00
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

cc: AND # 75-269 (original, duplicate), HFD-652 (Huang, Pradhan), HFD-650 (Director), Drug File, Division File.

Draft Date: 7-27-00
Final Pink Copy Date: 7-31-00

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #75-269 SPONSOR :Biovail
DRUG & DOSAGE FORM : Nifedipine ER Tablets
STRENGTH (s) : 30 mg & 60 mg
TYPE OF STUDY: SD X SDF X MULT X OTHER
STUDY SITE: CLINICAL : _____ ANALYTICAL : Biovail

STUDY SUMMARY :

Fasting Studies: Two-way crossover fasting studies on 30 mg tablets and on 60 mg tablets are acceptable.

Fed Studies: Three-way crossover studies on 30 mg tablets and on 60 mg tablets under fasting and fed conditions are acceptable.

Multiple dose Studies: The multiple dose studies on 30 mg tablets and on 60 mg tablets are acceptable.

DISSOLUTION :
Conditions: NON-USP Dissolution condition
The in vitro dissolution testing data are acceptable.

PRIMARY REVIEWER : Sikta Pradhan BRANCH : I

INITIAL : /S/ DATE : 12/1/98

BRANCH CHIEF : Yih Chain Huang BRANCH : I

INITIAL : /S/ DATE : 12/1/98

DIRECTOR : Dale P. Conner
DIVISION OF BIOEQUIVALENCE

INITIAL : /S/ DATE : 12/4/98

DIRECTOR : Douglas L. Sporn
OFFICE OF GENERIC DRUGS

INITIAL : _____ DATE : _____

FEB 5 1999

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-269 APPLICANT: Biovail Lab., Inc.

DRUG PRODUCT:Nifedipine ER Tablets, 30 mg and 60 mg

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

The following dissolution testing will need to be incorporated into your stability and quality control programs:

> The dissolution testing should be conducted in 900 mL of 0.5% sodium lauryl sulphate in simulated gastric fluid (SFG), pH 1.2 using USP XXIII apparatus II (paddle) at 100 rpm. The test product of both strengths (30 mg and 60 mg) should meet the following tentative specifications proposed by the Agency:

Time (hour)	Specifications
1	—
4	—
12	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,

/S/

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

SEP 1 1998

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-269 APPLICANT: Biovail Lab., Inc.

DRUG PRODUCT:Nifedipine ER Tablet, 60 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. The validation of assay method, without any stability data for nifedipine samples, standard and QC samples at -25°C and at room temperature, is incomplete.

2. The stability report should also contain the long-term stability data of samples covering at least a period equivalent to the actual sample storage duration. The study is considered incomplete until the stability data are found acceptable.

3. You should provide the first and last dates of sample analysis, and dates of nifedipine QC samples preparation.

4. Lot size and potency of the test product used in the bioequivalence study should be provided.

5. The dissolution testing is acceptable. However, you should be advised to conduct in vitro comparative dissolution testing on the test and reference products of same lots used in the in vivo bioequivalence study in the future. Your proposed dissolution specifications are acceptable.

Sincerely yours,

/S/

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

Nifedipine ER Tablets, 60 mg
ANDA # 75-269(
Reviewer: Sikta Pradhan
XWP# 75269S3D.498

Biovail Laboratories, Inc.
Mississauga, Ontario, Canada
Submission Date:
April 15, 1998

REVIEW OF THREE BIOEQUIVALENCE STUDIES (SINGLE DOSE FASTING, SINGLE DOSE FED, MULTIPLE DOSE FASTING) AND DISSOLUTION DATA

Nifedipine, a calcium-channel blocking agent with potent vasodilating properties, is used in the treatment of vasospastic angina, chronic stable angina and hypertension. It is marketed as liquid-filled (soft gelatin) 10 mg and 20 mg capsules (Procardia^{R}, Pfizer), and as 30, 60 and 90 mg extended release tablets. The therapy for either hypertension or angina should be initiated with 30 or 60 mg once daily.

Biovail Laboratories, Inc. (BLI) has currently submitted the results of three bioequivalence studies comparing its test product Nifedipine ER Tablets, 60 mg, with the reference product Adalat^{R} CC, 60 mg Tablets (Bayer Corp.): 1) single dose fasting study; 2) single dose food study; 3) multiple dose steady-state study.

The firm had also submitted three similar bioequivalence studies on its test product, Nifedipine ER Tablets, 30 mg to the Agency (Submission dated December 9, 1997). The firm has informed the Agency that Nifedipine ER Tablets, 30 mg and Nifedipine ER Tablets, 60 mg (currently submitted) were manufactured using the same raw materials, the same manufacturing processes for the intermediate and finished products, and the same packaging materials. The only difference between the two strengths were the disproportional quantitative compositions in some excipients.

I. SINGLE DOSE FASTING STUDY

Objective:

The objective of the study is to compare the relative bioavailability of Nifedipine ER Tablets, 60 mg, manufactured by Biovail Lab. Inc. with that of Adalat^{R} CC, 60 mg Tablets, manufactured by Bayer Corp., in healthy, male volunteers dosed under fasting condition.

Study Sites

Clinical Site: Biovail Corporation International, Contract Research Division, Toronto, Ontario, Canada.
Principal Investigator & Medical Director: Paul T. Tam, M.D., F.R.C.P., F.A.C.P.
Clinical Director: Lana Knape, B.Bc., R.N.
Study Director and
Director of Biopharmaceutics: Bhaswat Chakraborty, Ph. D.
Director of Bioanalytical Lab.: David MacDonald, Ph.D.

Analytical Site: Biovail Corporation International, Contract Research Division, Toronto, Ontario, Canada.

Study Design: Protocol #1869-1(B97-313PK-NIFB32)

This was a randomized, single dose, two-way crossover design comparing the test product Nifedipine ER Tablets, 60 mg, with the reference product Adalat^{R} CC, 60 mg Tablets, in sixty-six (66) normal, healthy, non-smoking male volunteers under fasting conditions with a one week washout between treatments.

Clinical Study Dates: Phase I - July 5, 1997
Phase II - July 12, 1997

Subject Selection

Sixty-six (66) subjects (out of 68, Subjects #46 & #57 could not meet the inclusion criteria) were selected for this study after meeting the inclusion and exclusion criteria, and after signing informed consent as mentioned earlier in 30 mg nifedipine study of Biovail.

Treatments:

A. 60 mg x 1 Nifedipine ER tablet (Biovail), Lot #97E004, Lot size not reported, Potency not reported

B. 60 mg x 1 Adalat^{R} CC tablet (Bayer Corp.), Lot #6KGJ, Potency 98.8%, Exp. Date: November, 1998.

Dose Administration:

A single dose of 60 mg nifedipine ER tablet (test or reference) was administered with 240 mL of water.

Vital signs (resting blood pressure and pulse rate) 12-lead ECG monitoring were conducted at 0.0 (pre-dose), 2.0, 4.0, 8.0, 16.0, and 24.0 hours post-dose. Blood pressure and pulse rate monitoring continued at hourly intervals until measurements returned to within normal limits.

Drug Washout Period: 7 days

Meal and Food Restrictions:

All volunteers fasted for 10 hours prior to and 4.5 hours after drug administration. No fluids were allowed from 1 hour before dosing until 1 hour after each dose. Water was given ad lib after 1 hour of dosing. Standard meal was served after 4 hours of dosing. No caffeine-containing food or beverages were served during the first 24 hours. All subjects were confined from 10 hours pre-dose to 48 hours post-dose.

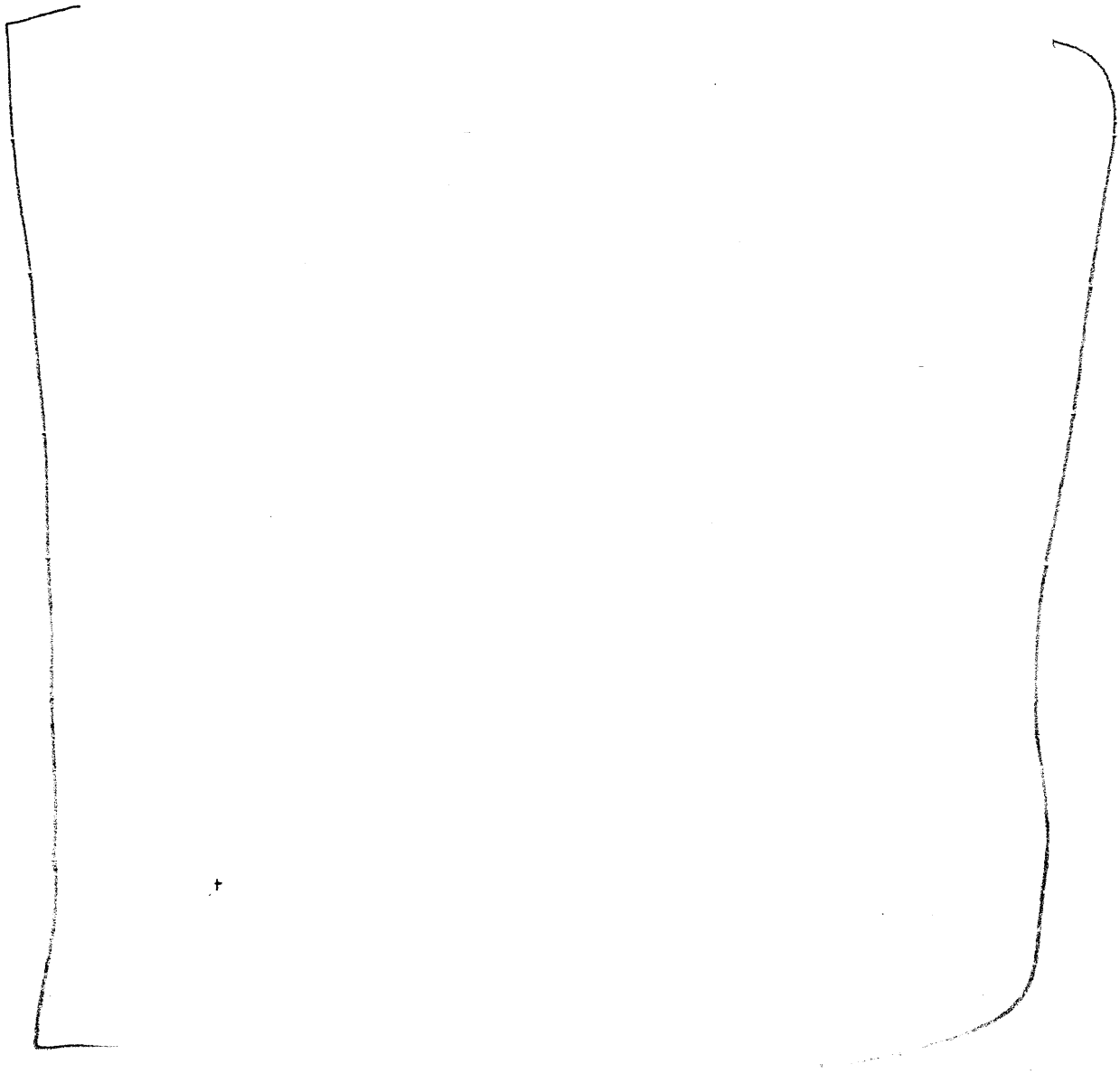
Blood Samples Collection

[redacted]

Protocol Deviation: No major protocol deviation

Assay Methodology

[redacted]



Stability: **Data not available**

Results:

Sixty-six (66) subjects were selected for the study and all 66 subjects completed the study. Ninety-five (95) adverse events, including mild episodes of sinus bradycardia, headache, nausea, lightheadedness, vomiting and 1^{0}AV block, were experienced by forty-four subjects during this study. However, none of these effects were severe, and no medication was required for any

clinical complaint. There were four (4) protocol deviations (minor) reported during the study. The actual blood collection times were used for the calculations of the values for the pharmacokinetic parameters.

All sixty-six (66) volunteers' plasma samples were analyzed. The mean plasma nifedipine levels for the test and the reference drugs are presented in Table 1 (and in Figure 1 attached).

Table 1
Mean Plasma Nifedipine Levels (ng/mL)

Time (hour)	TEST (A) (Biovail ER) Mean ± SD	Reference (B) (Adalat CC) Mean ± SD
Pre-dose	0	0
0.50	2.83 ± 3.92	6.90 ± 8.53
1.00	20.18 ± 17.29	32.38 ± 17.60
1.50	39.04 ± 26.46	49.96 ± 21.09
2.00	54.07 ± 29.77	65.86 ± 27.96
2.50	67.18 ± 35.68	77.03 ± 33.75
3.00	73.83 ± 45.68	80.23 ± 36.06
4.00	72.30 ± 43.82	84.40 ± 47.10
5.00	72.05 ± 37.25	88.81 ± 55.30
6.00	57.01 ± 28.37	67.90 ± 45.73
8.00	37.46 ± 20.09	45.96 ± 31.95
10.00	34.18 ± 17.37	40.30 ± 29.29
12.00	33.86 ± 18.43	36.70 ± 19.69
14.00	33.11 ± 19.66	34.41 ± 20.60
16.00	32.34 ± 19.38	31.53 ± 19.71
20.00	21.58 ± 15.81	19.50 ± 13.95
24.00	17.42 ± 13.77	15.46 ± 11.85
30.00	14.15 ± 11.41	11.20 ± 9.32
36.00	8.99 ± 9.66	6.75 ± 7.12
48.00	2.68 ± 4.75	1.60 ± 2.18

The mean pharmacokinetic parameters derived from the plasma Nifedipine levels are presented in Table 2.

Table 2
Mean Pharmacokinetic Parameters for Plasma Nifedipine

Parameters	Test (A)	Ref. (B)	A/B	90% C.I.**
AUC_{0-T} (ng.hr/mL)	1105.36 (50)*	1150.69 (52)		
AUC_{0-inf} (ng.hr/mL)	1135.43 (46)	1203.85 (52)		
C_{MAX} (ng/mL)	89.40 (50)	105.79 (52)		
T_{max} (hour)	4.62 (93)	4.39 (55)		
t1/2 (hour)	6.72 (24)	6.04 (23)		
KE (1/hour)	0.108 (21)	0.121 (24)		
$LnAUC_{0-T}$ Geometric Mean	6.8905 **(LSM) 982.89	6.9275 (LSM) 1019.94	0.96	93; 100
$LnAUC_{0-inf}$ Geometric Mean	6.9192 **(LSM) 1011.51	6.9444 (LSM) 1037.32	0.98	94; 101
LnC_{MAX} Geometric Mean	4.3866 **(LSM) 80.37	4.5310 (LSM) 92.85	0.87	80; 94

Number of Subjects 66
* Coefficient of Variation
** Calculated using LSM (Least Squares Means)
Intra-subject variability for: LnAUC(0-t)=13.52%
LnAUC(0-inf)=11.69%
LnCmax=27.01%

Both test and reference drugs produced peak concentration between 2.5 to 6 hours after their administration (see Table 1). The differences between the test and reference products in $LnAUC_{0-T}$ and $LnAUC_{0-inf}$ were 4% and 2%, respectively. The difference in the test and reference LnC_{MAX} was 13%. The 90% confidence intervals (data verified) for $LnAUC_{0-T}$, $LnAUC_{0-inf}$ and LnC_{MAX} of the test product remained within the 80% to 125% limit of the corresponding reference values.

II. LIMITED FOOD STUDY:

Protocol #BIOV-9701 (B98-337PK-NIFB32)
Study #109238

The firm has submitted the results of a single oral 60 mg dose three-way crossover post-prandial bioequivalence study conducted on the test (1x60 mg Nifedipine ER tablet of Biovail) and reference (1x60 mg Adalat[R] CC tablet) products in order to determine the effect of food on the bioavailability of those products.
Twenty-one (21) healthy male volunteers entered into the study after completing a physical examination and laboratory screening tests.

Clinical Study Site: [redacted]

Analytical Study Site: [redacted]

Principal Investigator(s) or
Responsible Medical Officer: [redacted]

Date of Study: Dosing in Period I: January 24, 1998
Dosing in period II: January 31, 1998
Dosing in Period III: February 7, 1998

Treatments:

A. 1x60 mg tablet of Nifedipine ER (test product) of Biovail, Lot #97E004, immediately after a standard breakfast

B. 1x60 mg tablet of Nifedipine ER (test product) of Biovail Corp., Lot #97E004, after an overnight fast for at least 10 hours.

C. 1x60 mg tablet Adalat[R] (Reference product) manufactured by Bayer Corp., Lot #6KGJ, immediately after a standard breakfast.

Following dosing, subjects remained ambulatory for 4 hours and were not allowed to engaged in any strenuous activity at any time during the study. For safety, sitting blood pressure and heart rate were measured predose and at 2, 4, 8, 16 and 24 hours after dosing.

Drug Washout Period: One week

Meal and Food Restrictions: Water was given ad lib until one hour pre-drug and after one hour post-drug. A standard meal was served after 4.5 hours post-dose. No alcohol, caffeine and xanthine-containing beverages was served during the study. Subjects remained at the clinic through the 48 hour post-drug blood draw.

[redacted]

Date of First Sample Analysis: February 19, 1998
Date of Last Sample Analysis: March 9,1998
Duration of Sample Storage: Less than three weeks

Assay Methodology:

[redacted]

[ ]

Stability: **Not Provided**

Results:

Twenty-one (21) healthy male volunteers entered into the study. One volunteer (subject #21) withdrew after completing Phase I of the study, and therefore, 20 volunteers completed the study. However, according to the protocol, 18 subjects (Subject #1 to Subject #18) were used in the pharmacokinetic and statistical data analysis. There were four (4) minor protocol deviations reported in the study. Thirty-four (34) adverse events were experienced by ten (10) subjects. Headache was the most frequently reported event. There were no serious or life-threatening medical events reported for this study. Mean plasma nifedipine levels are presented in Tables 3 (and in Figure 2 attached) below. The pharmacokinetic parameters derived from plasma nifedipine levels are presented in Table 4.

Table 3
Mean plasma nifedipine levels (ng/mL)

Time (hour)	Test (A) Fed	Test(B) Fasted	Ref.(C) Fed
0.0	0.0	0.0	0.0
0.5	0.16 (244)*	1.46 (105)	1.06 (290)
1.0	3.75 (154)	11.67 (75)	8.82 (179)
1.5	20.56 (133)	28.57 (66)	20.02 (136)
2.0	42.01 (109)	46.87 (59)	33.72 (110)
2.5	66.08 (94)	57.94 (57)	53.80 (97)
3.0	93.63 (66)	62.55 (52)	66.30 (69)
3.5	120.84 (55)	70.57 (51)	76.15 (54)
4.0	150.67 (58)	72.96 (47)	83.27 (51)
5.0	183.27 (46)	70.12 (47)	141.60 (56)
6.0	158.43 (57)	52.00 (47	138.88 (53)
8.0	81.44 (54)	38.33 (51)	107.08 (87)
10.0	47.27 (59)	35.45 (41)	69.21 (79)
12.0	16.50 (69)	33.10 (40)	44.32 (81)
16.0	5.71 (94)	24.35 (40)	19.22 (67)
24.0	1.48 (146)	13.20 (46)	5.77 (89)
36.0	0.30 (249)	4.35 (85)	1.72 (134)
48.0	1.12 (145)	0.93 (129)	0.35 (203)

* Coefficient of Variation
Number of Subjects = 20

Table 4

Mean Pharmacokinetic Parameters of Plasma Nifedipine

(Number of Subjects = 18)

Parameters (using arithmetic means)	Test(A) Fed	Test(B) Fasted	Ref.(C) Fed
AUC_{0-T} (ng.hrs/mL)	1226.99(44)*	921.78(39)	1217.06(48)
AUC_{0-inf} (ng.hrs/mL)	1237.06(44)	938.87(39)	1228.18(48)
C_{MAX} (ng/mL)	213.93(36)	87.22(42)	187.49(43)
T_{max} (hour)	5.06(23)	3.81(27)	5.83(37)
t1/2 (hour)	5.29(28)	6.70(28)	5.47(40)
KE (1/hour)	0.141(28)	0.109(21)	0.148(43)

Parameters (using LS means)	Test(A) Fed	Test(B) Fasted	Test(C) Fed	T/R (A/C)	T / T (A/B)
$LnAUC_{0-T}$ Geometric mean	7.0305** 1130.60	6.7539 857.40	7.0075 1104.89	1.02	1.32
$LnAUC_{0-inf}$ Geometric mean	7.0395 1140.82	6.7716 872.71	7.0175 1115.99	1.02	1.31
LnC_{MAX} Geometric mean	5.3036 201.06	4.3715 79.16	5.1494 172.33	1.17	2.54
T_{max}	5.0556	3.8056	5.8333	0.87	1.33

* Coefficient of Variation

** Calculated using LSM (Least Squares Means) Intra-subject variability for: LnAUC(0-t)=8.88%
LnAUC(0-inf)=8.90%
LnCmax=27.8%

When the test and reference formulations were administered after a meal, the differences between the test and reference products in AUC_{0-T} and AUC_{0-inf} were only 2%, and the difference in C_{MAX} was less than 20%. Results of this fed study indicated that food significantly increases the bioavailability. Both the rate and extent of absorption of a single dose of nifedipine test product were increased by administration with food.

III. MULTIPLE DOSE, STEADY-STATE STUDY

Objective:

The objective of this study was to compare the steady-state bioavailability of the test and reference (Adalat^R CC) 60 mg Nifedipine extended-release tablets under fasted conditions.

Study Design: Protocol #1871-1(B97-315PK-NIFB32)

This was a randomized, open-label, multiple-dose, steady-state, two-way crossover design comparing the test product nifedipine 30 mg extended-release tablets with the reference product Adalat^R CC 60 mg tablets under fasting conditions in 48 healthy male volunteers (45 completing) with a seven day washout between the last dose of Period 1 and the first dose of Period 2. Plasma was analyzed for the parent drug nifedipine concentrations.

Subject Selection:

Forty-eight (48) subjects were selected for this study after signing informed consent according to the criteria (inclusion and exclusion) mentioned in single dose fasting study before.

Study Sites: Same as mentioned in single dose fasting study

Study Dates: Period I: September 18, 1997 - September 24, 1997
Period II: October 2, 1997 - October 8, 1997

Dates of Sample Collection: 18-24/September/97 for Period I
2-8/October/97 for Period II

Date of First Sample Analysis: October 22, 1997
Dates of Last Sample Analysis: November 11, 1997

Duration of Sample Storage: Two months

Storage Temperature: -25°C

Study Procedures

Treatments:

1) Treatment A (test), nifedipine 60 mg extended-release tablet, 1 X 60 mg, Biovail Lot #97E004

2) Treatment B (reference), Adalat[R] CC 60 mg tablet, 1 X 60 mg, Bayer Corp. Lot #6KGJ, Expiry Date: 11/98.

Dose:

Each subject received a total oral dose of 60 mg nifedipine daily for seven days during each period as one (1) nifedipine CC 60 mg tablet (test), or as one (1) Adalat[R] CC 60 mg (reference), each with 240 ml of water. Each formulation was administered starting at 7 AM on Days 1 - 7.

Washout Period: Seven days between the last dose of Period 1 and the first dose of Period 2.

Fasting/Meals:

Subjects were required to fast overnight prior to, and for 4.5 hours after, each morning dose. Water was not be permitted for 1 hour before and 1 hour after each dose, but was allowed at all other times. Standard meals were provided at 4.5 and 9.5 hours, and snacks were provided at 13.5 hours after dose on each day. All meals and beverages were xanthine and caffeine-free and were identical for both periods.

[redacted]

Vital signs (resting blood pressure and pulse rate) were recorded at 0.0 (pre-dose), 2.0, 4.0, 8.0, 16.0, and 24.0 hours post-dose. Blood pressure and pulse rate monitoring continued at hourly intervals until measurements returned to within normal limits. ECG monitoring was conducted during each study phase at 0.0 (pre-drug), 2.0, 4.0, 8.0, 16.0 and 24.0 hour post-drug.

Assay Methodology:

[redacted]

Stability: **Not Provided**

Results:

Forty-eight (48) subject entered into the study. Forty-five (45) subjects completed the study and the statistical and the pharmacokinetic analyses were performed using data from 45 subjects. Subject #44 was dismissed prior to Period I, Day 6 dosing due to an adverse event, specifically a 2°AV block. Subject

#12 withdrew prior to drug administration due to adverse events consisting of headache, nausea and diarrhea. Subject #40 withdrew following drug administration on Day 2 due to personal reasons. The samples of subjects #12 and #44 were assayed for safety information only.

Two hundred and three (203) adverse events including mild episodes of sinus bradycardia, headache, nausea, lightheadedness, vomiting and 1^0AV block, were experienced by thirty-eight (38) subjects during this study (see Attachment #1). However, these effects were mild and no treatment was administered for these adverse events, with one exception. Subject #20 was given an ice pack to treat his mild headache. Subject #44 experienced a moderate 2^0AV block prior to dosing on Day 6 of Phase I, lasting for one hour and eleven minutes. The subject was dismissed due to this adverse event. There were eleven (11) protocol deviations (minor) reported during the study (see Attachment #2). The actual blood collection times were used for the calculations of the values for the pharmacokinetic parameters.

Mean plasma Nifedipine levels of 45 subjects at steady-state are presented in Tables 5 (and in Figure 3 attached). AUC_{0-24} at steady-state was the sum of the linear trapezoidal estimation of the areas from the time of the 7th dose to 24 hours post 7th dose. C_{ss} was AUC_{0-24} divided by the dosing interval (24 hours). C_{max} and T_{max} were determined from the observed plasma concentration-time profile over the sampling interval (Day7). Fluct1 was the percent fluctuation calculated as the difference between Cmax and Cmin divided by Css, Fluct2 was the percent fluctuation calculated as the difference between Cmax and Cmin divided by Cmin. Mean pharmacokinetic parameters of Nifedipine are presented in Tables 6.

Table 5
Mean plasma nifedipine levels (ng/mL)

Time (hour)	TEST (A) (Biovail ER)	Reference (B) (Adalat CC)
Pre-dose on Day 1	0	0
Pre-dose on Day 4	21.84 (56)*	18.73 (83)
Pre-dose on Day 5	22.40 (59)	21.34 (76)
Pre-dose on Day 6	21.85 (64)	22.34 (76)
Pre-dose on Day 7	23.28 (56)	22.25 (73)
and post dosing at:		
0.50	24.91 (56)	28.57 (63)
1.00	38.36 (49)	49.04 (52)
1.50	58.23 (49)	70.12 (44)
2.00	77.57 (41)	94.99 (48)
2.50	91.44 (40)	108.29 (49)
3.00	102.48 (40)	119.27 (60)
3.5	106.91 (45)	118.36 (55)
4.0	106.03 (48)	125.40 (66)
5.0	111.98 (59)	129.19 (67)
6.0	88.10 (63)	102.94 (72)
7.0	73.50 (62)	81.39 (72)
8.0	63.44 (57)	72.83 (75)
10.0	54.20 (56)	59.57 (63)
12.0	54.13 (52)	57.45 (54)

16.0	48.36 (61)	46.16 (58)
20.0	32.31 (72)	28.68 (62)
24.0	27.60 (72)	21.23 (65)

* Coefficient of Variation; Total number of subjects = 45

Table 6: Mean Pharmacokinetic Parameters for Plasma Nifedipine

Parameters Arithmetic mean	Test (A)	Ref. (B)	A/B (%)	90% C.I.**
AUC_{0-T} (ng.hr/mL)	1352.72 (47)*	1450.03 (52)		
C_{MAX} (ng/mL)	130.21 (47)	149.74 (58)		
Cmin (ng/mL)	27.60 (72)	21.23 (65)		
T_{max} (hour)	4.54 (54)	3.63 (30)		
$LnAUC_{0-T}$ (LSM) Geometric Mean	7.1087 1222.56	7.1648 1293.10	95	89; 101
LnC_{MAX} (LSM) Geometric Mean	4.7695 117.86	4.8745 130.91	90	82; 99
LnCmin (LSM) Geometric Mean	3.0885 21.94	2.8670 17.58	125	110; 141
Css (LSM) (ng/mL)	50.94	53.88		
Fluct1%	95.92/50.94x100 = 188.30	113.33/53.88x100 = 210.34		
Fluct2%	9592/21.94 = 437.19	11,333/17.58 = 644.65		

No. of Subjects: 45; Fluct1=(Cmax-Cmin)/Css; Fluct2=(Cmax-Cmin)/Cmin
* Coefficient of Variation
Intra-subject variability for: LnAUC(0-t)=17.63%, LnCmax=28.02% and LnCmim=34.90%

The results show that the 90% confidence intervals for $LnAUC_{ss}$ and $LnCmax_{ss}$ are within 80-125% range. The firm has reported that no significant difference in log-transformed trough levels between Days 5, 6, and 7 was detected by ANOVA, indicating that the steady-state was achieved.

In-Vitro Dissolution:

The firm has conducted dissolution testing on the test and reference products using different dissolution medium with different pH, and finally proposed to use 0.5% sodium lauryl sulphate (SLS) in simulated gastric fluid (SGF), pH 1.2 as the dissolution medium. Dissolution data are presented in Table 7.

Table 7. In Vitro Dissolution Testing

Drug: Nifedipine ER Tablets
Dose Strengths: 60 mg
ANDA No.: 75-269
Firm: Biovail Laboratories Incorporated
Submission Date: April 15, 1998

I. Conditions for Dissolution Testing:

USP XXIII Paddle RPM: 100
No. Units Tested: 12
Medium: 0.5% Sodium lauryl sulphate in Simulated Gastric Fluid (SGF), pH 1.2
Volume: 900 mL
Specifications: Proposed by Biovail Corp.
Assay Methodology: [illegible]

II. Results of In Vitro Dissolution Testing:

Sampling Times (Hour)	**Test Product** **Nifedipine ER Tablets** of Biovail Bulk Tablet Lot # 97D052 (not bio lot) Strength 60 mg			**Reference Product** Bayer's Adalat CC Lot # 6KGJ Strength 60 mg		
	Mean %	Range%	%CV	Mean %	Range%	%CV
1	20	[illegible]	14.5	7	[illegible]	11.5
2	31	[illegible]	10.9	16	[illegible]	11.6
4	51	[illegible]	8.2	35	[illegible]	17.3
6	69	[illegible]	6.4	57	[illegible]	25.6
8	86	[illegible]	6.2	87	[illegible]	11.1
10	99	[illegible]	4.3	99	[illegible]	2.2
12	103	[illegible]	1.6	101	[illegible]	2.0
14	104	[illegible]	1.5	101	[illegible]	2.2

Sampling Times (Hour)	**Test Product** **Nifedipine ER Tablets** of Biovail Bio-Batch (Firm has stated bio-batch without giving Lot #) Strength 60 mg					
	Mean %	Range%	%CV			
1	22	[illegible]				

2	34	[redacted]	Not Provided			
4	54	[redacted]				
6	73	[redacted]				
8	90	[redacted]				
12	104	[redacted]				

Proposed Dissolution Specifications:

Time (hour)	Specifications
1	[redacted]
4	[redacted]
12	NLT [redacted]

Compositions:

The compositions of the test tablets are presented in Table 8 attached herewith.

Comments:

The single dose bioequivalence studies (under fasting and fed conditions) and the multiple dose study (under fasting condition) conducted on the test product, Biovail's Nifedipine Tablet, 60 mg, and the reference product, Adalat^{R} CC 60 mg tablet of Bayer Corporation is incomplete due to the following reasons:

1. The validation of assay method, without any stability data for nifedipine samples, standard and QC samples at -25^{0}C and at room temperature, is incomplete.

2. The stability report should also contain the long-term stability data of samples covering at least a period equivalent to the actual sample storage duration. The study is considered incomplete until the stability data are found acceptable.

3. The firm should provide the first and last dates of sample analysis, and dates of nifedipine QC samples preparation.

4. Lot size of the test product used in the bioequivalence study

should be provided.

5. The dissolution testing is acceptable. However, the firm should be advised to conduct in vitro comparative dissolution testing on the test and reference products of same lots used in the in vivo bioequivalence study in the future. The firm's proposed dissolution specifications are acceptable.

Recommendation:

The single dose bioequivalence studies (under fasting and fed conditions) and the multiple dose study (under fasting condition) conducted on the test product, Biovail's Nifedipine ER 60 mg Tablet and the reference product, Adalat^{R} CC 60 mg tablet of Bayer Corporation have been found incomplete by the Division of Bioequivalence due to the reasons cited in comments #1-4.

/S/

Sikta Pradhan, Ph. D.
Division of Bioequivalence
Review Branch I

/S/ 8/24/98

RD INITIALED YCHUANG
FT INITIALED YCHUANG

Concur. /S/ Date: 8/26/98

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

cc: AND # 75-269(75-359) (original, duplicate), HAD-652 (Huang, Pradhan), HAD-650 (Director),Drug File, Division File.

SP/8-14-98//X:\wpfile\Pradhan\75269S3D.499

Section 6.5:
Formulation for Nifedipine Extended-release Tablets, 60 mg
B32 ANDA
Nifedipine Extended-release Tablets, 60 mg

Table - 8

The formulation for Nifedipine Extended-release Tablets, 60 mg is indicated as follows:

	Raw Material	Extended-release Tablet (mg/tablet)
1.	Nifedipine, USP	60 mg/tablet
2.	Anhydrous Lactose, NF	
3.	Ethylcellulose N-100, NF	
4.		
5.	Hydroxyethylcellulose, NF	
6.	Hydroxypropylmethyl Cellulose	
7.		
8.	Magnesium Stearate, NF	
9.		
10.	Microcrystalline Cellulose, NF	
11.	Polyethylene Glycol 600, NF	
12.		
13.	Silicon Dioxide, NF	
14.	Sodium Lauryl Sulphate, NF	
15.	Talc	
16.	Titanium Dioxide, USP	
17.	Yellow 10 Ferric Oxide, NF	

Nifedipine Extended-release

contain NMT

, Finished Product contains NMT

* Finished Product contains NMT

APPEARS THIS WAY
ON ORIGINAL

BIOVAIL CORPORATION INTERNATIONAL
STUDY # 109238 (B98-337PK-NIFB32)

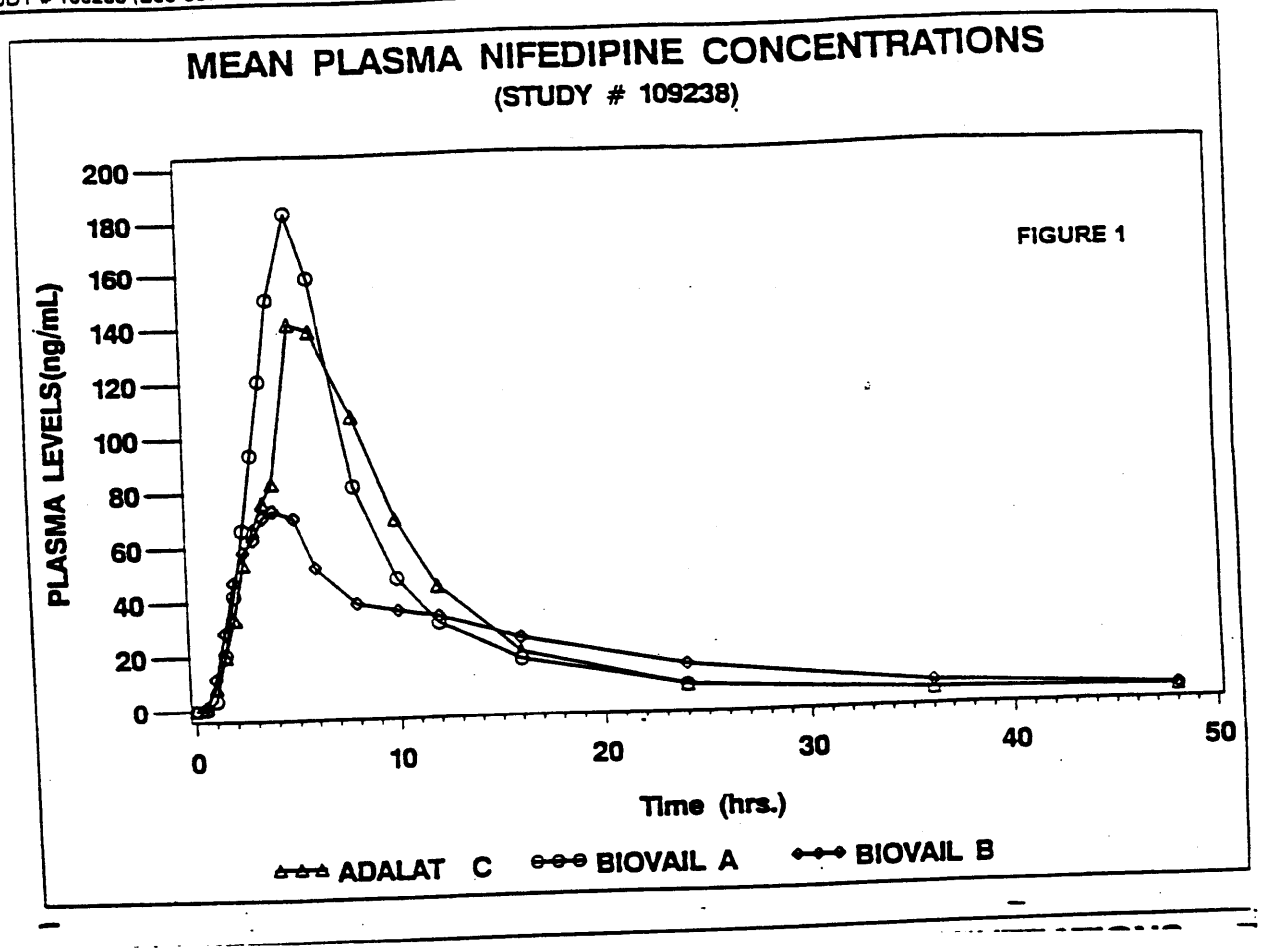


Fig 2. (Fed Study)

APPEARS THIS WAY
ON ORIGINAL

MEAN PLASMA NIFEDIPINE CONCENTRATIONS

STUDY # (1869 – 1)

FIGURE 1

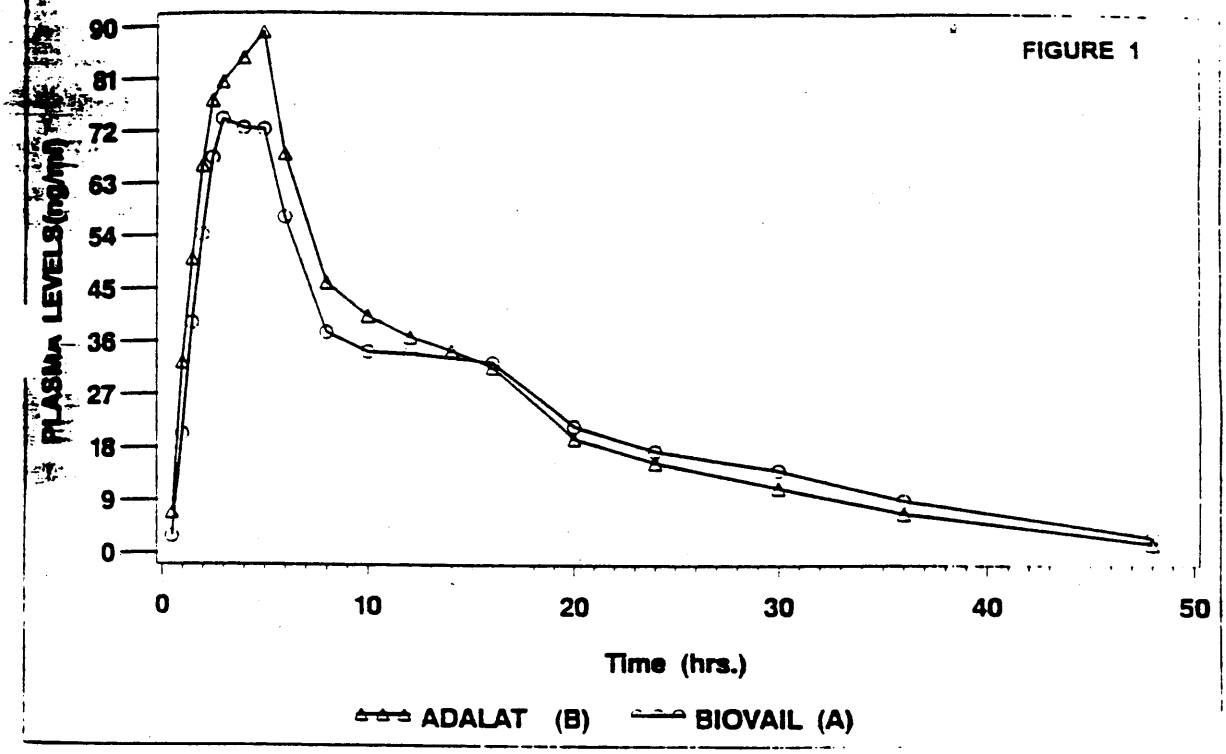


Fig. 1 (Fasting Study)

APPEARS THIS WAY
ON ORIGINAL

BIOVAIL CORPORATION INTERNATIONAL
STUDY # 1871-1 (B97-315PK-NIFB32)

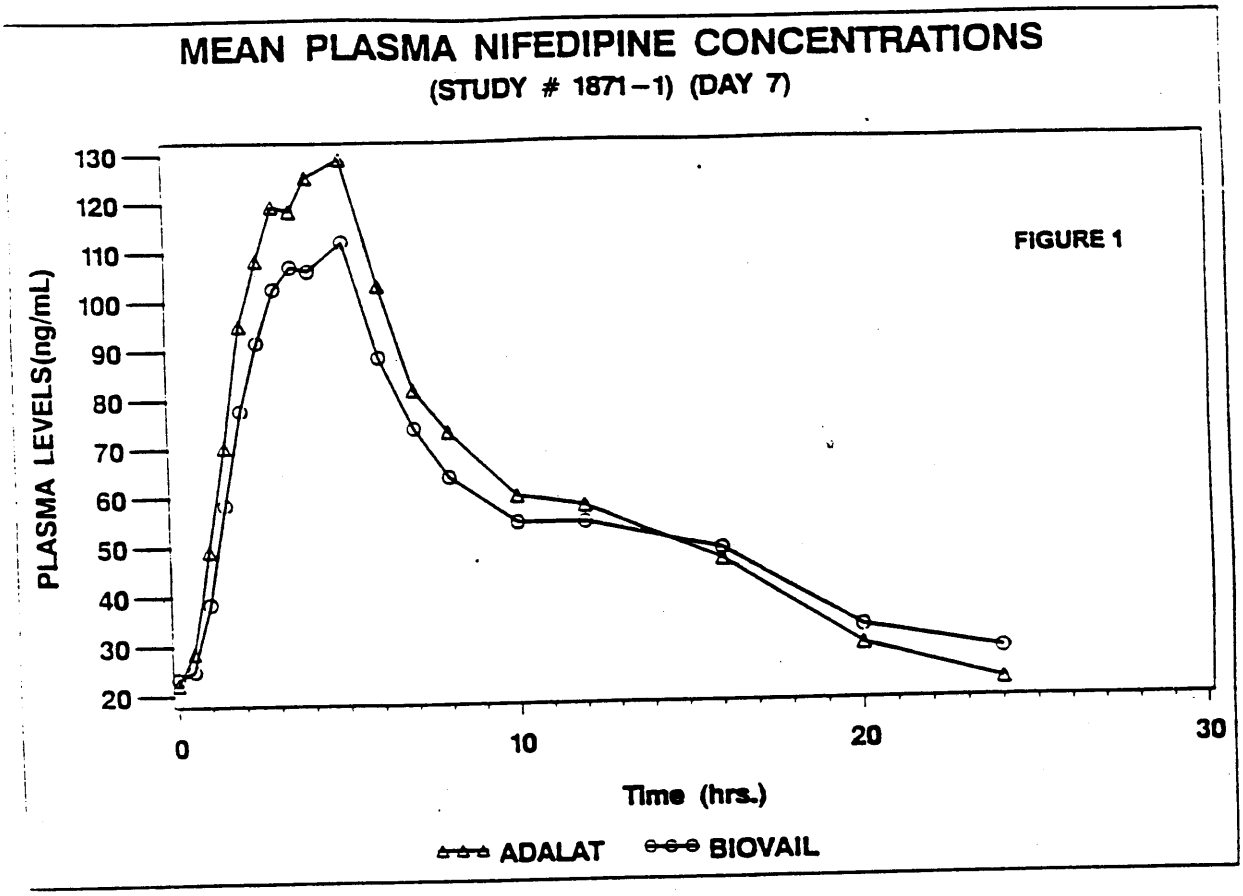
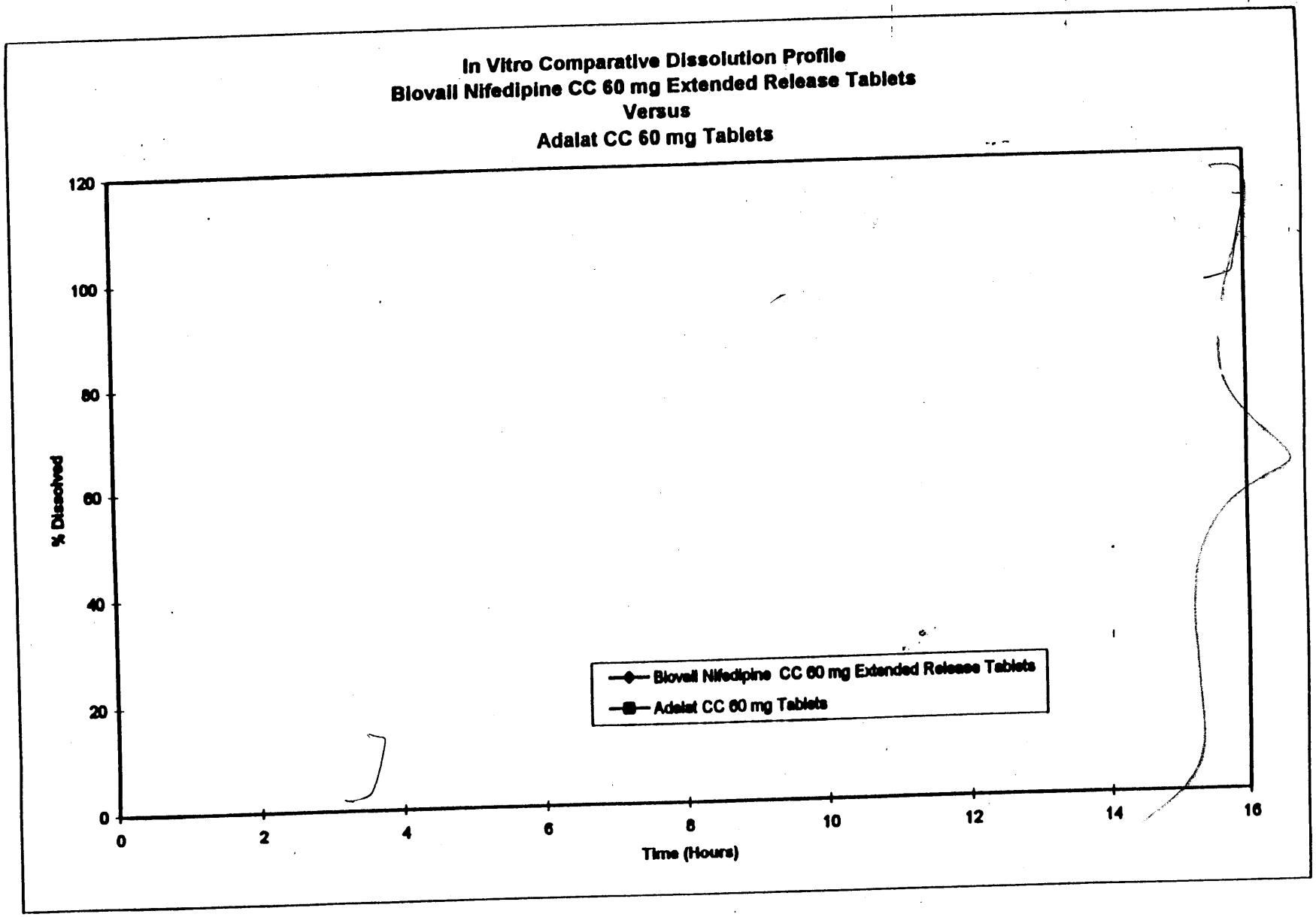


Fig. 3 (Multiple-dose Study.)

APPEARS THIS WAY
ON ORIGINAL

15-21



10443

Reviewed By: Angelo Santos

Date: June 26/97

NIFEDIPINE CC 60 mg TABLETS
STUDY #1869-1 (B97-313PK-NIFB32)
PROTOCOL DEVIATIONS

PHASE	DATE	DEVIATION	PROTOCOL STATES
I	July 5, 1997	Due to sampling difficulty, the 1.0 hour blood sample of Subject #58 was obtained one minute late.	A 7 mL blood sample will be collected at exactly 1.0 hour post-drug.
II	July 11, 1997	Subject #56 arrived 52 minutes after the institutionalization time of 9 PM.	The subjects will be institutionalized at 9 PM of the evening before and until at least the final 48 hour blood sample of each phase.
II	July 11, 1997	Subject #66 arrived 1 hour and 45 minutes after the institutionalization time of 9 PM.	The subjects will be institutionalized at 9 PM of the evening before and until at least the final 48 hour blood sample of each phase.
II	July 12, 1997	Due to sampling difficulty, the 10.0 hour blood sample of Subject #61 was obtained two minutes late.	A 7 mL blood sample will be collected at exactly 10.0 hours post-drug.

BIOVAIL CORPORATION INTERNATIONAL
STUDY # 1869-1 (B97-313PK-NIFB32)

NIFEDIPINE 60 mg CC TABLETS
STUDY # 1869-1 (B97-313PK-NIFB32)
ADVERSE EVENTS

SUBJECT'S NUMBER	SUBJECT'S INITIALS	PHASE	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET (m/d/y)	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
02	JJ	I	B	Headache	1000	07/05/97	9 hrs, 20 min	Mild	None	Probably drug related
				Nausea	1230	07/05/97	30 min	Mild	None	Probably drug related
07	LS	I	B	Dizziness	1000	07/05/97	1 hr	Mild	None	Drug related
08	SB	I	B	Headache	1030	07/05/97	8 hrs, 30 min	Mild	None	Probably drug related
09	WM	I	A	1° AV Block	0714	07/06/97	3 hrs, 22 min	Mild	None	Drug related
11	JS	I	A	Sinus Bradycardia	0716	07/06/97	3 hrs, 22 min	Mild	None	Drug related
13	BK	I	A	Headache	1200	07/05/97	11 hrs	Mild	None	Probably drug related
14	BA	I	A	Headache	1230	07/05/97	4 hrs	Mild	None	Probably drug related
15	JA	I	A	Headache	1230	07/05/97	6 hrs, 30 min	Mild	None	Probably drug related
16	MCH	I	A	Nausea	1020	07/05/97	1 min	Mild	None	Probably not drug related
17	NH	I	B	Headache	0830	07/05/97	3 hrs, 50 min	Mild	None	Probably drug related
				Headache	1220	07/05/97	1 hr, 50 min	Moderate	Ice pack	Probably drug related
20	AAI	I	B	Headache	0945	07/05/97	10 hrs, 45 min	Mild	None	Probably drug related
23	VK	I	A	Headache	0800	07/05/97	10 hrs	Mild	None	Probably drug related
25	KE	I	B	Headache	0900	07/05/97	5 hrs	Mild	None	Probably drug related
26	MCN	I	B	Headache	0850	07/05/97	6 hrs, 55 min	Mild	None	Probably drug related

225

CODES:

*SEVERITY

MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.

MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.

SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health.

**REGIMEN

A: Nifedipine 60 mg CC Tablets (Biovail Corporation International, Research and Development Division; Lot Number: 97E004) following an overnight fast

B: Adalat® CC 60 mg Tablets (Bayer Corp.; Lot Number: 6KGJ; Expiry Date: 11/98) following an overnight fast

NIFEDIPINE 60 mg CC TABLETS
STUDY # 1869-1 (B97-313PK-NIFB32)
ADVERSE EVENTS (Cont'd)

SUBJECT'S NUMBER	SUBJECT'S INITIALS	PHASE	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET (m/d/y)	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
28	TS	I	A	Sinus Bradycardia	0734	07/06/97	3 hrs, 6 min	Mild	None	Drug related
31	TDY	I	A	Sinus Tachycardia	0939	07/05/97	1 hr, 59 min	Mild	None	Drug related
33	CM	I	A	Headache	0905	07/05/97	5 hrs	Mild	None	Probably drug related
37	JW	I	B	Headache	0900	07/05/97	10 hrs	Mild	None	Probably drug related
39	SG	I	B	Lightheadedness	0840	07/05/97	3 min	Mild	Advised to arise slowly	Drug related
				Lightheadedness	0908	07/05/97	4 min	Mild	Placed on right side in bed	Drug related
				Lightheadedness	0925	07/05/97	25 sec	Mild	Monitoring continued	Drug related
40	WB	I	B	1° AV Block	0752	07/06/97	2 hrs, 51 min	Mild	None	Drug related
44	NR	I	A	Headache	1330	07/05/97	13 hrs, 30 min	Mild	None	Drug related
46	AB	I	A	Headache	1300	07/05/97	2 hrs, 45 min	Mild	Ice pack	Drug related
				Headache	0345	07/06/97	4 hrs	Moderate	Ice pack and elevation	Not drug related
47	JV	I	B	Pain to left ankle	1545	07/04/97	18 hrs	Moderate	Ice pack continued	Not drug related
				Pain to left ankle	0900	07/05/97	12 hrs	Mild		Not drug related

226

CODES:

*SEVERITY

MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.

MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.

SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health

**REGIMEN

A: Nifedipine 60 mg CC Tablets (Biovail Corporation International, Research and Development Division; Lot Number: 97E004) following an overnight fast

B: Adalat® CC 60 mg Tablets (Bayer Corp.; Lot Number: 6KGJ; Expiry Date: 11/98) following an overnight fast

018

TABLE 4. ADVERSE EVENTS

Adverse Event	Nifedipine Fed Conditions (N=20)		Nifedipine Fasting Conditions (N=20)		ADALAT®CC Fed Conditions (N=21)	
	n	%	n	%	n	%
Headache	5	25.0	3	15.0	6	28.6
Lightheadedness	2	10.0	1	5.0	1	4.8
Sore throat	1	5.0	1	5.0	1	4.8
Palpitations	1	5.0	0	0.0	0	0.0
Nasal congestion	0	0.0	1	5.0	1	4.8
Sneezing	0	0.0	1	5.0	0	0.0
Nausea	0	0.0	0	0.0	2	9.5
Shortness of breath	0	0.0	0	0.0	1	4.8
Red eyes	0	0.0	0	0.0	1	4.8
Itchy eyes	0	0.0	0	0.0	1	4.8
Fatigue	0	0.0	0	0.0	1	4.8
Drowsiness	0	0.0	0	0.0	1	4.8
Dizziness	0	0.0	0	0.0	1	4.8
Diarrhea	0	0.0	0	0.0	1	4.8

NIFEDIPINE CC 60 mg TABLETS
STUDY #1871-1 (B97-315PK-NIFB32)
PROTOCOL DEVIATIONS

PERIOD	DATE	DEVIATION	PROTOCOL STATES
I	September 20, 1997	On Day 3, Subject #32 was unable to complete part of the 13.5 hour post-drug snack due to intolerance to muffins.	A snack will be provided to all subjects at 13.5 hours post-drug.
I	September 22, 1997	On Day 5, the 0.0 hour (pre-drug) blood draw of Subject #25 was 2 minutes late due to sampling difficulty.	A 7 mL blood sample will be collected at exactly 0.0 hour, prior to drug administration.
I	September 22, 1997	On Day 5, the 0.0 hour (pre-drug) blood draw of Subject #34 was 2 minutes late due to sampling difficulty.	A 7 mL blood sample will be collected at exactly 0.0 hour, prior to drug administration.
I	September 22, 1997	Subject #32 was unable to consume part of the 13.5 hour post-drug snack on Day 5 due to intolerance to the muffins.	A snack will be provided to all subjects at 13.5 hours post-drug.
I	September 23, 1997	On Day 6, the 0.0 hour (pre-drug) blood draw of Subject #05 was 2 minutes late due to sampling difficulty.	A 7 mL blood sample will be collected at exactly 0.0 hour, prior to drug administration.
I	September 23, 1997	On Day 6, the 0.0 hour (pre-drug) blood draw of Subject #22 was 2 minutes late due to sampling difficulty.	A 7 mL blood sample will be collected at exactly 0.0 hour, prior to drug administration.
I	September 23, 1997	On Day 6, Subject #28 began eating the 13.5 hour post-drug snack 13 minutes late due to being in the shower.	A snack will be provided to all subjects at 13.5 hours post-drug.
II	October 4, 1997	Subject #32 was unable to consume part the 13.5 hour post-drug snack on Day 3 due to intolerance to muffins.	A snack will be provided to all subjects at 13.5 hours post-drug.
II	October 6, 1997	On Day 5, Subject #17 vomited the entire 9.5 hour post-drug meal due to nausea.	At 9.5 hours post-drug, a standardized, xanthine-free meal will be provided to all subjects, with a non-caffeine containing beverage.
II	October 6, 1997	Subject #32 was unable to consume part the 13.5 hour post-drug snack on Day 5 due to intolerance to muffins.	A snack will be provided to all subjects at 13.5 hours post-drug.
II	October 8, 1997	On Day 7, the 6.0 hour post-drug blood draw of Subject #45 was 2 minutes late due to sampling difficulty.	A 7 mL blood sample will be collected at exactly 6.0 hours post-drug administration.

NIFEDIPINE CC 60 mg TABLETS
STUDY # 1871-1 (B97-315PK-NIFB32)
ADVERSE EVENTS

SUBJECT'S NUMBER	SUBJECT'S INITIALS	PERIOD	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET (m/d/y)	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
02	FK	I	B	1°AV Block	1504	09/20/97	2 hrs., 4 min.	Mild	None	Drug related
				Headache	1100	09/23/97	1 hr.	Mild	None	Probably drug related
04	MF	I	A	Borderline 1°AV Block	1505	09/18/97	6 hrs., 26 min.	Mild	None	Drug related
				Sinus Bradycardia	1105	09/21/97	1 hr., 59 min.	Mild	None	Drug related
				Sinus Bradycardia	0901	09/22/97	2 hrs., 3 min.	Mild	None	Drug related
				Sinus Bradycardia	1102	09/23/97	2 hrs., 2 min.	Mild	None	Drug related
				Sinus Bradycardia	2305	09/23/97	6 hrs., 8 min.	Mild	None	Drug related
05	JSY	I	A	Headache	1300	09/18/97	7 hrs.	Mild	None	Probably drug related
				Borderline 1°AV Block	1505	09/18/97	2 hrs., 33 min.	Mild	None	Drug related
				Borderline 1°AV Block	0907	09/19/97	2 hrs., 4 min.	Mild	None	Drug related
				Sinus Bradycardia	0904	09/20/97	4 hrs., 3 min.	Mild	None	Drug related
				1°AV Block	1506	09/20/97	2 hrs., 6 min.	Mild	None	Drug related
				1°AV Block	1112	09/21/97	1 hr., 56 min.	Mild	None	Drug related
				Borderline 1°AV Block	0901	09/22/97	4 hrs., 15 min.	Mild	None	Drug related
				Sinus Bradycardia	0901	09/22/97	2 hrs., 9 min.	Mild	None	Drug related
				Rash to Upper Eyelids	1820	09/22/97	20 hrs., 40 min.	Mild	None	Probably not drug related
				Sinus Bradycardia	0904	09/23/97	2 hrs.	Mild	None	Drug related
				1°AV Block	0904	09/23/97	2 hrs.	Mild	None	Drug related
				Borderline 1°AV Block	0901	09/24/97	1 hr., 8 min.	Mild	None	Drug related
				1°AV Block	0715	09/25/97	27 hrs., 54 min.	Mild	None	Drug related

CODES:

*SEVERITY
MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.
MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.
SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health.

**REGIMEN
A: One nifedipine CC 60 mg tablet (Biovail Corporation International; Lot Number: 97E004) (Test drug) with 240 mL of water, following an overnight fast on Days 1 - 7.
B: One Adalat® CC 60 mg tablet (Bayer Corporation; Lot Number: 6KGJ; Expiry Date: 11/98) (Reference drug) with 240 mL of water, following an overnight fast on Days 1 - 7.

NIFEDIPINE 60 mg CC TABLETS
STUDY # 1869-1 (B97-313PK-NIFB32)
ADVERSE EVENTS (Cont'd)

SUBJECT'S NUMBER	SUBJECT'S INITIALS	PHASE	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET (m/d/y)	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
49	DM	I	B	Headache	2300	07/05/97	5 hrs	Moderate	None	Probably drug related
51	JR	I	A	Sinus Bradycardia	0800	07/06/97	2 hrs, 46 min	Mild	None	Drug related
				Headache	1300	07/05/97	2 hrs	Moderate	None	Probably drug related
				Headache	1500	07/05/97	7 hrs, 40 min	Mild	None	Probably drug related
52	PB	I	B	Sinus Bradycardia	0804	07/06/97	2 hrs, 48 min	Mild	None	Drug related
53	SNN	I	A	Headache	1400	07/05/97	3 hrs	Mild	None	Probably drug related
56	PO	I	B	Sinus Bradycardia	0808	07/06/97	2 hrs, 51 min	Mild	None	Drug related
57	MT	I	B	1° AV Block	1008	07/05/97	1 hr, 58 min	Mild	None	Drug related
				Headache	1000	07/05/97	3 hrs, 52 min	Mild	None	Probably drug related
				Nausea	1000	07/05/97	10 hrs	Mild	None	Probably drug related
				1° AV Block	0807	07/06/97	6 hrs, 19 min	Mild	None	Drug related
58	NS	I	A	Sinus Bradycardia	0808	07/06/97	2 hrs, 53 min	Mild	None	Drug Related
59	KW	I	A	Nausea	1300	07/05/97	5 hrs	Mild	None	Probably drug related
61	SK	I	A	Sinus Bradycardia	1210	07/05/97	3 hrs, 12 min	Mild	None	Drug related
				Sinus Bradycardia	0811	07/06/97	2 hrs, 52 min	Mild	None	Drug related
64	NB	I	A	Headache	1100	07/05/97	4 hrs	Mild	Ice pack given	Probably drug related

CODES:

*SEVERITY

MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.

MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.

SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health

**REGIMEN

A: Nifedipine 60 mg CC Tablets (Biovail Corporation International, Research and Development Division; Lot Number: 97E004) following an overnight fast

B: Adalat® CC 60 mg Tablets (Bayer Corp.; Lot Number: 6KGJ; Expiry Date: 11/98) following an overnight fast

NIFEDIPINE 60 mg CC TABLETS
STUDY # 1869-1 (B97-313PK-NIFB32)
ADVERSE EVENTS (Cont'd)

SUBJECT'S NUMBER	SUBJECT'S INITIALS	PHASE	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET (m/d/y)	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
01	KSE	II	B	Borderline 1° AV Block	2305	07/12/97	7 hrs, 58 min	Mild	None	Drug related
02	JJ	II	A	Headache	0830	07/12/97	7 hrs	Mild	None	Probably drug related
				Sinus Bradycardia	0906	07/12/97	2 hrs, 1 min	Mild	None	Drug related
				Chills	1030	07/12/97	5 hrs	Moderate	None	Probably not drug related
03	ML	II	A	Headache	1030	07/12/97	11 hrs	Mild	None	Probably drug related
04	MV	II	A	Headache	0930	07/12/97	4 hrs, 30 min	Mild	None	Probably drug related
08	SB	II	A	Headache	0915	07/12/97	9 hrs, 45 min	Mild	None	Probably drug related
09	WM	II	B	Borderline 1° AV Block	0710	07/13/97	1 hr, 46 min.	Mild	None	Drug related
11	JS	II	B	Sinus Bradycardia	0915	07/12/97	2 hrs, 1 min	Mild	None	Drug related
				Sinus Bradycardia	0714	07/13/97	1 hr, 45 min	Mild	None	Drug related
14	BA	II	B	Headache	0930	07/12/97	12 hrs, 30 min	Mild	None	Probably drug related
				Sinus Bradycardia	0918	07/12/97	2 hrs	Mild	None	Drug related
				Sinus Bradycardia	0717	07/13/97	1 hr, 43 min	Mild	None	Drug related
19	SH	II	A	Headache	0930	07/12/97	9 hrs, 30 min	Mild	None	Probably drug related
20	AAI	II	A	Headache	0930	07/12/97	6 hrs, 5 min	Mild	None	Probably drug related
				Headache	1535	07/12/97	4 hrs	Moderate	None	Probably drug related
22	RJ	II	B	Lightheaded	0900	07/12/97	2 hrs	Mild	None	Probably drug related

CODES:

*SEVERITY

MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.

MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.

SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health.

**REGIMEN

A: Nifedipine 60 mg CC Tablets (Biovail Corporation International, Research and Development Division; Lot Number: 97E004) following an overnight fast

B: Adalat® CC 60 mg Tablets (Bayer Corp.; Lot Number: 6KGJ; Expiry Date: 11/98) following an overnight fast

NIFEDIPINE CC 60 mg TABLETS
STUDY # 1871-1 (B97-315PK-NIFB32)
ADVERSE EVENTS (Cont'd)

SUBJECT'S NUMBER	SUBJECT'S INITIALS	PERIOD	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET (m/d/y)	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
07	TA	I	A	Headache	1030	09/18/97	4 hrs., 30 min.	Mild	None	Probably drug related
				Headache	1130	09/22/97	9 hrs.	Mild	None	Probably drug related
				Headache	1100	09/24/97	3 hrs., 30 min.	Mild	None	Probably drug related
08	DD	I	A	1°AV Block	1314	09/20/97	1 hr., 54 min.	Mild	None	Drug related
				Borderline 1°AV Block	0527	09/21/97	3 hrs., 44 min.	Mild	None	Probably drug related
				1°AV Block	2309	09/22/97	5 hrs., 12 min.	Mild	None	Drug related
				1°AV Block	0911	09/24/97	2 hr.	Mild	None	Drug related
				1°AV Block	2313	09/24/97	36 hrs., 8 min.	Mild	None	Drug related
09	MS	I	B	Sinus Tachycardia	1516	09/24/97	2 hrs., 5 min.	Mild	None	Probably drug related
10	JK	I	B	Headache	1000	09/18/97	20 hrs.	Mild	None	Probably drug related
				Headache	1055	09/19/97	19 hrs., 5 min.	Mild	None	Probably drug related
				Headache	1300	09/24/97	4 hrs.	Mild	None	Probably drug related
				Sinus Tachycardia	1516	09/24/97	7 hrs., 57 min.	Mild	None	Probably drug related
11	WMY	I	B	Sinus Bradycardia	1115	09/19/97	1 hr., 47 min.	Mild	None	Drug related
				1°AV Block	2316	09/19/97	6 hrs., 7 min.	Mild	None	Drug related
				Sinus Bradycardia	0912	09/23/97	3 hrs., 55 min.	Mild	None	Drug related

4836

CODES:

***SEVERITY**

MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.

MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.

SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health.

****REGIMEN**

A: One nifedipine CC 60 mg tablet (Biovail Corporation International; Lot Number: 97E004) (Test drug) with 240 mL of water, following an overnight fast on Days 1 - 7.

B: One Adalat® CC 60 mg tablet (Bayer Corporation; Lot Number: 6KGJ; Expiry Date: 11/98) (Reference drug) with 240 mL of water, following an overnight fast on Days 1 - 7.

020

NIFEDIPINE 60 mg CC TABLETS
STUDY # 1869-1 (B97-313PK-NIFB32)
ADVERSE EVENTS (Cont'd)

SUBJECT'S NUMBER	SUBJECT'S INITIALS	PHASE	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET (m/d/y)	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
25	KE	II	A	Headache	1000	07/12/97	12 hrs	Mild	None	Probably drug related
26	MCN	II	A	Headache	0945	07/12/97	8 hrs, 45 min	Mild	None	Probably drug related
28	TS	II	B	Headache	1105	07/12/97	4 hrs, 5 min	Mild	None	Probably drug related
				Sinus Bradycardia	0729	07/13/97	1 hr, 39 min	Mild	None	Drug related
29	NK	II	A	Headache	1320	07/12/97	7 hrs, 40 min	Mild	None	Probably drug related
				Sinus Bradycardia	0732	07/13/97	1 hr, 30 min	Mild	None	Drug related
31	TDY	II	B	Drowsiness	0830	07/12/97	30 min	Mild	None	Probably drug related
				Sinus Tachycardia	0935	07/12/97	10 hrs, 4 min	Mild	None	Drug related
				Sinus Tachycardia	2331	07/13/97	8 hrs, 1 min	Mild	None	Drug related
32	TM	II	B	Headache	1000	07/12/97	12 hrs	Mild	None	Probably drug related
33	CM	II	B	Headache	0700	07/12/97	6 hrs, 30 min	Mild	None	Probably drug related
				Headache	1540	07/12/97	2 hrs	Mild	None	Probably drug related
34	AP	II	A	Sinus Bradycardia	1137	07/12/97	2 hrs, 7 min	Mild	None	Drug related
				Sinus Bradycardia	0736	07/13/97	1 hr, 37 min	Mild	None	Drug related
44	NR	II	B	Headache	1030	07/12/97	8 hrs	Mild	None	Drug related
50	PC	II	A	Headache	1000	07/12/97	12 hrs	Mild	None	Probably drug related

CODES:

*SEVERITY

MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.

MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.

SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health

**REGIMEN

A: Nifedipine 60 mg CC Tablets (Biovail Corporation International, Research and Development Division; Lot Number: 97E004) following an overnight fast

B: Adalat® CC 60 mg Tablets (Bayer Corp.; Lot Number: 6KGJ; Expiry Date: 11/98) following an overnight fast

NIFEDIPINE CC 60 mg TABLETS
STUDY # 1871-1 (B97-315PK-NIFB32)
ADVERSE EVENTS (Cont'd)

SUBJECT'S NUMBER	SUBJECT'S INITIALS	PERIOD	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET (m/d/y)	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
12	EA	I	A	Headache	1230	09/20/97	4 hrs.	Mild	None	Probably drug related
				Headache	1200	09/21/97	4 hrs., 30 min.	Mild	None	Probably drug related
				Headache	1400	09/23/97	3 hrs.	Mild	None	Probably drug related
13	MCS	I	A	Headache	0815	09/23/97	2 hrs., 25 min.	Mild	None	Probably drug related
17	JSD	I	B	Headache	0400	09/20/97	10 hrs.	Mild	None	Probably drug related
18	GMT	I	B	Runny Nose	0600	09/19/97	4 hrs.	Mild	None	Not drug related
				Sinus Bradycardia	1116	09/20/97	1 hr., 53 min.	Mild	None	Drug related
				Sinus Bradycardia	1120	09/22/97	2 hrs.	Mild	None	Drug related
				Sinus Bradycardia	1122	09/24/97	1 hr., 43 min.	Mild	None	Drug related
19	WM	I	B	Headache	0730	09/18/97	11 hrs., 30 min.	Mild	None	Probably drug related
				1°AV Block	0730	09/25/97	35 min.	Mild	None	Drug related
20	SW	I	A	Headache	0800	09/22/97	14 hrs., 30 min.	Mild	None	Probably drug related
				Headache	1400	09/24/97	6 hrs.	Mild	Given Ice pack	Probably drug related
21	PF	I	B	Sinus Bradycardia	0928	09/21/97	3 hrs., 44 min.	Mild	None	Drug related
				Headache	1400	09/24/97	2 hrs., 30 min.	Mild	None	Probably drug related

CODES:

*SEVERITY
MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.
MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.
SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health.

**REGIMEN
A: One nifedipine CC 60 mg tablet (Biovail Corporation International; Lot Number: 97E004) (Test drug) with 240 mL of water, following an overnight fast on Days 1 - 7.
B: One Adalat® CC 60 mg tablet (Bayer Corporation; Lot Number: 6KGJ; Expiry Date: 11/98) (Reference drug) with 240 mL of water, following an overnight fast on Days 1 - 7.

NIFEDIPINE 60 mg CC TABLETS
STUDY # 1869-1 (B97-313PK-NIFB32)
ADVERSE EVENTS (Cont'd)

SUBJECT'S NUMBER	SUBJECT'S INITIALS	PHASE	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET (m/d/y)	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
51	JR	II	B	Sinus Bradycardia	1153	07/12/97	1 hr, 54 min	Mild	None	Drug related
				Sinus Bradycardia	0754	07/13/97	1 hr, 21 min	Mild	None	Drug related
52	PB	II	A	Drowsy	0855	07/12/97	6 hrs, 5 min	Mild	None	Probably drug related
				Headache	1500	07/12/97	4 hrs	Mild	None	Probably drug related
				Lightheaded	0855	07/12/97	6 hrs, 55 min	Mild	None	Probably drug related
53	SNN	II	B	Headache	1000	07/12/97	45 min	Mild	None	Probably drug related
54	SHI	II	B	Headache	1100	07/12/97	7 hrs	Mild	None	Probably drug related
56	PO	II	A	Sinus Bradycardia	1000	07/12/97	3 hrs, 50 min	Mild	None	Drug related
				Lightheadedness	1400	07/12/97	1 hr	Mild	None	Probably drug related
				Sinus Bradycardia	0802	07/13/97	1 hr, 16 min	Mild	None	Drug related
57	MT	II	A	Borderline 1° AV Block	1002	07/12/97	1 hr, 57 min	Mild	None	Drug related
				Borderline 1° AV Block	1600	07/12/97	1 hr, 48 min	Mild	None	Drug related
				Borderline 1° AV Block	0759	07/13/97	3 hrs, 6 min	Mild	None	Drug related
60	FC	II	A	Isolated Junctional Premature Beats	2358	07/12/97	8 hrs, 4 min	Mild	None	Drug related
61	SK	II	B	Sinus Bradycardia	2359	07/12/97	9 hrs, 23 min	Mild	None	Drug related
64	NB	II	B	Headache	1055	07/12/97	10 hrs, 35 min	Mild	None	Probably drug related
65	AS	II	B	Headache	0900	07/12/97	13 hrs, 30 min	Mild	None	Probably drug related

CODES:

*SEVERITY

MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.

MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.

SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health.

**REGIMEN

A: Nifedipine 60 mg CC Tablets (Biovail Corporation International, Research and Development Division; Lot Number: 97E004) following an overnight fast

B: Adalat® CC 60 mg Tablets (Bayer Corp.; Lot Number: 6KGJ; Expiry Date: 11/98) following an overnight fast

NIFEDIPINE CC 60 mg TABLETS
STUDY # 1871-1 (B97-315PK-NIFB32)
ADVERSE EVENTS (Cont'd)

SUBJECT'S NUMBER	SUBJECT'S INITIALS	PERIOD	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET (m/d/y)	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
22	SB	I	B	Headache	0815	09/18/97	22 hrs., 15 min.	Mild	None	Probably drug related
				Headache	0830	09/19/97	3 hrs.	Mild	None	Probably drug related
				Sinus Tachycardia	1519	09/19/97	4 hrs., 9 min.	Mild	None	Drug related
				Headache	1130	09/20/97	3 hrs.	Mild	None	Probably drug related
				Sinus Tachycardia	0929	09/21/97	1 hr., 56 min.	Mild	None	Drug related
				Sinus Tachycardia	1730	09/22/97	12 hrs., 15 min.	Mild	None	Drug related
				Sinus Tachycardia	1120	09/23/97	12 hrs., 19 min.	Mild	None	Drug related
				Sinus Tachycardia	0926	09/24/97	1 hr., 59 min.	Mild	None	Drug related
23	MSR	I	A	Accelerated Junctional	0920	09/19/97	1 hr., 54 min.	Mild	None	Drug related
				Sinus Bradycardia	0921	09/20/97	1 hr., 58 min.	Mild	None	Drug related
				Atrial Bigeminy & Junctional Premature Beats	1119	09/20/97	1 hr., 54 min.	Mild	None	Drug related
				Junctional Premature Beats	1521	09/20/97	2 hrs., 33 min.	Mild	None	Probably not drug related
				Atrial Bigeminy	1636	09/20/97	1 hr., 18 min.	Mild	None	Drug related
				Junctional Premature Beats	0932	09/21/97	1 hr., 23 min.	Mild	None	Drug related
				Atrial Premature Beats & Junctional Escape & Premature Beats	1055	09/21/97	1 hr., 6 min.	Mild	None	Drug related
				Junctional Premature Beats	1533	09/21/97	2 hrs., 21 min.	Mild	None	Drug related

CODES:

***SEVERITY**

MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.

MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.

SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health.

****REGIMEN**

A: One nifedipine CC 60 mg tablet (Biovail Corporation International; Lot Number: 97E004) (Test drug) with 240 mL of water, following an overnight fast on Days 1 - 7.

B: One Adalat® CC 60 mg tablet (Bayer Corporation; Lot Number: 6KGJ; Expiry Date: 11/98) (Reference drug) with 240 mL of water, following an overnight fast on Days 1 - 7.

NIFEDIPINE CC 60 mg TABLETS
STUDY # 1871-1 (B97-315PK-NIFB32)
ADVERSE EVENTS (Cont'd)

SUBJECT'S NUMBER	SUBJECT'S INITIALS	PERIOD	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET (m/d/y)	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
25	PP	I	B	Sinus Bradycardia	0937	09/18/97	2 hrs., 1 min.	Mild	None	Drug related
				Sinus Bradycardia	1126	09/19/97	1 hr., 42 min.	Mild	None	Drug related
				Sinus Bradycardia	0923	09/20/97	2 hrs.	Mild	None	Drug related
				Sore Neck	0630	09/21/97	1 hr., 30 min.	Mild	None	Not drug related
				Sinus Bradycardia	1128	09/24/97	1 hr., 39 min.	Mild	None	Drug related
26	WB	I	A	Borderline 1°AV Block	0925	09/19/97	2 hrs., 1 min.	Mild	None	Drug related
				1°AV Block	2331	09/19/97	6 hrs. 15 min.	Mild	None	Drug related
				1°AV Block	1522	09/20/97	20 hrs., 8 min.	Mild	None	Drug related
				1°AV Block	2321	09/21/97	7 hrs., 31 min.	Mild	None	Drug related
				Borderline 1°AV Block	0920	09/22/97	2 hrs., 5 min.	Mild	None	Drug related
				1°AV Block	1125	09/22/97	3 hrs., 54 min.	Mild	None	Drug related
				Borderline 1°AV Block	0640	09/23/97	4 hrs., 44 min.	Mild	None	Drug related
				Borderline 1°AV Block	1527	09/23/97	1 hr., 58 min.	Mild	None	Drug related
				Borderline 1°AV Block	2331	09/24/97	8 hrs., 5 min.	Mild	None	Drug related
27	GS	I	A	Sinus Bradycardia	0925	09/19/97	2 hrs.	Mild	None	Drug related
				Sinus Bradycardia	0922	09/20/97	2 hrs., 3 min.	Mild	None	Drug related
				Sinus Bradycardia	1129	09/22/97	2 hrs.	Mild	None	Drug related

CODES:

*SEVERITY
MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.
MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.
SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health.

**REGIMEN
A: One nifedipine CC 60 mg tablet (Biovail Corporation International; Lot Number: 97E004) (Test drug) with 240 mL of water, following an overnight fast on Days 1 - 7.
B: One Adalat® CC 60 mg tablet (Bayer Corporation; Lot Number: 6KGJ; Expiry Date: 11/98) (Reference drug) with 240 mL of water, following an overnight fast on Days 1 - 7.

NIFEDIPINE CC 60 mg TABLETS
STUDY # 1871-1 (B97-315PK-NIFB32)
ADVERSE EVENTS (Cont'd)

SUBJECT'S NUMBER	SUBJECT'S INITIALS	PERIOD	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET (m/d/y)	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
31	RS	I	A	Sinus Tachycardia	1533	09/23/97	1 hr., 56 min.	Mild	None	Drug related
32	WS	I	B	Headache	1100	09/18/97	5 hrs.	Mild	None	Probably drug related
				Headache	0925	09/23/97	4 hrs., 35 min.	Mild	None	Probably drug related
33	JS	I	A	Headache	1500	09/23/97	30 min.	Mild	None	Probably drug related
34	JB	I	B	Headache	1100	09/21/97	5 hrs., 30 min.	Mild	None	Probably drug related
				Dizziness	0730	09/22/97	10 min.	Mild	None	Probably drug related
35	IR	I	B	Headache	0700	09/22/97	12 hrs.	Mild	None	Probably drug related
36	MC	I	A	Headache	1030	09/18/97	11 hrs., 30 min.	Mild	None	Probably drug related
				Dizziness	0900	09/19/97	30 min.	Mild	None	Probably drug related
				Headache	1030	09/19/97	8 hrs.	Mild	None	Probably drug related
				Headache	1040	09/20/97	5 hrs., 50 min.	Mild	None	Probably drug related
				Headache	1110	09/23/97	10 hrs., 50 min.	Mild	None	Probably drug related
				Headache	1515	09/24/97	7 hrs., 45 min.	Mild	None	Probably drug related

4840

CODES:

*SEVERITY
MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.
MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.
SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health.

**REGIMEN
A: One nifedipine CC 60 mg tablet (Biovail Corporation International; Lot Number: 97E004) (Test drug) with 240 mL of water, following an overnight fast on Days 1 - 7.
B: One Adalat® CC 60 mg tablet (Bayer Corporation; Lot Number: 6KGJ; Expiry Date: 11/98) (Reference drug) with 240 mL of water, following an overnight fast on Days 1 - 7.

024

NIFEDIPINE CC 60 mg TABLETS
STUDY # 1871-1 (B97-315PK-NIFB32)
ADVERSE EVENTS (Cont'd)

SUBJECT'S NUMBER	SUBJECT'S INITIALS	PERIOD	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET (m/d/y)	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
38	SM	I	A	Headache	1500	09/18/97	1 hr.	Mild	None	Probably drug related
				Lightheadedness	0900	09/19/97	45 min.	Mild	None	Probably drug related
39	RB	I	A	Headache	0200	09/18/97	44 hrs., 30 min.	Mild	None	Probably drug related
				Headache	0615	09/20/97	11 hrs., 15 min.	Mild	None	Probably drug related
				Headache	0900	09/22/97	13 hrs., 15 min.	Mild	None	Probably drug related
				Headache	1300	09/23/97	7 hrs., 15 min.	Mild	None	Probably drug related
				Headache	1300	09/24/97	6 hrs., 15 min.	Mild	None	Probably drug related
40	CC	I	A	Headache	1730	09/23/97	2 hrs., 55 min.	Mild	None	Probably drug related
				Headache	0910	09/24/97	11 hrs., 30 min.	Mild	None	Probably drug related
41	SG	I	A	Lightheadedness	0820	09/24/97	8 hrs., 40 min.	Mild	None	Probably drug related
				Headache	1115	09/24/97	4 hrs., 45 min.	Mild	None	Probably drug related
43	TT	I	B	Headache	0630	09/22/97	9 hrs., 30 min.	Mild	None	Probably drug related
44	SC	I	B	2°AV Block	0643	09/23/97	1 hr., 11 min.	Moderate	None	Drug related
45	CCS	I	A	Sinus Bradycardia	0943	09/22/97	2 hrs., 6 min.	Mild	None	Drug related
				Sinus Bradycardia	1148	09/24/97	1 hr., 22 min.	Mild	None	Drug related

CODES:

***SEVERITY**

MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.
MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.
SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health.

****REGIMEN**

A: One nifedipine CC 60 mg tablet (Biovail Corporation International; Lot Number: 97E004) (Test drug) with 240 mL of water, following an overnight fast on Days 1 - 7.
B: One Adalat® CC 60 mg tablet (Bayer Corporation; Lot Number: 6KGJ; Expiry Date: 11/98) (Reference drug) with 240 mL of water, following an overnight fast on Days 1 - 7.

NIFEDIPINE CC 60 mg TABLETS
STUDY # 1871-1 (B97-315PK-NIFB32)
ADVERSE EVENTS (Cont'd)

SUBJECT'S NUMBER	SUBJECT'S INITIALS	PERIOD	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET (m/d/y)	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
46	JV	I	B	Occasional Ventricular Premature Beats	1150	09/20/97	3 hrs., 6 min.	Mild	None	Probably not drug related
47	JW	I	A	Headache	0850	09/18/97	32 hrs., 10 min.	Mild	None	Probably drug related
				Borderline 1°AV Block	1559	09/18/97	14 hrs., 2 min.	Mild	None	Drug related
				Lightheadedness	1120	09/19/97	10 min.	Mild	None	Probably drug related
				Headache	0600	09/20/97	12 hrs., 30 min.	Mild	None	Probably drug related
				Borderline 1°AV Block	0619	09/23/97	3 hrs., 25 min.	Mild	None	Drug related
05	JSY	II	B	Borderline 1°AV Block	1107	10/04/97	1 hr., 56 min.	Mild	None	Drug related
				Borderline 1°AV Block	2304	10/04/97	6 hrs., 9 min.	Mild	None	Drug related
				Borderline 1°AV Block	0904	10/05/97	2 hrs., 1 min.	Mild	None	Drug related
				Sinus Bradycardia	0912	10/06/97	3 hrs., 52 min.	Mild	None	Drug related
				Borderline 1°AV Block	1511	10/06/97	2 hrs., 43 min.	Mild	None	Drug related
				Borderline 1°AV Block	2305	10/06/97	6 hrs., 2 min.	Mild	None	Drug related
				Sinus Bradycardia	0906	10/07/97	2 hrs.	Mild	None	Drug related
				Borderline 1°AV Block	1106	10/07/97	2 hrs., 2 min.	Mild	None	Drug related
				Headache	1400	10/07/97	6 hrs.	Mild	None	Probably drug related
				Sinus Bradycardia	0909	10/08/97	1 hr., 59 min.	Mild	None	Drug related
				Borderline 1°AV Block	0909	10/08/97	1 hr., 59 min.	Mild	None	Drug related

48412

CODES:

***SEVERITY**
MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.
MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.
SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health.

****REGIMEN**
A: One nifedipine CC 60 mg tablet (Biovail Corporation International; Lot Number: 97E004) (Test drug) with 240 mL of water, following an overnight fast on Days 1 - 7.
B: One Adalat® CC 60 mg tablet (Bayer Corporation; Lot Number: 6KGJ; Expiry Date: 11/98) (Reference drug) with 240 mL of water, following an overnight fast on Days 1 - 7.

NIFEDIPINE CC 60 mg TABLETS
STUDY # 1871-1 (B97-315PK-NIFB32)
ADVERSE EVENTS (Cont'd)

SUBJECT'S NUMBER	SUBJECT'S INITIALS	PERIOD	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET (m/d/y)	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
06	PS	II	A	Sinus Bradycardia	0909	10/08/97	2 hrs., 2 min.	Mild	None	Drug related
07	TA	II	B	Headache	0930	10/02/97	13 hrs., 30 min.	Mild	None	Probably drug related
				Headache	0930	10/03/97	8 hrs.	Mild	None	Probably drug related
08	DD	II	B	Borderline 1°AV Block	2308	10/02/97	7 hrs., 54 min.	Mild	None	Drug related
				Borderline 1°AV Block	0906	10/03/97	2 hrs., 2 min.	Mild	None	Drug related
				Borderline 1°AV Block	1111	10/04/97	2 hrs.	Mild	None	Drug related
				Borderline 1°AV Block	0518	10/05/97	8 hrs., 21 min.	Mild	None	Drug related
				Borderline 1°AV Block	0920	10/06/97	1 hr., 56 min.	Mild	None	Drug related
				Borderline 1°AV Block	2308	10/07/97	12 hrs., 5 min.	Mild	None	Drug related
12	EA	II	B	Headache	1700	10/02/97	16 hrs., 5 min.	Mild	None	Not drug related
				Nausea	2400	10/02/97	9 hrs., 5 min.	Mild	None	Not drug related
				Diarrhea	0200	10/03/97	3 hrs., 30 min.	Mild	None	Not drug related
13	MCS	II	B	Sinus Bradycardia	1114	10/03/97	1 hr., 46 min.	Mild	None	Drug related
15	WMS	II	B	Sinus Bradycardia	0912	10/03/97	3 hrs., 53 min.	Mild	None	Drug related
				Sore Throat	0030	10/04/97	22 hrs., 30 min.	Mild	None	Not drug related

CODES:

*SEVERITY
MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.
MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.
SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health.

**REGIMEN
A: One nifedipine CC 60 mg tablet (Biovail Corporation International; Lot Number: 97E004) (Test drug) with 240 mL of water, following an overnight fast on Days 1 - 7.
B: One Adalat® CC 60 mg tablet (Bayer Corporation; Lot Number: 6KGJ; Expiry Date: 11/98) (Reference drug) with 240 mL of water, following an overnight fast on Days 1 - 7.

NIFEDIPINE CC 60 mg TABLETS
STUDY # 1871-1 (B97-315PK-NIFB32)
ADVERSE EVENTS (Cont'd)

SUBJECT'S NUMBER	SUBJECT'S INITIALS	PERIOD	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET (m/d/y)	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
17	JSD	II	A	Vomiting	1800	10/06/97	2 min.	Mild	None	Not drug related
				Nausea	1800	10/06/97	5 hrs.	Mild	None	Not drug related
18	GMT	II	A	Headache	0930	10/06/97	8 hrs., 30 min.	Mild	None	Probably drug related
				Headache	1130	10/08/97	5 hrs., 30 min.	Mild	None	Probably drug related
19	WM	II	A	Headache	0930	10/02/97	6 hrs., 30 min.	Mild	None	Probably drug related
				Headache	1045	10/04/97	5 hrs., 45 min.	Mild	None	Probably drug related
				Headache	1130	10/06/97	3 hrs., 38 min.	Mild	None	Probably drug related
				Headache	1200	10/07//97	6 hrs.	Mild	None	Probably drug related
				Headache	1130	10/08/97	4 hrs., 30 min.	Mild	None	Probably drug related
20	SW	II	B	Headache	1000	10/02/97	19 hrs.	Mild	None	Probably drug related
				Headache	1400	10/06/97	2 hrs., 30 min.	Mild	None	Probably drug related
				Lightheadedness	1230	10/07/97	2 hrs., 30 min.	Mild	None	Probably drug related
21	PF	II	A	Borderline 1°AV Block	0539	10/03/97	3 hrs., 39 min.	Mild	None	Drug related
				Borderline 1°AV Block	0649	10/05/97	2 hrs., 32 min.	Mild	None	Drug related
				Borderline 1°AV Block	1136	10/06/97	1 hr., 34 min.	Mild	None	Drug related
				Borderline 1°AV Block	2319	10/06/97	6 hrs., 13 min.	Mild	None	Drug related

CODES:

***SEVERITY**
MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.
MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.
SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health.

****REGIMEN**
A: One nifedipine CC 60 mg tablet (Biovail Corporation International; Lot Number: 97E004) (Test drug) with 240 mL of water, following an overnight fast on Days 1 - 7.
B: One Adalat® CC 60 mg tablet (Bayer Corporation; Lot Number: 6KGJ; Expiry Date: 11/98) (Reference drug) with 240 mL of water, following an overnight fast on Days 1 - 7.

NIFEDIPINE CC 60 mg TABLETS
STUDY # 1871-1 (B97-315PK-NIFB32)
ADVERSE EVENTS (Cont'd)

SUBJECT'S NUMBER	SUBJECT'S INITIALS	PERIOD	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET (m/d/y)	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
22	SB	II	A	Sinus Tachycardia	1517	10/05/97	4 hrs., 14 min.	Mild	None	Drug related
23	MSR	II	B	Atrial Bigeminy	1143	10/02/97	1 hr., 19 min.	Mild	None	Drug related
				Atrial Bigeminy & Trigeminy with Occasional Aberrancy	1530	10/02/97	1 hr., 47 min.	Mild	None	Drug related
				Sinus Rhythm with Atrial Bigeminy & Trigeminy	1125	10/03/97	1 hr., 56 min.	Mild	None	Drug related
				Sinus Rhythm with Atrial Bigeminy & Trigeminy	1520	10/03/97	2 hrs., 8 min.	Mild	None	Drug related
				Sinus Rhythm with Atrial Bigeminy with Aberrancy	1128	10/04/97	1 hr., 38 min.	Mild	None	Drug related
				Sinus Rhythm with Atrial Bigeminy & Trigeminy	1528	10/04/97	2 hrs., 1 min.	Mild	None	Drug related
				Sinus Rhythm with Atrial Bigeminy	1523	10/07/97	15 hrs., 15 min.	Mild	None	Drug related
				Sinus Rhythm with Atrial Bigeminy with Aberrancy	2333	10/07/97	7 hrs., 16 min.	Mild	None	Drug related

CODES:

***SEVERITY**
MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.
MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.
SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health.

****REGIMEN**
A: One nifedipine CC 60 mg tablet (Biovail Corporation International; Lot Number: 97E004) (Test drug) with 240 mL of water, following an overnight fast on Days 1 - 7.
B: One Adalat® CC 60 mg tablet (Bayer Corporation; Lot Number: 6KGJ; Expiry Date: 11/98) (Reference drug) with 240 mL of water, following an overnight fast on Days 1 - 7.

NIFEDIPINE CC 60 mg TABLETS
STUDY # 1871-1 (B97-315PK-NIFB32)
ADVERSE EVENTS (Cont'd)

SUBJECT'S NUMBER	SUBJECT'S INITIALS	PERIOD	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET (m/d/y)	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
25	PP	II	A	Sinus Bradycardia	1146	10/02/97	1 hr., 18 min.	Mild	None	Drug related
				Sinus Bradycardia	0953	10/06/97	1 hr., 51 min.	Mild	None	Drug related
				Sore Neck	0800	10/08/97	9 hrs., 30 min.	Mild	None	Not drug related
				Headache	1300	10/08/97	4 hrs., 30 min.	Mild	None	Probably drug related
26	WB	II	B	Borderline 1°AV Block	0949	10/02/97	1 hr., 59 min.	Mild	None	Drug related
				Borderline 1°AV Block	1128	10/03/97	1 hr., 41 min.	Mild	None	Drug related
				Borderline 1°AV Block	1528	10/04/97	17 hrs., 56 min.	Mild	None	Drug related
				Borderline 1°AV Block	1523	10/05/97	8 hrs., 1 min.	Mild	None	Drug related
				Borderline 1°AV Block	0926	10/07/97	3 hrs., 46 min.	Mild	None	Drug related
				Borderline 1°AV Block	1526	10/07/97	1 hr., 57 min.	Mild	None	Drug related
				Borderline 1°AV Block	2329	10/08/97	7 hrs., 11 min.	Mild	None	Drug related
27	GS	II	B	Sinus Bradycardia	2332	10/02/97	6 hrs., 15 min.	Mild	None	Drug related
				Headache	1500	10/04/97	62 hrs., 30 min.	Mild	None	Probably drug related
30	KO	II	A	Sinus Tachycardia	1555	10/06/97	2 hrs., 3 min.	Mild	None	Drug related
				Drowsiness	0800	10/07/97	7 hrs., 30 min.	Mild	None	Probably drug related
31	RS	II	B	Runny Nose	0700	10/03/97	144 hrs.	Mild	None	Not drug related
				Sore Throat	0700	10/03/97	144 hrs.	Mild	None	Not drug related

CODES:

*SEVERITY
MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.
MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.
SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health.

**REGIMEN
A: One nifedipine CC 60 mg tablet (Biovail Corporation International; Lot Number: 97E004) (Test drug) with 240 mL of water, following an overnight fast on Days 1 - 7.
B: One Adalat® CC 60 mg tablet (Bayer Corporation; Lot Number: 6KGJ; Expiry Date: 11/98) (Reference drug) with 240 mL of water, following an overnight fast on Days 1 - 7.

NIFEDIPINE CC 60 mg TABLETS
STUDY # 1871-1 (B97-315PK-NIFB32)
ADVERSE EVENTS (Cont'd)

SUBJECT'S NUMBER	SUBJECT'S INITIALS	PERIOD	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET (m/d/y)	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
35	IR	II	A	Headache	1500	10/07/97	3 hrs.	Mild	None	Probably drug related
36	MC	II	B	Headache	0830	10/02/97	20 hrs., 30 min.	Mild	None	Probably drug related
				Headache	0900	10/03/97	13 hrs.	Mild	None	Probably drug related
				Headache	0900	10/04/97	6 hrs.	Mild	None	Probably drug related
				Sinus Tachycardia	1542	10/04/97	2 hrs., 2 min.	Mild	None	Drug related
				Headache	1700	10/04/97	37 hrs., 30 min.	Mild	None	Probably drug related
				Sinus Tachycardia	1137	10/05/97	3 hrs., 55 min.	Mild	None	Drug related
				Headache	0900	10/07/97	13 hrs.	Mild	None	Probably drug related
				Headache	1200	10/08/97	18 hrs.	Moderate	None	Probably drug related
39	RB	II	B	Headache	1300	10/02/97	2 hrs., 25 min.	Mild	None	Probably drug related
				Headache	1100	10/03/97	4 hrs., 30 min.	Mild	None	Probably drug related
				Headache	1355	10/04/97	15 hrs., 50 min.	Mild	None	Probably drug related
				Headache	1100	10/05/97	12 hrs.	Mild	None	Probably drug related
				Headache	0845	10/07/97	9 hrs., 45 min.	Mild	None	Probably drug related
				Headache	1200	10/08/97	10 hrs., 45 min.	Mild	None	Probably drug related
43	TT	II	A	Headache	1300	10/07/97	10 hrs.	Mild	None	Probably drug related
45	CCS	II	B	Sinus Bradycardia	0951	10/08/97	1 hr., 57 min.	Mild	None	Drug related

CODES:

*SEVERITY
MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.
MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.
SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health.

**REGIMEN
A: One nifedipine CC 60 mg tablet (Biovail Corporation International; Lot Number: 97E004) (Test drug) with 240 mL of water, following an overnight fast on Days 1 - 7.
B: One Adalat® CC 60 mg tablet (Bayer Corporation; Lot Number: 6KGJ; Expiry Date: 11/98) (Reference drug) with 240 mL of water, following an overnight fast on Days 1 - 7.

Nifedipine 30 & 60 mg ER Tablets
ANDA # 75-269
Reviewer: Sikta Pradhan
XWP# 75269AD.798

Biovail Laboratories, Inc.
Mississauga,Ontario, Canada
Submission Date:
July 28, 1998
September 18, 1998

REVIEW OF AN AMENDMENT TO A BIOEQUIVALENCE STUDY

Background:

The single dose bioequivalence studies (under fasting and fed conditions) and the multiple dose study (under fasting condition) conducted on the test product, Biovail's Nifedipine ER Tablets, 30 mg and 60 mg, comparing them with the reference product, Adalat^{R} CC (Bayer Corporation), 30 mg and 60 mg tablets, respectively, were found to be incomplete by the Division of Bioequivalence.

In this amendment the firm has reported the additional stability data and responded all comments made by the Agency.

Agency's Comments on the **30mg and 60 mg** Bioequivalence Studies:

1. The validation of assay method, without any stability data for nifedipine samples, standard and QC samples at -25^{0}C and at room temperature, is incomplete.

2. The stability report should also contain the long-term stability data of samples covering at least a period equivalent to the actual sample storage duration. The study is considered incomplete until the stability data are found acceptable.

3. The firm should provide the first and last dates of sample analysis, and dates of nifedipine QC samples preparation.

4. In the single dose fasting study on **30 mg tablets**, subjects were enrolled on two separate occasions
(Study Dates of Group I: Period 1 dosing, 6/14/97;
Period 2 dosing, 6/21/97; and
Study Dates of Group II: Period 1 dosing, 6/21/97;
Period 2 dosing, 6/28/97), and therefore, an additional ANOVA model should be used to determine if the makeup group was significantly different from the first group with respect to the pharmacokinetic

parameters of nifedipine. This model should include, group, sequence, sequence*group, subject(sequence*group), period(group), treatment, treatment*group.

5. Lot size of the test product used in the bioequivalence study should be provided.

Firm's Responses:

1. The firm has reported (presented in Tables #1 - 3) the long term stability of nifedipine in plasma stored at-25 ^{0}C. The in-process stability of nifedipine in plasma at room temperature is presented in Table #4.

2. The firm has reported that the long-term stability of nifedipine in plasma stored at -25^{0}C was 14 weeks, which was much longer period than the actual sample storage duration. With 30 mg tablets, the studies #1866-1, #1867-1 and #1868-1, had the actual storage duration times, 58, 50 & 48 days, respectively. Similarly, the longest duration time for any study with 60 mg tablets was 42 days.

3. The firm has provided the first and last dates of QC sample preparation for all studies with 30 mg and 60 mg tablets. In no case, the actual QC sample duration was more than 43 days. The firm has also reported the first and last days of sample analysis of all studies, and the longest period of analysis of all samples in a study was 33 days.

4. The firm agreed that the model recommended by the Agency for the single dose (with 30 mg tablets) fasting study data analysis is the correct one for analyzing pharmacokinetic parameters derived from a study where the volunteers are dosed in groups. When the recommended model was used in statistically analyzing the data, bioequivalence between the test and reference drug products was maintained. A summary of the statistical analyses on the pharmacokinetic parameters of interest in bioequivalence determination is presented below :

PK Parameter (using geometric means)	Original ANOVA Model		New (Correct) ANOVA Model	
	90% C.I.	Intra-subj. CV (%)	90% C.I.	Intra-subj. CV (%)

AUC(0-t)	86; 93	13.58	85; 98	13.76
AUC(0-inf)	86; 95	13.96	84; 98	14.22
Cmax	82; 94	24.35	88; 112	23.86

It should be mentioned here, the statistical analysis indicated that there is a significant group effect which could be attributed to the sampling variation of the group means, especially for the second group that has only 8 subjects. With the overall sample size of 63 subjects, the statistical power for detecting the group difference is high, or a small sampling variation can be detected to be significantly different from zero. The firm has further indicated that, this significant group effect did not have major influence on the outcome of the bioequivalence evaluation as a crossover design was used. In fact, inclusion of the group factor into the ANOVA model improved the goodness of fit of the model, as the R^2 was improved for both Cmax and AUC compared with the ANOVA ignoring the group factor.

5. The firm provided the bulk lot sizes (more than ——— , of both strengths, 30 mg and 60 mg Nifedipine Extended-release Tablets.

Comments:

1. The firm's responses to all comments made by the Agency on the test product, Nifedipine Extended-release Tablets, 30 mg and 60 mg, are acceptable.

2. The firm had conducted acceptable <u>in vitro</u> dissolution testing on its Nifedipine ER 30 mg tablets (submission dated 12/09/97) and proposed the following tentative specifications:

Time (hour)	Specifications
1	———
4	———
12	NLT ———

The firm had also conducted acceptable <u>in vitro</u> dissolution testing on its Nifedipine ER 60 mg tablets (submission dated 4/15/98) and proposed the following tentative specifications:

Time (hour)	Specifications
1	———
4	———
12	NLT ———

Based on these data, the Division of Bioequivalence proposes the following tentative specifications for both strengths of the test product:

Time (hour)	Specifications
1	[redacted]
4	[redacted]
12	NLT [redacted]

Recommendation:

1. The single dose bioequivalence studies (under fasting and fed conditions) and the multiple dose study (under fasting condition) conducted on the test product, Biovail's Nifedipine ER 30 mg and 60 mg Tablets, comparing them with the reference products, Adalat^{R} CC, 30 mg and 60 mg tablets, respectively, of Bayer Corporation have been found acceptable by the Division of Bioequivalence. These studies demonstrate that Nifedipine ER 30 mg and 60 mg Tablets of Biovail Laboratories, Inc. are bioequivalent to the reference products, Adalat^{R} CC, 30 mg and 60 mg tablets, respectively, manufactured by Bayer Corporation.

2. The in vitro dissolution testing conducted by Biovail Laboratories, Inc. on its Nifedipine ER 30 mg tablets (lot #97E003 & lot #97D042) and 60 mg tablets (lot #97E004 & lot #97D052), comparing them to the reference products, Adalat^{R} CC, 30 mg and 60 mg tablets, respectively, of Bayer Corporation is acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of 0.5% sodium lauryl sulphate in simulated gastric fluid (SFG), pH 1.2 using USP XXIII apparatus II (paddle) at 100 rpm. The test product of both strengths (30 mg and 60 mg) should meet the following tentative specifications proposed by the Agency:

Time (hour)	Specifications
1	[redacted]
4	[redacted]
12	NLT [redacted]

[redacted]

Sikta Pradhan, Ph. D.
Division of Bioequivalence
Review Branch I

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-269 APPLICANT: Biovail Lab., Inc.

DRUG PRODUCT:Nifedipine ER Tablets, 30 mg and 60 mg

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

The following dissolution testing will need to be incorporated into your stability and quality control programs:

> The dissolution testing should be conducted in 900 mL of 0.5% sodium lauryl sulphate in simulated gastric fluid (SFG), pH 1.2 using USP XXIII apparatus II (paddle) at 100 rpm. The test product of both strengths (30 mg and 60 mg) should meet the following tentative specifications proposed by the Agency:

Time (hour)	Specifications
1	—
4	—
12	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,

/S/

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

Nifedipine ER Tablets, 30 mg
ANDA # 75-269
Reviewer: Sikta Pradhan
XWP# 75269S3D.D97

Biovail Laboratories, Inc.
Mississauga, Ontario, Canada
Submission Date:
December 9,1997

REVIEW OF THREE BIOEQUIVALENCE STUDIES (SINGLE DOSE FASTING, SINGLE DOSE FED, MULTIPLE DOSE FASTING)

Nifedipine, a calcium-channel blocking agent with potent vasodilating properties, is used in the treatment of vasospastic angina, chronic stable angina and hypertension. Immediate-release formulations of nifedipine are rapidly and fully absorbed after its oral administration. Bioavailability is proportional to dose from 10 to 30 mg. It has a half-life in plasma of approximately 2 hours. With the extended release formulation, nifedipine levels plateau at approximately 6 hours post-dose. Pharmacokinetics of nifedipine in an extended release formulation are linear over the dose range 30 to 180 mg. The drug has high affinity for binding to plasma proteins. Nifedipine is dehydrogenated in the liver producing two pharmacologically inactive metabolites. Approximately 80% of parent drug and metabolites are eliminated via the kidneys. Nifedipine is marketed as liquid-filled (soft gelatin) 10 mg and 20 mg capsules (Procardia^{R}, Pfizer), and as 30, 60 and 90 mg extended release tablets. The therapy for either hypertension or angina should be initiated with 30 or 60 mg once daily.

Biovail Laboratories, Inc. has submitted the results of three bioequivalence studies comparing its test product Nifedipine ER Tablets, 30 mg, with the reference product Adalat^{R} CC, 30 mg Tablets (Bayer Corp.): 1) single dose fasting study; 2) single dose food study; 3) multiple dose steady-state study.

I. SINGLE DOSE FASTING STUDY

Objective:

The objective of the study is to compare the relative bioavailability of Nifedipine ER Tablets, 30 mg, manufactured by Biovail Lab. Inc. with that of Adalat^{R} CC, 30 mg Tablets,

manufactured by Bayer Corp., in healthy, male volunteers dosed under fasting condition.

Study Sites

Clinical Site: Biovail Corporation International, Contract Research Division, Toronto, Ontario, Canada.
Principal Investigator & Medical Director: Paul T. Tam, M.D., F.R.C.P., F.A.C.P.

Clinical Director: Lana Knape, B.Bc., R.N.
Study Director and
Director of Biopharmaceutics: Bhaswat Chakraborty, Ph. D.
Director of Bioanalytical Lab.: David MacDonald, Ph.D.

Study Dates of Group I: Period 1 dosing, 6/14/97;
Period 2 dosing, 6/21/97
Study Dates of Group II: Period 1 dosing, 6/21/97;
Period 2 dosing, 6/28/97
Analytical Site: Biovail Corporation International, Contract Research Division, Toronto, Ontario, Canada.

Date of Sample Analysis: All samples of both Groups (I&II) were analyzed at the same time (July9, 1997 - August 11, 1997) under the same experimental conditions.

Study Design: Protocol #1866-1 (B97-310PK-NIFB32)

This was a randomized, single dose, two-way crossover design comparing the test product Nifedipine ER Tablets, 30 mg, with the reference product Adalat^{R} CC, 30 mg Tablets, in sixty-three (63) normal, healthy, non-smoking male volunteers under fasting conditions with a one week washout between treatments.

The study was conducted in two groups, from **June 13, 1997 to June 23, 1997 for Subjects #01-#59 (Group I)**, and from **June 20, 1997 to June 30, 1997 for Subjects #60-#68.** Plasma was analyzed for the parent drug nifedipine.

Subject Selection

Sixty-six (66) subjects (out of 68, Subjects #46 & #57 could not meet the inclusion criteria) were selected for this study after

signing informed consent according to the following criteria:

1. Inclusion Criteria:

- Non-smoking males, 18-45 years old
- Within 10% of ideal body weight (Metropolitan Life Insurance Bulletin, 1983)
- Good health as determined by interview, physical examination hematology, serum chemistry, ECG, and urinalysis
- Laboratory values not to exceed 10% of normal limits (with the exception of parameters that are not clinically relevant)
-Normal findings in the physical examination, vital signs and ECG (blood pressure $\geq$ 100/60 mm/Hg, pulse rate $\geq$ 50 beats per minute)

2. Exclusion Criteria:

- Known history of hypersensitivity to nifedipine (Adalat^{R} CC), or related drugs.
- History or presence of alcohol or drug of abuse, use of psychotropic agents, cardiac arrhythmias, adverse reactions or allergy to any methylxanthine
- Presence of significant systemic or organ disease, or acute illness or surgery in the four weeks prior to study start
- Exposure to an investigational drug in the four weeks prior to study start
- Use of tobacco products
- Use of any medication within two weeks of study start
- BP < 90/60 after a five minute rest
- Ingestion of alcohol or xanthine-containing beverages within 48 hours of study start

Treatments:

A. 30 mg x 1 Nifedipine ER tablet (Biovail), Lot #97E003, Lot size not provided, Potency 100.0%

B. 30 mg x 1 Adalat^{R} CC tablet (Bayer Corp.), Lot #6LCT, Potency 100.8%, Exp. Date: December, 1998.

Component/Composition of the test product is attached (Attachment #1).

Dose Administration:

A single dose of 30 mg nifedipine ER tablet (test or reference) was administered with 240 mL of water.

Vital signs (resting blood pressure and pulse rate) were recorded at 0.0 (pre-dose), 2.0, 4.0, 8.0, 16.0, and 24.0 hours post-dose. Blood pressure and pulse rate monitoring continued at hourly intervals until measurements returned to within normal limits. In addition, 12-lead ECG monitoring was conducted during each study phase at 0.0 (pre-drug), 2.0, 4.0, 8.0, 16.0 and 24.0 hour post-drug.

Drug Washout Period: 7 days

Meal and Food Restrictions:

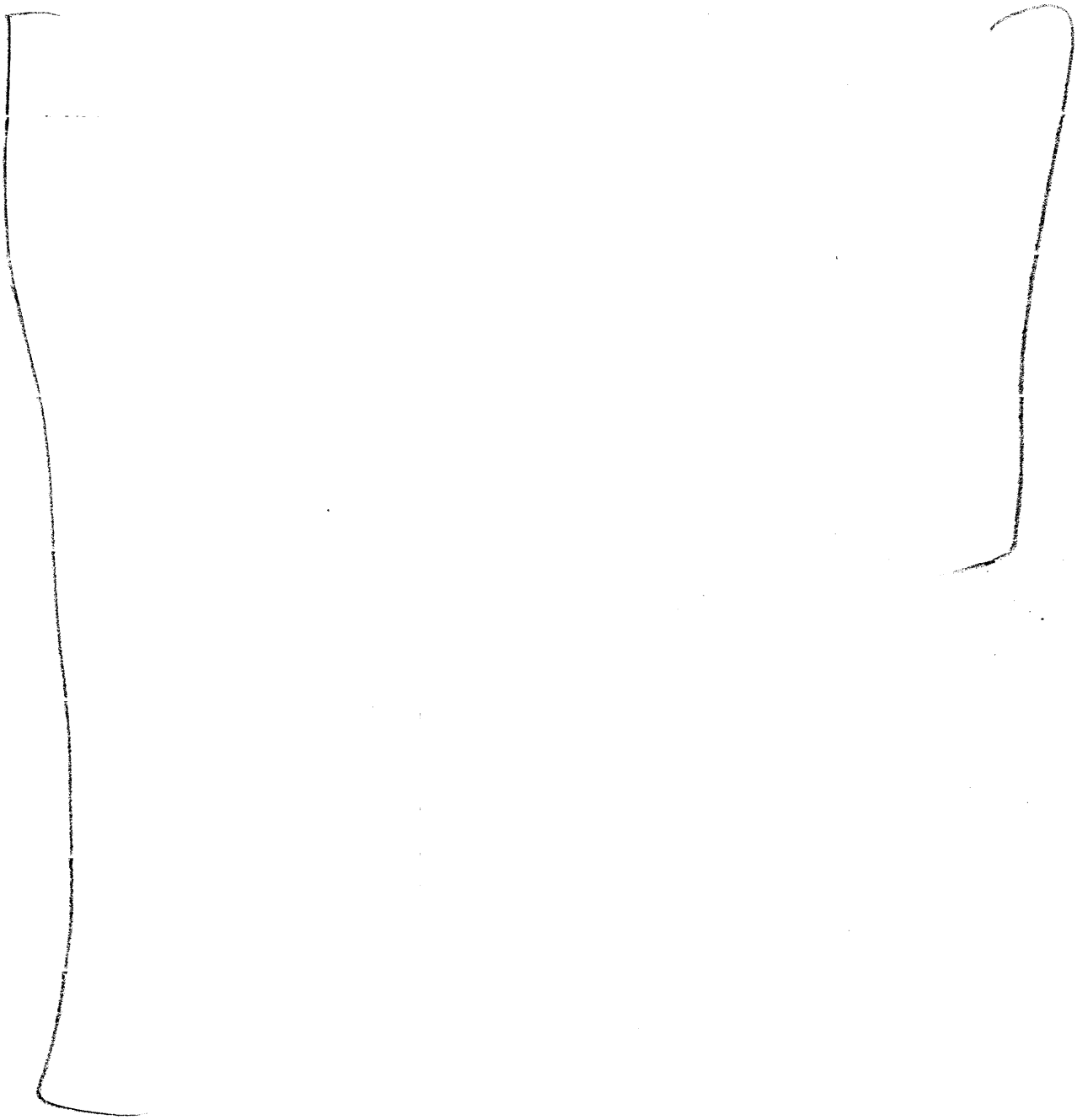
All volunteers fasted for 10 hours prior to and 4 hours after drug administration. No fluids were allowed from 1 hour before dosing until 1 hour after each dose. Water was given ad lib after 1 hour of dosing. Standard meal was served after 4 hours of dosing. No caffeine-containing food or beverages were served during the first 24 hours. All subjects were confined from 10 hours pre-dose to 48 hours post-dose.

Blood Samples Collection

[redacted]

Assay Methodology

[redacted]



Stability: Data not available

Results:

Sixty-eight (68) subjects were selected for the study and 63 subjects completed the study. Subjects #46 and #57 were dismissed prior to Phase 1. Subject #17 withdrew prior to Phase2 dosing for

personal reasons. Subject #35 withdrew during the washout period as he was experiencing headache and cold symptoms. Subject #67 withdrew following Phase 1 dosing due to an adverse event. The samples of subject #67 were assayed for safety information only. Ninety-one (91) adverse events, including mild episodes of sinus bradycardia, headache, nausea, lightheadedness, vomiting and 1^0AV block, were experienced by forty-four subjects during this study. However, none of these effects were severe, and no medication was required for any clinical complaint. There were twenty-six (26) protocol deviations (minor) reported during the study. The actual blood collection times were used for the calculations of the values for the pharmacokinetic parameters.

All sixty-three (63) volunteers' plasma samples were analyzed. The mean plasma nifedipine levels for the test and the reference drugs are presented in Table 1 (and in Figure 1 attached).

Table 1

Mean Plasma Nifedipine Levels (ng/mL)

Time (hour)	TEST (A) (Biovail ER) Lot #97E003 Mean ± SD	Reference (B) (Adalat CC) Lot #6LCT Mean ± SD
Pre-dose	0	0
0.17	1.22 ± 1.41	3.80 ± 3.31
0.50	8.81 ± 6.50	16.38 ± 10.23
1.00	19.70 ± 12.81	27.02 ± 15.19
1.50	27.33 15.65	33.46 ± 15.77
2.00	33.97 ± 21.17	37.50 ± 18.79
2.50	36.76 ± 21.63	40.24 ± 22.34
3.00	38.76 ± 27.90	42.18 ± 27.84
5.00	40.94 ± 31.03	49.89 ± 47.65
6.00	31.35 ± 19.15	38.82 ± 33 75
8.00	21.76 ± 14.12	26.86 ± 21.38
10.00	19.25 ± 14.52	24.19 ± 15.62
12.00	19.00 ± 13.17	22.02 ± 13.59
14.00	17.86 ± 13.91	16.87 ± 9.97
16.00	15.93 ± 13.20	14.40 ± 9.04
20.00	9.23 ± 8.04	7.95 ± 5.53
24.00	6.46 ± 6.23	5.73 ± 4.65
30.00	3.61 ± 3.60	3.17 ± 2.91
36.00	1.84 ± 2.01	1.62 ± 1.67
48.00	0.35 ± 0.72	0.17 ± 0.48

The mean pharmacokinetic parameters derived from the plasma Nifedipine levels are presented in Table 2.

Table 2

Mean Pharmacokinetic Parameters for Plasma Nifedipine

Parameters	Test(A)	Ref.(B)	A/B	90% C.I.**
AUC_{0-T}(ng.hr/mL)	507.80 (64)*	551.68 (56)	0.98	
$LnAUC_{0-T}$ Geometric Mean	6.0671 **(LSM) 431.43	6.1812 (LSM) 483.57	0.89	 86; 93
AUC_{0-inf} (ng.hr/mL)	543.84 (63)	611.98 (50)	1.03	
$LnAUC_{0-inf}$ Geometric Mean	6.1323 **(LSM) 460.49	6.2354 (LSM) 510.50	0.90	 86; 95
C_{MAX} (ng/mL)	50.24 (64)	58.96 (51)	1.01	
LnC_{MAX} Geometric Mean	3.7591 **(LSM) 42.91	3.8902 (LSM) 48.92	0.88	 82; 94
T_{max} (hour)	4.03 (45)	4.60 (55)	1.08	
t1/2 (hour)	6.40 (31)	6.27 (47)	1.15	
KE (1/hour)	0.118 (30)	0.124 (31)	0.93	

Number of Subjects 63

* Coefficient of Variation

** Calculated using LSM (Least Squares Means)

Intra-subject variability for: LnAUC(0-t)=13.58%
LnAUC(0-inf)=13.96%
LnCmax=24.35%

Both test and reference drugs produced peak concentration between 3 to 6 hours after their administration (see Table 1). The differences between the test and reference products in $LnAUC_{0-T}$ and $LnAUC_{0-inf}$ were 11% and 10%, respectively. The difference in the test and reference LnC_{MAX} was 12%. The 90% confidence intervals for $LnAUC_{0-T}$, $LnAUC_{0-inf}$ and LnC_{MAX} of the test product remained within the 80% to 125% limit of the corresponding reference values.

II. LIMITED FOOD STUDY:

Protocol #1867-1(B97-311PK-NIFB32)

The firm has submitted the results of a single oral 30 mg dose three-way crossover post-prandial bioequivalence study conducted on the test (1x30 mg Nifedipine ER tablet of Biovail) and reference (1x30 mg Adalat^{R} CC tablet) products in order to determine the effect of food on the bioavailability of those products.
Twenty-two (22) healthy male volunteers entered into the study after completing a physical examination and laboratory screening tests.

Date of Study: Dosing in Period I: May 21, 1997
Dosing in period II: May 28, 1997
Dosing in Period III: June 4, 1997

Treatments:

A. 1x30 mg tablet of Nifedipine ER (test product) of Biovail, Lot #97E003, immediately after a standard breakfast

B. 1x30 mg tablet Adalat^{R} (Reference product) manufactured by Bayer Corp., Lot #6LCT, immediately after a standard breakfast.

C. 1x30 mg tablet of Nifedipine ER (test product) of Biovail Corp., Lot #97E003, after an overnight fast for at least 10 hours.

Following dosing, subjects remained ambulatory for 4 hours and were not allowed to engaged in any strenuous activity at any time during the study. For safety, sitting blood pressure and heart rate were measured predose and at 2, 4, 8, 16 and 24 hours after dosing.

Drug Washout Period: One week

Meal and Food Restrictions: Water was given ad lib until one hour pre-drug and after one hour post-drug. A standard meal was served after 4.5 hours post-dose. No alcohol, caffeine and xanthine-containing beverages was served during the study. Subjects remained at the clinic through the 48 hour post-drug blood draw.

Samples were assayed at Biovail Corporation International, Contract Research Division, Toronto, Ontario, Canada.

Date of First Sample Analysis: June 24, 1997
Date of Last Sample Analysis: July 10, 1997
Duration of Sample Storage: Seven weeks (May 21 - July 10)

Assay Methodology:

Results:

Twenty-two (22) healthy male volunteers entered into the study. One volunteer (subject #14) withdrew during Phase I, on Day 2, due to personal reasons. Twenty-one (21) male volunteers were able to complete the study. There were five (5) protocol deviations reported in the study (see attached table). Fifty (50) adverse events were experienced by the subjects, which included nineteen (19) mild episodes of headaches, one (1) moderate episode of a headache, six (6) mild episodes of sinus tachycardia, nineteen (19) mild episodes of sinus bradycardia, one (1) mild episode of light-headedness, two (2) mild episodes of 1^0 AV block and two (2) mild episodes of borderline 1^0 AV block. There were no serious or life-threatening medical events reported for this study. Mean plasma nifedipine levels are presented in Tables 3 (and in Figure 2 attached) below. The pharmacokinetic parameters derived from plasma nifedipine levels are presented in Table 4.

Table 3
Mean plasma nifedipine levels (ng/mL)

Time (hour)	**Test (A)** 1x30 mg Tab. Lot#97E003 **Fed**	**Ref.(B)** 1x30 mg Tab Lot#6LCT **Fed**	**Test (C)** 1x30 mg Tab. Lot#97E003 **Fasted**
0.0	0.0	0.0	0.0
0.5	0.89 (326)*	2.91 (306)	1.870 (112)
1.0	7.37 (180)	10.58 (194)	10.02 (65)
1.5	25.75 (100)	22.70 (157)	19.98 (56)
2.0	46.67 (94)	32.00 (101)	27.23 (53)
2.5	59.76 (78)	42.38 (77)	32.66 (52)
3.0	75.33 (63)	57.69 (73)	32.05 (50)
4.0	82.12 (57)	62.87 (59)	32.32 (59)
5.0	60.66 (44)	71.85 (57)	32.34 (63)
6.0	43.33 (16)	50.72 (66)	27.11 (65)
8.0	35.10 (54)	41.10 (77)	19.73 (64)
10.0	22.47 (61)	36.51 (98)	18.96 (59)
12.0	16.41 (64)	24.31 (62)	18.00 (70)
14.0	10.71 (68)	16.09 (58)	17.77 (67)
16.0	7.66 (73)	11.23 (62)	17.46 (63)
20.0	3.97 (84)	5.50 (66)	9.51 (76)
24.0	2.16 (96)	3.09 (63)	7.09 (75)
30.0	1.12 (145)	1.39 (86)	4.08 (93)
36.0	0.40 (233)	0.63 (101)	1.88 (129)
48.0	0.06 (323)	0.05 (316)	0.35 (355)

* Coefficient of Variation
Number of Subjects = 21

APPEARS THIS WAY
ON ORIGINAL

Table 4

Mean Pharmacokinetic Parameters of Plasma Nifedipine

(Number of Subjects = 21)

Parameters (using arithmetic means)	Test(A) Fed	Ref.(B) Fed	Test(C) Fasted
AUC_{0-T} (ng.hrs/mL)	617.90(46)*	627.05(47)	486.94(51)
AUC_{0-inf} (ng.hrs/mL)	622.93(45)	633.35(47)	501.56(51)
C_{MAX} (ng/mL)	106.65(41)	94.18(49)	40.76(49)
T_{max} (hour)	4.07(25)	4.33(40)	4.19(62)
t1/2 (hour)	4.57(29)	5.25(31)	4.94(24)
KE (1/hour)	0.167(35)	0.145(33)	0.148(23)

Parameters (using LS means)	Test(A) Fed	Ref.(B) Fed	Test(C) Fasted	T/R (A/B)	T/T (A/C)
$LnAUC_{0-T}$	6.3340**	6.3438	6.0674		
Geometric mean	563.41	568.95	431.56	0.99	1.31
$LnAUC_{0-inf}$	6.3440	6.3553	6.0804		
Geometric mean	569.07	575.51	437.20	0.99	1.30
LnC_{MAX}	4.6005	4.4317	3.6193		
Geometric mean	99.53	84.07	37.31	1.18	2.67
T_{max}	4.0132	4.2620	4.1068		
	55.32	70.95	60.75	0.78	0.91

* Coefficient of Variation

** Calculated using LSM (Least Squares Means)

Intra-subject variability for: LnAUC(0-t)=17.73%
LnAUC(0-inf)=18.23%
LnCmax=34.13%

When the test and reference formulations were administered after a meal, the differences between the test and reference products in AUC_{0-T} and AUC_{0-inf} were only 1%, and the difference in C_{MAX} was less than 20%. Results of this fed study indicated that food significantly increases the bioavailability. Both the rate and extent of absorption of a single dose of nifedipine test product were increased by administration with food.

III. MULTIPLE DOSE, STEADY-STATE STUDY

Objective:

The objective of this study was to compare the steady-state bioavailability of the test and reference (Adalat^{R} CC) 30 mg Nifedipine extended-release tablets under fasted conditions.

Study Design: Protocol #1868-1(B97-312PK-NIFB32)

This was a randomized, open-label, multiple-dose, steady-state, two-way crossover design comparing the test product nifedipine 30 mg extended-release tablets with the reference product Adalat^{R} CC 30 mg tablets under fasting conditions in 48 healthy male volunteers (38 completing) with a seven day washout between the last dose of Period 1 and the first dose of Period 2. Plasma was analyzed for the parent drug nifedipine concentrations.

Subject Selection:

Forty-eight (48) subjects were selected for this study after signing informed consent according to the criteria (inclusion and exclusion) mentioned in single dose fasting study before.

Study Sites: Same as mentioned in single dose fasting study

Study Dates: Period I: August 20, 1997 - August 26, 1997
Period II: September 3, 1997 - September 9, 1997

Dates of Sample Collection: 20-26/August/97 for Period I
3-9/September/97 for Period II

Date of First Sample Analysis: Not provided
Dates of Last Sample Analysis: Not provided

Duration of Sample Storage: not provided

Storage Temperature: -25°C

Study Procedures

Treatments:

1) Treatment A (test), nifedipine 30 mg extended-release tablet, 1 X 30 mg, Biovail Lot #97E003

2) Treatment B (reference), Adalat[R] CC 30 mg tablet, 1 X 30 mg, Bayer Corp. Lot #6LCT, Expiry Date: 12/98.

Dose:

Each subject received a total oral dose of 30 mg nifedipine daily for seven days during each period as one (1) nifedipine CC 30 mg tablet (test), or as one (1) Adalat[R] CC 30 mg (reference), each with 240 ml of water. Each formulation was administered starting at 7 AM on Days 1 - 7.

Washout Period: Seven days between the last dose of Period 1 and the first dose of Period 2.

Fasting/Meals:

Subjects were required to fast overnight prior to, and for 4.5 hours after, each morning dose. Water was not be permitted for 1 hour before and 1 hour after each dose, but was allowed at all other times. Standard meals were provided at 4.5 and 9.5 hours, and snacks were provided at 13.5 hours after dose on each day. All meals and beverages were xanthine and caffeine-free and were identical for both periods.

Blood Sampling:

[redacted]

Vital signs (resting blood pressure and pulse rate) were recorded at 0.0 (pre-dose), 2.0, 4.0, 8.0, 16.0, and 24.0 hours post-dose.

Blood pressure and pulse rate monitoring continued at hourly intervals until measurements returned to within normal limits. ECG monitoring was conducted during each study phase at 0.0 (pre-drug), 2.0, 4.0, 8.0, 16.0 and 24.0 hour post-drug.

Assay Methodology:

[redacted]

Results:

Forty-eight (48) subject entered into the study. Thirty-eight (38) subjects completed the study and the statistical and the pharmacokinetic analyses were performed using data from 38 subjects. Two subjects (#14 & #1) withdrew for personal reasons prior to drug administration on Day 1 and Day 2. Six (6) subjects (#13, #18, #24, #37, #38, and #43) withdrew due to adverse events

in Period I study. Subject #25 and #33 were both dismissed prior to drug administration on Day 4 of Period I due to adverse events. Subject #67 withdrew following Phase 1 dosing due to an adverse event. The samples of subjects #25 and #33 were assayed for safety information only. One hundred and eighty-six (186) adverse events, including mild episodes of sinus bradycardia, headache, nausea, lightheadedness, vomiting and 1^0AV block, were experienced by forty (40) subjects during this study (see Attachment #1). However, none of these effects were severe, and no medication was required for any clinical complaint. Subjects vomitted at the drug elimination phase did not affect the values of the pharmacokinetic parameters. There were seventeen (17) protocol deviations (minor) reported during the study (see Attachment #2). The actual blood collection times were used for the calculations of the values for the pharmacokinetic parameters.

Mean plasma Nifedipine levels of 38 subjects at steady-state are presented in Tables 5 (and in Figure 3 attached). AUC_{0-24} at steady-state was the sum of the linear trapezoidal estimation of the areas from the time of the 7th dose to 24 hours post 7th dose. C_{ss} was AUC_{0-24} divided by the dosing interval (24 hours). C_{max} and T_{max} were determined from the observed plasma concentration-time profile over the sampling interval (Day7). Fluct1 was the percent fluctuation calculated as the difference between Cmax and Cmin divided by Css, Fluct2 was the percent fluctuation calculated as the difference between Cmax and Cmin divided by Cmin. Mean pharmacokinetic parameters of Nifedipine are presented in Tables 6.

Table 5
Mean plasma nifedipine levels (ng/mL)

Time (hour)	TEST (A) (Biovail ER) Lot #97E003	Reference (B) (Adalat CC) Lot #6LCT
Pre-dose on Day 1	0	0
Pre-dose on Day 4	9.31 (55)*	8.55 (73)
Pre-dose on Day 5	8.00 (64)	6.66 (75)
Pre-dose on Day 6	8.62 (63)	6.23 (66)
Pre-dose on Day 7	7.64 (58)	6.15 (59)
and post dosing at:		
0.50	8.99 (60)	11.52 (71)
1.00	16.59 (51)	22.64 (82)
1.50	27.25 (49)	31.58 (67)
2.00	38.86 (48)	39.91 (49)
2.50	43.39 (38)	43.14 (43)
3.00	46.34 (39)	44.66 (43)
3.5	46.04 (40)	43.98 (48)
4.0	47.56 (45)	44.06 (53)
5.0	45.96 (47)	45.21 (54)
6.0	37.85 (40)	36.17 (48)
7.0	30.80 (41)	30.35 (51)
8.0	27.23 (46)	27.82 (55)
10.0	24.41 (52)	26.09 (53)
12.0	25.09 (50)	24.06 (53)
16.0	16.75 (59)	16.51 (64)
20.0	10.39 (66)	10.12 (76)
24.0	8.01 (79)	7.66 (97)

* Coefficient of Variation

Table 6: Mean Pharmacokinetic Parameters for Plasma Nifedipine

Parameters	Test(A)	Ref.(B)	A/B	90% C.I.**
AUC_{0-T}(ng.hr/mL)	555.43 (38)*	552.93 (39)		
$LnAUC_{0-T}$ Geometric Mean	6.2604** 523.43	6.2268** 506.13	1.03	94; 114
C_{MAX} (ng/mL)	58.52 (36)	59.07 (44)		
LnC_{MAX} Geometric Mean	4.0169** 55.53	3.9846** 53.76	1.03	91; 117
Cmin(ng/mL)	8.01 (79)	7.66 (97)		
LnCmin Geometric Mean	1.8196** 6.17	1.7201** 5.58		
T_{max}(hour)	3.57 (33)	3.97 (67)		
Css (ng/mL)	21.81**	21.01**		
Fluct1%	226.32**	229.32		
Fluct2%	800.0**	863.0**		

No. of Subjects: 38; Fluct1=(Cmax-Cmin)/Css; Fluct2=(Cmax-Cmin)/Cmin
* Coefficient of Variation
** Calculated using LSM (Least Squares Means)
Intra-subject variability for: LnAUC(0-t)=25.92%, LnCmax=31.74% and LnCmim=59.93%

The results show that the 90% confidence intervals for $LnAUC_{SS}$ and $LnCmax_{SS}$ are within 80-125% range. The firm has reported that no significant difference in log-transformed trough levels between Days 5, 6, and 7 was detected by ANOVA, indicating that the steady-state was achieved.

In-Vitro Dissolution:

The firm has conducted dissolution testing on the test and reference products using different dissolution medium with different pH, and finally proposed to use 0.5% sodium lauryl sulphate (SLS) in simulated gastric fluid (SGF), pH 1.2 as the dissolution medium. Dissolution data are presented in Table 7.

Table 7. In Vitro Dissolution Testing

Drug: Nifedipine ER Tablets
Dose Strengths: 30 mg
ANDA No.: 75-269
Firm: Biovail Laboratories Incorporated
Submission Date: December 9, 1997

I. Conditions for Dissolution Testing:

USP XXIII Paddle RPM: 100
No. Units Tested: 12
Medium: 0.5% Sodium lauryl sulphate in Simulated Gastric Fluid (SGF), pH 1.2
Volume: 900 mL
Specifications: Proposed by Biovail Corp.
Assay Methodology: ——

II. Results of In Vitro Dissolution Testing:

Sampling Times (Hour)	**Test Product** **Nifedipine ER Tablets** of Biovail Bulk Tablet Lot # 97D042 Strength 30 mg			**Reference Product** Bayer's Adalat CC Lot # 6LCT Strength 30 mg		
	Mean %	Range%	%CV	Mean %	Range%	%CV
1	26	——	10.3	7	——	8.6
2	38	——	8.8	15	——	6.6
4	58	——	6.7	32	——	4.7
6	76	——	5.7	49	——	8.4
8	93	——	6.2	69	——	14.9
10	105	——	2.2	96	——	5.0
12	108	——	1.2	103	——	2.6
14	108	——	1.1	104	——	3.1

Sampling Times (Hour)	**Test Product** **Nifedipine ER Tablets** of Biovail Bio-Batch (Lot # 97E003) Strength 30 mg					
	Mean %	Range%	%CV			
1	25	——				
2	37	——	Not Provided			
4	57	——				
6	74	——				
8	91	——				
12	107	——				

Proposed Dissolution Specifications:

Time (hour)	Specifications
1	~
4	~
12	NLT ~

Compositions:

The compositions of the test tablets are presented in Table 8 attached herewith.

Comments:

The single dose bioequivalence studies (under fasting and fed conditions) and the multiple dose study (under fasting condition) conducted on the test product, Biovail's Nifedipine Tablet, 30 mg, and the reference product, Adalat^{R} CC 30 mg tablet of Bayer Corporation is incomplete due to the following reasons:

1. The validation of assay method, without any stability data for nifedipine samples, standard and QC samples at -25°C and at room temperature, is incomplete.

2. The stability report should also contain the long-term stability data of samples covering at least a period equivalent to the actual sample storage duration. The study is considered incomplete until the stability data are found acceptable.

3. The firm should provide the first and last dates of sample analysis, and dates of nifedipine QC samples preparation.

4. In the single dose fasting study, subjects were enrolled on two separate occasions
   (Study Dates of Group I: Period 1 dosing, 6/14/97;
   Period 2 dosing, 6/21/97; and
   Study Dates of Group II: Period 1 dosing, 6/21/97;
   Period 2 dosing, 6/28/97), and therefore, an additional ANOVA model should be used to

determine if the makeup group was significantly different from the first group with respect to the pharmacokinetic parameters of nifedipine. This model should include, group, sequence, sequence*group, subject(sequence*group), period(group), treatment, treatment*group.

5. Lot size of the test product used in the bioequivalence study should be provided.

6. The dissolution testing is acceptable. However, the firm should be advised to conduct in vitro comparative dissolution testing on the test and reference products of same lots used in the in vivo bioequivalence study in the future. The firm's proposed dissolution specifications are acceptable.

Recommendation:

The single dose bioequivalence studies (under fasting and fed conditions) and the multiple dose study (under fasting condition) conducted on the test product, Biovail's Nifedipine ER 30 mg Tablet and the reference product, Adalat^{R} CC 30 mg tablet of Bayer Corporation have been found incomplete by the Division of Bioequivalence due to the reasons cited in comments #1-5.

/S/

Sikta Pradhan, Ph. D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG
FT INITIALED YCHUANG ---------- /S/ ---------- 4/28/98

Concur: /S/ ---------- Date: 4/29/98

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

cc: AND # 75-269 (original, duplicate), HAD-652 (Huang, Pradhan), HAD-650 (Director),Drug File, Division File.

SP/4-1-98//X:\wpfile\Pradhan\75269S3D.D97

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-269 APPLICANT: Biovail Lab., Inc.

DRUG PRODUCT:Nifedipine ER Tablet

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. The validation of assay method, without any stability data for nifedipine samples, standard and QC samples at -25°C and at room temperature, is incomplete.

2. The stability report should also contain the long-term stability data of samples covering at least a period equivalent to the actual sample storage duration. The study is considered incomplete until the stability data are found acceptable.

3. You should provide the first and last dates of sample analysis, and dates of nifedipine QC samples preparation.

4. In the single dose fasting study, subjects were enrolled on two separate occasions
(Study Dates of Group I: Period 1 dosing, 6/14/97;
Period 2 dosing, 6/21/97; and
Study Dates of Group II: Period 1 dosing, 6/21/97;
Period 2 dosing, 6/28/97), and therefore, an additional ANOVA model should be used to determine if the makeup group was significantly different from the first group with respect to the pharmacokinetic parameters of nifedipine. This model should include, group, sequence, sequence*group, subject(sequence*group), period(group), treatment, treatment*group.

5. Lot size of the test product used in the bioequivalence study should be provided.

6. The dissolution testing is acceptable. However, you should be advised to conduct in vitro comparative dissolution testing on the test and reference products of same lots used in the in

vivo bioequivalence study in the future. Your proposed dissolution specifications are acceptable.

Sincerely yours,

/S/

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

CC: ANDA 75-269
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-651/ Bio Secretary - Bio Drug File
HFD-650/ Reviewer

Endorsements: (Final with Dates)
HFD-652/ S. Pradhan /S/
HFD-650/ Y. Huang /S/ 4/21/98
HFD-617/ L. Sanchez
HFD-650/ D. Conner /S/ 4/29/98

X:\NEW\FIRMSAM\Biovail\LTRS&REV\75269S3D.D97

Printed in final on 04/16/98

BIOEQUIVALENCY - DEFICIENCIES submission date: 12/09/97

1. **FASTING STUDY** (STF) Strengths: 30 mg
Clinical: _____ **Outcome:** IC
Analytical: IC

2. **FOOD STUDY** (STP) Strengths: _____
Clinical: _____ **Outcome:** IC
Analytical: IC

3. **Multiple Dose Study** Strengths:
Clinical: _____ **Outcome:** IC
Analytical: IC

WinBio: Bio-study **IC** - Incomplete
OUTCOME DECISIONS: **IC** - Incomplete

Table - 8

Formulation for Nifedipine Extended-release Tablets, 30 mg
B32 ANDA
Nifedipine Extended-release Tablets, 30 mg

The formulation for Nifedipine Extended-release Tablets, 30 mg is indicated as follows:

	Raw Materials	Extended-release Tablet (mg/tablet)
1.	Nifedipine, USP	30 mg/tablet
2.	Hydroxypropylmethyl Cellulose	
3.	Hydroxyethylcellulose	
4.	Anhydrous Lactose, NF	
5.	Silicon Dioxide, NF	
6.	Microcrystalline Cellulose	
7.	Sodium Lauryl Sulphate , NF	
8.		
9.	Ethylcellulose N-100, NF	
10.	Magnesium Stearate, NF	
11.		
12.	Polyethylene Glycol 600 , NF	
13.	Talc USP	
14.	Titanium Dioxide, USP	
15.	Yellow 10 Ferric Oxide, NF	
16.		
17.		

. Nifedipine Extended-release

contain NMT

Finished Product contains NMT

Finished Product contains NMT

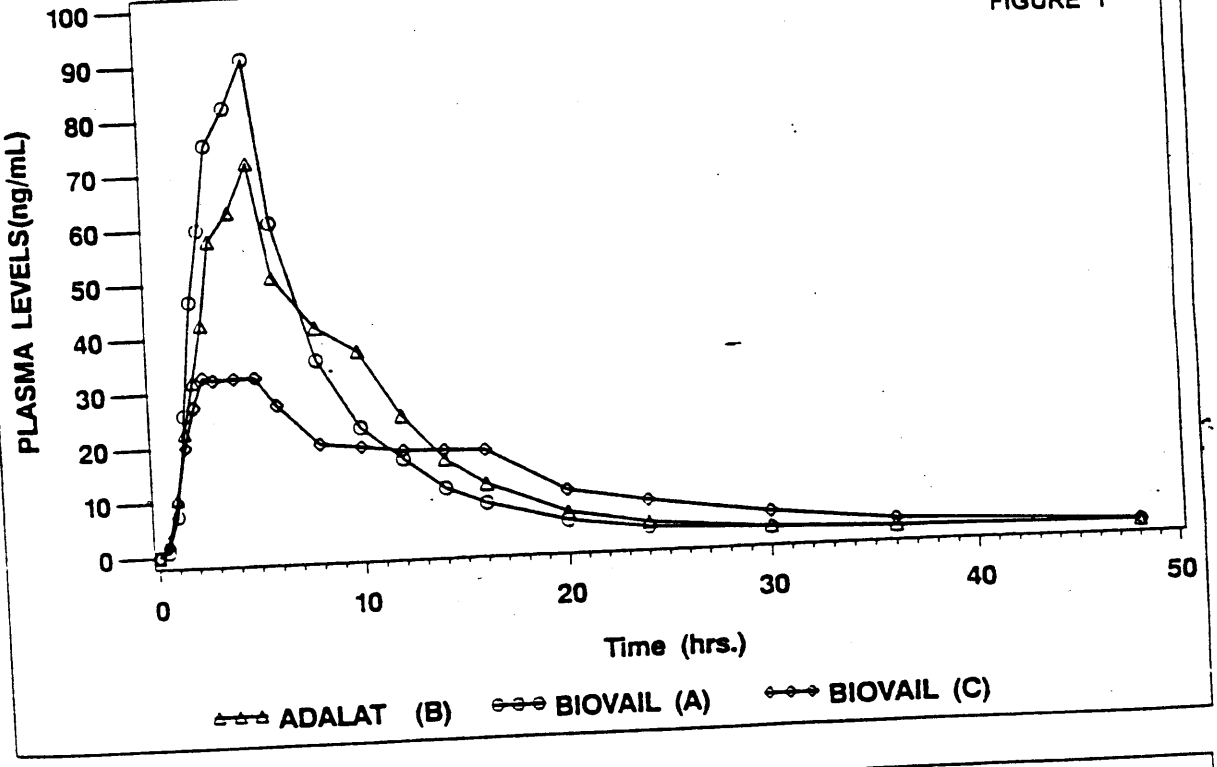
Fed Study

Figure -2

BIOVAIL CORPORATION INTERNATIONAL
STUDY # 1867-1 (B97-311PK-NIFB32)

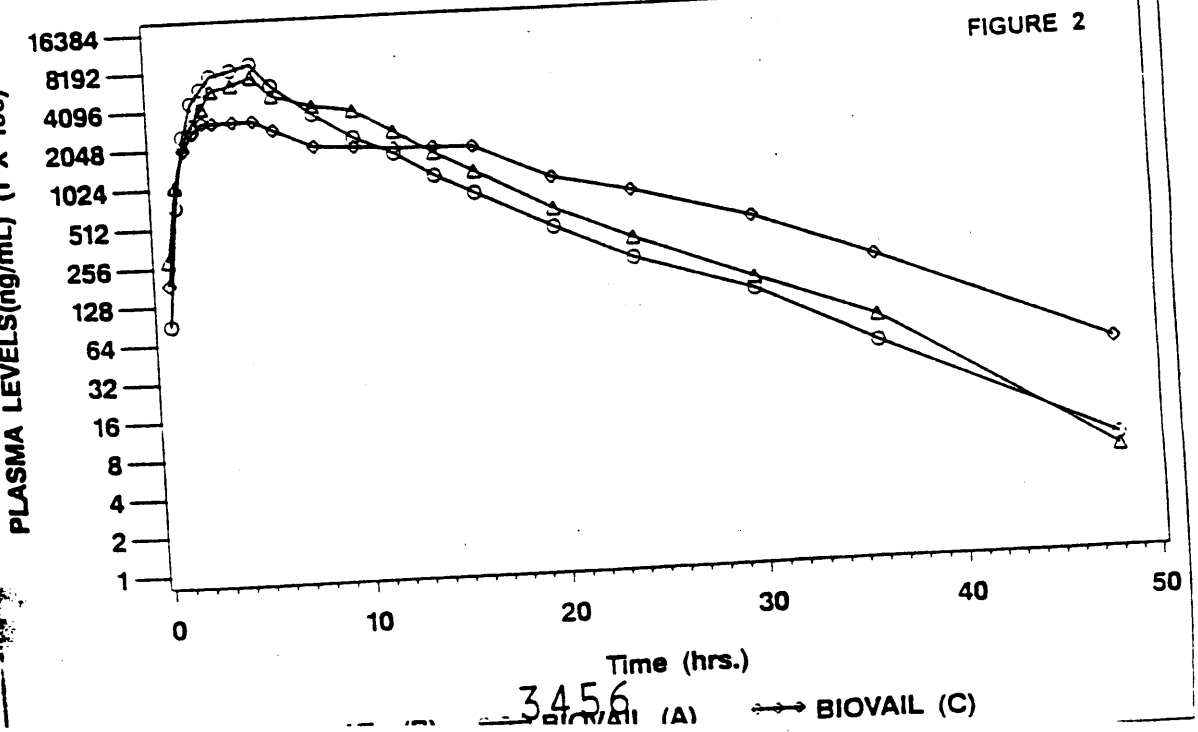
MEAN PLASMA NIFEDIPINE CONCENTRATIONS
(STUDY # 1867 – 1)

FIGURE 1



SEMI LOG MEAN PLASMA NIFEDIPINE CONCENTRATIONS
(STUDY # 1867 – 1)

FIGURE 2



NIFEDIPINE CC 30 mg TABLETS
STUDY # 1867-1 (B97-311PK-NIF32)
PROTOCOL DEVIATIONS

PHASE	*DATE*	*DEVIATION*	*PROTOCOL STATES*
II	May 28, 1997	The 1.5 hour post-drug blood sample of Subject #04 was obtained one minute late due to sampling difficulty.	A 7 mL blood sample will be collected at exactly 1.5 hours post-drug administration.
II	May 28, 1997	The 2.0 hour post-drug blood sample of Subject #10 was obtained one minute late due to sampling difficulty.	A 7 mL blood sample will be collected at exactly 2.0 hours post-drug administration.
II	May 28, 1997	The 1.5 hour post-drug blood sample of Subject #21 was obtained two minutes late due to sampling difficulty.	A 7 mL blood sample will be collected at exactly 1.5 hours post-drug administration.
III	June 4, 1997	The 8.0 hour post-drug blood sample of Subject #01 was obtained three minutes late due to patient unavailability.	A 7 mL blood sample will be collected at exactly 8.0 hours post-drug administration.
III	June 4, 1997	Subject #08 ate only one-half of the bun at dinner.	At 9.5 hours post-drug, standardized xanthine-free meals will be provided to all subjects, with a non-caffeine containing beverage.

NIFEDIPINE CC 30 mg TABLETS
STUDY # 1867-1 (B97-311PK-NIFB32)
ADVERSE EVENTS

SUBJECTS NUMBER	SUBJECTS INITIALS	PHASE	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
01	RK	I	C	Sinus Bradycardia	0732	May 22, 1997	2 hrs., 1 min.	Mild	None	Probably drug related
04	PS	I	A	Sinus Bradycardia	0741	May 22, 1997	1 hr., 56 min.	Mild	None	Probably drug related
05	BW	I	A	Sinus Bradycardia	2346	May 21, 1997	9 hrs., 58 min.	Mild	None	Drug related
				Headache	1115	May 21, 1997	2 hrs., 45 min.	Mild	None	Probably drug related
06	TC	I	B	Sinus Tachycardia	0943	May 21, 1997	7 hrs., 15 min.	Mild	None	Probably drug related
14	JE	I	B	Headache	1230	May 21, 1997	7 hrs., 30 min.	Mild	None	Probably drug related
15	AM	I	A	Sinus Bradycardia	1558	May 21, 1997	1 hr., 5 min.	Mild	None	Probably drug related
				Sinus Bradycardia	0759	May 21, 1997	1 hr., 50 min.	Mild	None	Probably drug related
				1° AV Block	0759	May 21, 1997	1 hr., 50 min.	Mild	None	Probably drug related
16	II	I	C	Sinus Bradycardia	1157	May 21, 1997	1 hr., 32 min.	Mild	None	Probably drug related
17	SMA	I	A	Headache	1330	May 21, 1997	2 hrs.	Mild	None	Probably drug related
18	AD	I	B	Headache	1530	May 21, 1997	1 hr.	Mild	None	Probably drug related
19	ML	I	A	Sinus Tachycardia	1003	May 21, 1997	11 hrs., 28 min.	Mild	None	Probably drug related
				Headache	1400	May 21, 1997	4 hrs.	Mild	Ice pack	Probably drug related
20	RM	I	B	Headache	1545	May 21, 1997	8 hrs., 15 min.	Mild	None	Probably drug related

3498

CODES:

*SEVERITY

MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.

MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.

SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health.

**REGIMEN

A: One (1) nifedipine CC 30 mg tablet (Biovail Corporation International, Research and Development Division; Lot Number: 97E003) five (5) minutes following complete ingestion of a standard high fat breakfast.

B: One (1) Adalat® CC 30 mg tablet (Bayer Corporation; Lot Number: 61CT; Expiry Date: 12/98) five (5) minutes following complete ingestion of a standard high fat breakfast.

C: One (1) nifedipine CC 30 mg tablet (Biovail Corporation International, Research and Development Division; Lot Number: 97E003) following an overnight fast.

NIFEDIPINE CC 30 mg TABLETS
STUDY # 1867-1 (B97-311PK-NIFB32)
ADVERSE EVENTS (Cont'd)

SUBJECTS NUMBER	SUBJECTS INITIALS	PHASE	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
01	RK	II	B	Headache	1030	May 28, 1997	5 hrs.	Moderate	None	Probably drug related
				Sinus Bradycardia	0743	May 29, 1997	1 hr., 48 min.	Mild	None	Probably drug related
04	PS	II	C	Sinus Bradycardia	0747	May 29, 1997	1 hr., 47 min.	Mild	None	Drug related
05	BW	II	B	Sinus Bradycardia	1610	May 28, 1997	1 hr., 15 min.	Mild	None	Drug related
				Sinus Bradycardia	0749	May 29, 1997	1 hr., 47 min.	Mild	None	Drug related
06	TC	II	A	Sinus Tachycardia	1611	May 28, 1997	3 hrs.	Mild	None	Drug related
10	DS	II	A	Headache	1500	May 28, 1997	4 hrs.	Mild	None	Probably drug related
12	JR	II	A	Headache	0840	May 28, 1997	2 hrs., 25 min.	Mild	None	Probably drug related
13	KL	II	C	Sinus Bradycardia	1208	May 28, 1997	1 hr., 25 min.	Mild	None	Drug related
				Headache	1330	May 28, 1997	6 hrs.	Mild	None	Probably drug related
				Sinus Bradycardia	0755	May 29, 1997	1 hr., 44 min.	Mild	None	Drug related
15	AM	II	B	Sinus Bradycardia	1026	May 28, 1997	1 hr., 42 min.	Mild	None	Drug related
				Light-headed	1130	May 28, 1997	1 hr., 10 min.	Mild	Encouraged to stand up slowly	Probably drug related
				Headache	1240	May 28, 1997	10 hrs., 20 min.	Mild	None	Probably drug related
				Sinus Bradycardia	0756	May 29, 1997	1 hr., 46 min.	Mild	None	Drug related
				1° AV Block	0756	May 29, 1997	1 hr., 46 min.	Mild	None	Drug related
16	II	II	A	Sinus Bradycardia	1210	May 28, 1997	1 hr., 25 min.	Mild	None	Drug related
17	SMA	II	B	Headache	1100	May 28, 1997	10 hrs.	Mild	None	Probably drug related
18	AD	II	A	Headache	1130	May 28, 1997	8 hrs.	Mild	None	Probably drug related
19	ML	II	B	Sinus Tachycardia	1031	May 28, 1997	8 hrs., 48 min.	Mild	None	Probably drug related

3469

CODES:

*SEVERITY

MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.

MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.

SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health.

**REGIMEN

A: One (1) nifedipine CC 30 mg tablet (Biovail Corporation International, Research and Development Division; Lot Number: 97E003) five (5) minutes following complete ingestion of a standard high fat breakfast.

B: One (1) Adalat® CC 30 mg tablet (Bayer Corporation; Lot Number: 6LCT; Expiry Date: 12/98) five (5) minutes following complete ingestion of a standard high fat breakfast.

C: One (1) nifedipine CC 30 mg tablet (Biovail Corporation International, Research and Development Division; Lot Number: 97E003) following an overnight fast.

0180

NIFEDIPINE CC 30 mg TABLETS
STUDY # 1867-1 (B97-311PK-NIFB32)
ADVERSE EVENTS (Cont'd)

SUBJECTS NUMBER	SUBJECTS INITIALS	PHASE	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
01	RK	III	A	Headache	0942	June 4, 1997	3 hrs., 52 min.	Mild	None	Probably drug related
04	PS	III	B	Sinus Bradycardia	0741	June 5, 1997	1 hr., 52 min.	Mild	None	Drug related
05	BW	III	C	Sinus Bradycardia	0741	June 5, 1997	1 hr., 54 min.	Mild	None	Drug related
07	CH	III	A	Headache	1020	June 5, 1997	7 hrs., 40 min.	Mild	None	Probably drug related
13	KL	III	A	Sinus Bradycardia	1156	June 4, 1997	1 hr., 49 min.	Mild	None	Drug related
				Headache	1330	June 4,1997	4 hrs., 30 min.	Mild	None	Probably drug related
15	AM	III	C	Borderline I° AV Block	1002	June 4, 1997	3 hrs., 45 min.	Mild	None	Drug related
				Sinus Bradycardia	0751	June 5, 1997	1 hr., 47 min.	Mild	None	Drug related
				Borderline I° AV Block	0751	June 5, 1997	1 hr., 47 min.	Mild	None	Drug related
				Headache	1225	June 4, 1997	5 hrs., 35 min.	Mild	None	Probably drug related
17	SMA	III	C	Headache	1400	June 4, 1997	2 hrs., 45 min.	Mild	None	Probably drug related
19	ML	III	C	Sinus Tachycardia	1007	June 4, 1997	7 hrs., 51 min.	Mild	None	Drug related
				Sinus Tachycardia	0756	June 5, 1997	1 hr., 45 min.	Mild	None	Drug related
				Headache	1400	June 4, 1997	3 hrs., 30 min.	Mild	None	Probably drug related
20	RM	III	A	Headache	1125	June 4, 1997	10 hrs., 50 min.	Mild	None	Probably drug related

3470

CODES:

*SEVERITY

MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.

MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.

SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health.

**REGIMEN

A: One (1) nifedipine CC 30 mg tablet (Biovail Corporation International, Research and Development Division; Lot Number: 97E003) five (5) minutes following complete ingestion of a standard high fat breakfast.

B: One (1) Adalat® CC 30 mg tablet (Bayer Corporation; Lot Number: 6LCT; Expiry Date: 12/98) five (5) minutes following complete ingestion of a standard high fat breakfast.

C: One (1) nifedipine CC 30 mg tablet (Biovail Corporation International, Research and Development Division; Lot Number: 97E003) following an overnight fast.

Multiple dose Study

BIOVAIL CORPORATION INTERNATIONAL
STUDY # 1868-1 (B97-312PK-NIFB32)

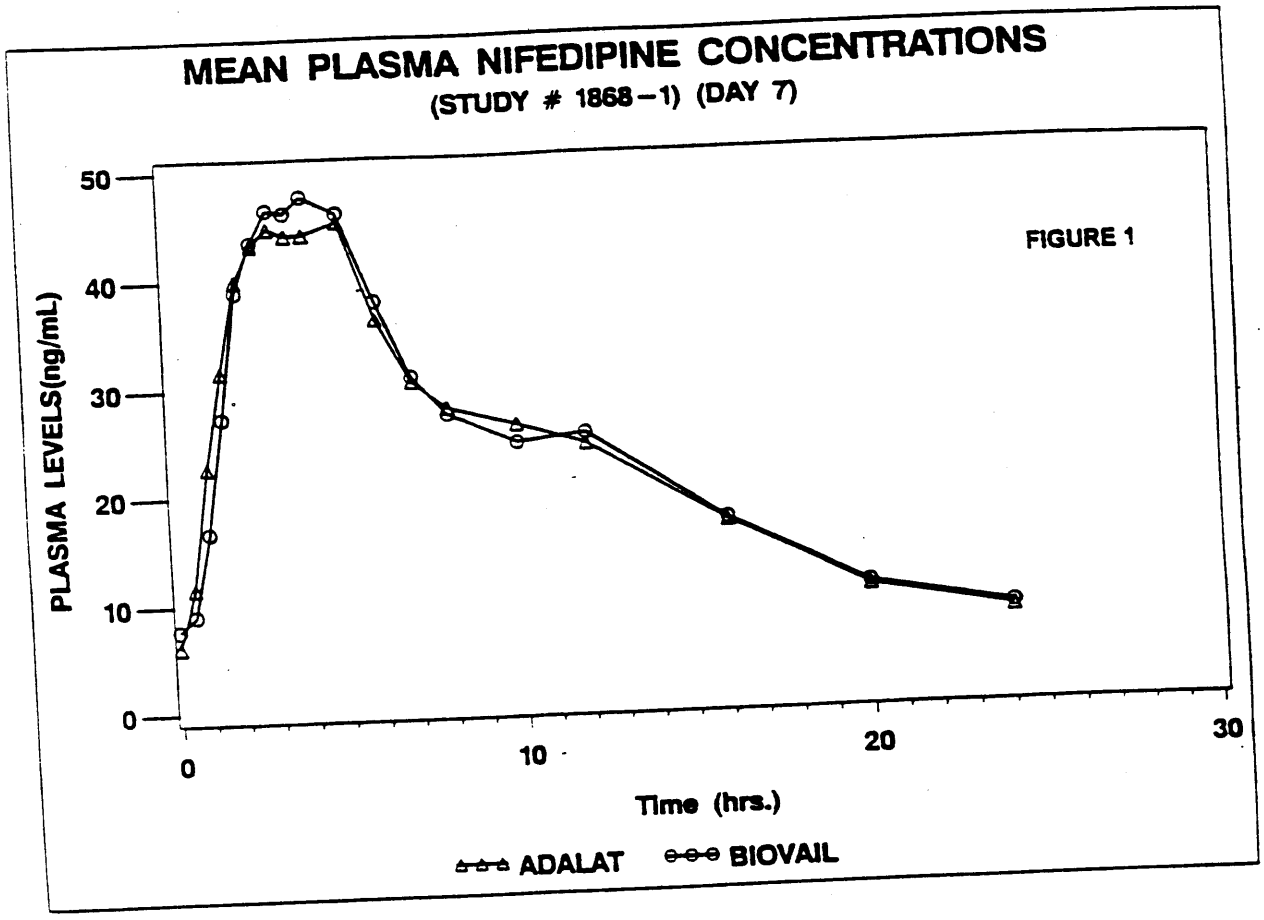


Figure 3

Fasting Study

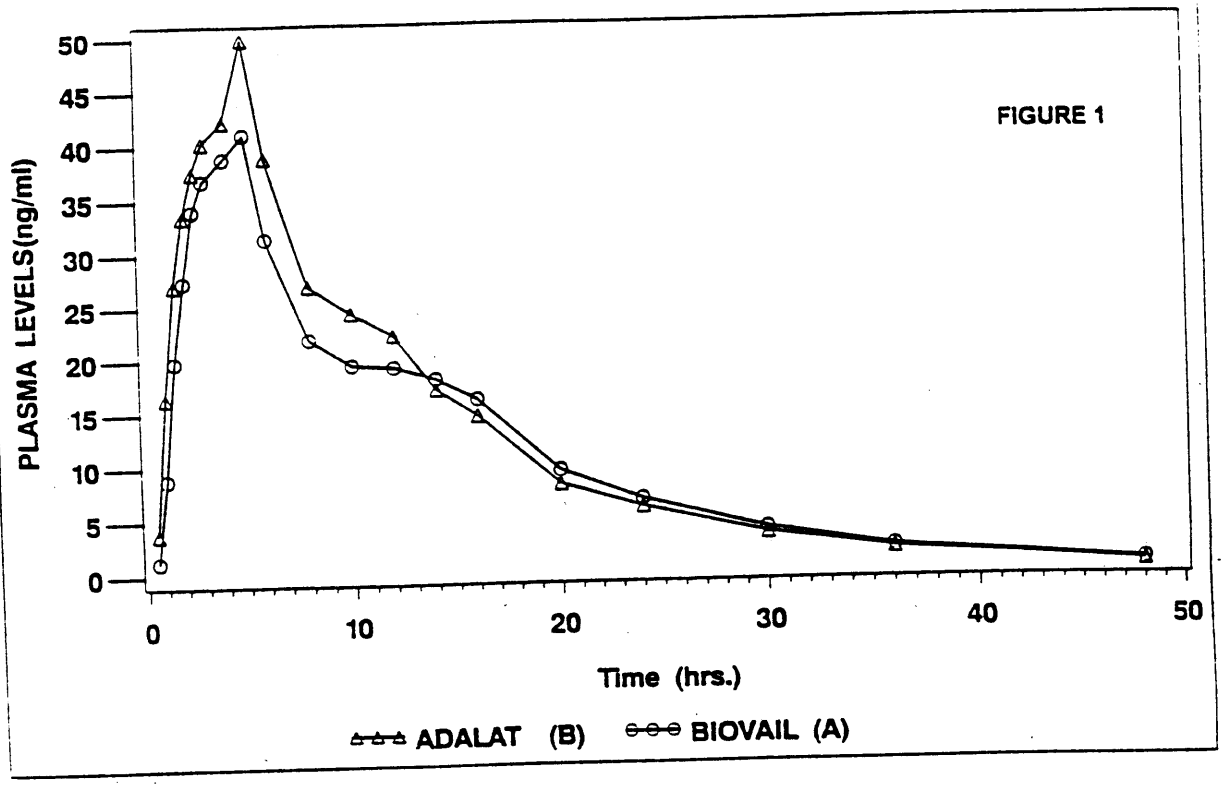
BIOVAIL CORPORATION INTERNATIONAL
STUDY # 1866-1 (B97-310PK-NIFB32)

Figure 1

NIFEDIPINE

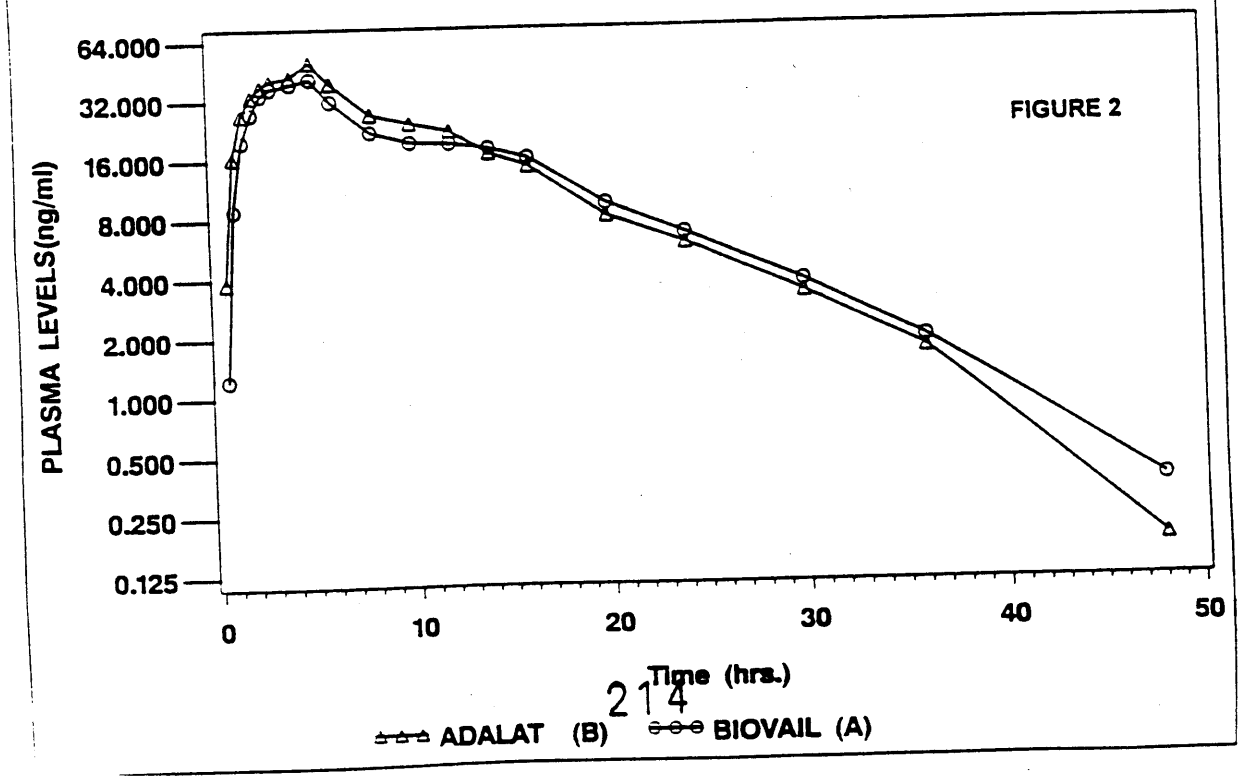
MEAN PLASMA NIFEDIPINE CONCENTRATIONS

STUDY # (1866-1)



SEMI LOG MEAN PLASMA NIFEDIPINE CONCENTRATIONS

STUDY # (1866-1)



Fasting Study.

NIFEDIPINE CC 30 mg TABLETS
STUDY # 1866-1 (B97-310PK-NIFB32)
PROTOCOL DEVIATIONS

PHASE	*DATE*	*DEVIATION*	*PROTOCOL STATES*
I	June 14, 1997	The 0.50 hour blood sample of Subject #41 was obtained 5 minutes late due to sampling difficulty.	A 7 mL blood sample will be collected at exactly 0.50 hour post-drug administration.
I	June 14, 1997	The 1.0 hour blood sample of Subject #41 was obtained 4 minutes late due to sampling difficulty.	A 7 mL blood sample will be collected at exactly 1.0 hour post-drug administration.
I	June 14, 1997	The 2.50 hour blood sample of Subject #41 was obtained 2 minutes late due to sampling difficulty.	A 7 mL blood sample will be collected at exactly 2.50 hours post-drug administration.
I	June 14, 1997	The 3.0 hour blood sample of Subject #41 was obtained 3 minutes late due to sampling difficulty.	A 7 mL blood sample will be collected at exactly 3.0 hours post-drug administration.
I	June 14, 1997	The 1.0 hour blood sample of Subject #22 was obtained 1 minute late due to sampling difficulty.	A 7 mL blood sample will be collected at exactly 1.0 hour post-drug administration.
I	June 14, 1997	The 0.50 hour blood sample of Subject #51 was obtained 1 minute late due to sampling difficulty.	A 7 mL blood sample will be collected at exactly 0.50 hour post-drug administration.
I	June 14, 1997	The 0.50 hour blood sample of Subject #53 was obtained 3 minutes late due to sampling difficulty.	A 7 mL blood sample will be collected at exactly 0.50 hour post-drug administration.
I	June 14, 1997	The 1.50 hour blood sample of Subject #22 was obtained 1 minute late due to sampling difficulty.	A 7 mL blood sample will be collected at exactly 1.50 hours post-drug administration.
I	June 14, 1997	The 2.0 hour blood sample of Subject #22 was obtained 1 minute late due to sampling difficulty.	A 7 mL blood sample will be collected at exactly 2.0 hours post-drug administration.
I	June 14, 1997	The 2.50 hour blood sample of Subject #53 was obtained 2 minutes late due to sampling difficulty.	A 7 mL blood sample will be collected at exactly 2.50 hours post-drug administration.
I	June 14, 1997	The 3.0 hour blood sample of Subject #59 was obtained 1 minute late due to sampling difficulty.	A 7 mL blood sample will be collected at exactly 3.0 hours post-drug administration.
I	June 14, 1997	Subject #10 refused to eat the banana provided at the 4.5 hour post-drug meal (lunch) due to nausea.	At 4.5 hours and 9.5 hours post-drug, standardized xanthine-free meals will be provided to all the subjects, with a non-caffeine containing beverage.

NIFEDIPINE CC 30 mg TABLETS
STUDY # 1866-1 (B97-310PK-NIFB32)
PROTOCOL DEVIATIONS (Cont'd)

PHASE	*DATE*	*DEVIATION*	*PROTOCOL STATES*
I	June 15, 1997	Due to technician's error, the blood pressure of Subject #24 was not monitored until the measurement returned to within ±10% of baseline.	Vital signs (blood pressure and heart rate) will be monitored at hourly intervals, if necessary, until the measurements return within ±10% of baseline.
I	June 15, 1997	Due to technician's error, the pulse of Subject #27 was not monitored until the measurement returned to within ±10% of baseline.	Vital signs (blood pressure and heart rate) will be monitored at hourly intervals, if necessary, until the measurements return within ±10% of baseline.
I	June 15, 1997	Due to technician's error, the blood pressure of Subject #47 was not monitored until the measurement returned to within within ±10% of baseline.	Vital signs (blood pressure and heart rate) will be monitored at hourly intervals, if necessary, until the measurements return within ±10% of baseline.
I	June 15, 1997	Due to technician's error, the pulse of Subject #12 was not monitored until the measurement returned to within ±10% of baseline.	Vital signs (blood pressure and heart rate) will be monitored at hourly intervals, if necessary, until the measurements return within ±10% of baseline.
II (Group I)	June 21, 1997	The 1.50 hour blood sample of Subject #34 was obtained 2 minutes late due to sampling difficulty.	A 7 mL blood sample will be collected at exactly 1.50 hours post-drug administration.
II (Group I)	June 21, 1997	The 2.0 hour blood sample of Subject #28 was obtained 1 minute late due to sampling difficulty.	A 7 mL blood sample will be collected at exactly 2.0 hours post-drug administration.
II (Group I)	June 21, 1997	The 2.50 hour blood sample of Subject #03 was obtained 1 minute late due to sampling difficulty.	A 7 mL blood sample will be collected at exactly 2.50 hours post-drug administration.
II (Group I)	June 21, 1997	The 3.0 hour blood sample of Subject #08 was obtained 3 minutes late due to sampling difficulty.	A 7 mL blood sample will be collected at exactly 3.0 hours post-drug administration.
II (Group I)	June 21, 1997	The 3.0 hour blood sample of Subject #28 was obtained 2 minutes late due to sampling difficulty.	A 7 mL blood sample will be collected at exactly 3.0 hours post-drug administration.
II (Group I)	June 21, 1997	The 3.0 hour blood sample of Subject #37 was obtained 1 minute late due to sampling difficulty.	A 7 mL blood sample will be collected at exactly 3.0 hours post-drug administration.
II (Group I)	June 21, 1997	The 4.0 hour blood sample of Subject #08 was obtained 1 minute late due to sampling difficulty.	A 7 mL blood sample will be collected at exactly 4.0 hours post-drug administration.

NIFEDIPINE CC 30 mg TABLETS
STUDY # 1866-1 (B97-310PK-NIFB32)
PROTOCOL DEVIATIONS (Cont'd)

PHASE	*DATE*	*DEVIATION*	*PROTOCOL STATES*
II (Group I)	June 22, 1997	Due to technician's error, the 38.0 hour post-drug snack was served to Subjects #01 - #59 one hour later, at 39.0 hours post-drug.	A snack will be provided at 38.0 hours post-drug.
I (Group II)	June 22, 1997	Due to technician's error, the 38.0 hour post-drug snack was served to Subjects #60 - #68 one hour later, at 39.0 hours post-drug.	A snack will be provided at 38.0 hours post-drug.
II (Group II)	June 28, 1997	Subject #62 was dosed at 8:45 AM instead of theoretical time of 8:02 AM because there was no packaged drug for this subject.	One (1) 30 mg tablet will be administered during each phase, starting at 7 AM with 240 mL of water, following an overight fast.

NIFEDIPINE CC 30 mg TABLETS
STUDY # 1866-1 (B97-310PK-NIFB32)
ADVERSE EVENTS

SUBJECTS NUMBER	SUBJECTS INITIALS	PHASE	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
04	LMY	I	B	Sinus Bradycardia	0905	June 14, 1997	4 hrs., 1 min.	Mild	None	Drug related
				Headache	1425	June 14, 1997	5 hrs., 45 min.	Mild	None	Probably drug related
06	MR	I	A	Headache	1130	June 14, 1997	15 hrs., 30 min.	Mild	None	Probably drug related
07	JBD	I	A	Headache	1430	June 14, 1997	15 hrs., 28 min.	Mild	None	Probably drug related
08	SK	I	B	Sinus Bradycardia	0909	June 14, 1997	4 hrs.	Mild	None	Drug related
09	WC	I	B	Sinus Bradycardia	1110	June 14, 1997	2 hrs., 2 min.	Mild	None	Drug related
				Sinus Bradycardia	0713	June 15, 1997	2 hrs., 2 min.	Mild	None	Drug related
				Lightheadedness	0830	June 14, 1997	2 hrs., 30 min.	Mild	None	Drug related
10	DH	I	B	Sinus Bradycardia	0712	June 15, 1997	2 hrs., 5 min.	Mild	None	Drug related
11	AHY	I	B	Sinus Bradycardia	1117	June 14, 1997	2 hrs., 1 min.	Mild	None	Drug related
12	ST	I	B	Headache	0900	June 14, 1997	22 hrs.	Mild	None	Probably drug related
				Nausea	1425	June 14, 1997	15 min.	Mild	None	Probably drug related
				Vomiting	1425	June 14, 1997	15 min.	Mild	None	Probably drug related
				Nausea	1235	June 15, 1997	20 min.	Mild	None	Probably drug related
13	WD	I	A	Headache	1415	June 14, 1997	8 hrs., 45 min.	Mild	None	Probably drug related

CODES:

***SEVERITY**

MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.

MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.

SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health.

****REGIMEN**

A: One (1) nifedipine CC 30 mg tablet (Biovail Corporation International, Research and Development Division; Lot Number: 97E003) at 7 AM with 240 mL of water following an overnight fast.

B: One (1) Adalat® CC 30 mg tablet (Bayer Corporation; Lot Number: 6LCT; Expiry Date: 12/98) at 7 AM with 240 mL of water following an overnight fast.

NIFEDIPINE CC 30 mg TABLETS
STUDY # 1866-1 (B97-310PK-NIFB32)
ADVERSE EVENTS (Cont'd)

SUBJECTS NUMBER	SUBJECTS INITIALS	PHASE	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
14	RG	I	B	Sinus Bradycardia	0719	June 15, 1997	2 hrs., 1 min.	Mild	None	Drug related
15	RC	I	A	1°AV Block	0721	June 15, 1997	2 hrs.	Mild	None	Drug related
16	RW	I	B	Sinus Bradycardia	1120	June 14, 1997	2 hrs., 3 min.	Mild	None	Drug related
18	KL	I	B	Headache	1030	June 14, 1997	19 hrs., 20 min.	Mild	None	Probably drug related
21	HS	I	A	Headache	1000	June 14, 1997	4 hrs., 15 min.	Moderate	Placed in bed on right side with an ice pack	Probably drug related
				Headache	2330	June 14, 1997	6 hrs., 30 min.	Mild	None	Probably drug related
24	RF	I	A	Sinus Bradycardia	0728	June 15, 1997	1 hr., 56 min.	Mild	None	Drug related
25	LV	I	B	Headache	1100	June 14, 1997	11 hrs., 15 min.	Moderate	Ice pack placed on forehead	Probably drug related
28	SM	I	B	Headache	1100	June 14, 1997	6 hrs., 30 min.	Mild	None	Probably drug related
				Headache	1730	June 14, 1997	7 hrs.	Moderate	Placed in bed on right side with an ice pack	Probably drug related
30	GC	I	B	Sinus Bradycardia	0931	June 14, 1997	2 hrs., 3 min.	Mild	None	Drug related
32	SA	I	B	Lightheadedness	1042	June 14, 1997	4 hrs., 38 min.	Mild	None	Probably drug related
				Headache	1520	June 14, 1997	8 hrs., 10 min.	Mild	None	Probably drug related
35	SP	I	B	Headache	1315	June 14, 1997	10 hrs., 25 min.	Mild	None	Probably drug related
				Headache	1530	June 15, 1997	15 min.	Mild	None	Probably drug related

CODES:

***SEVERITY**

MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.

MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.

SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health.

****REGIMEN**

A: One (1) nifedipine CC 30 mg tablet (Biovail Corporation International, Research and Development Division; Lot Number: 97E003) at 7 AM with 240 mL of water following an overnight fast.

B: One (1) Adalat® CC 30 mg tablet (Bayer Corporation; Lot Number: 6LCT; Expiry Date: 12/98) at 7 AM with 240 mL of water following an overnight fast.

NIFEDIPINE CC 30 mg TABLETS
STUDY # 1866-1 (B97-310PK-NIFB32)
ADVERSE EVENTS (Cont'd)

SUBJECTS NUMBER	SUBJECTS INITIALS	PHASE	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
38	MGA	I	A	Headache	1100	June 14, 1997	6 hrs.	Mild	None	Probably drug related
				Headache	1700	June 14, 1997	6 hrs., 30 min.	Moderate	Placed in bed on right side with an ice pack	Probably drug related
40	DL	I	B	Sinus Bradycardia	1140	June 14, 1997	2 hrs., 3 min.	Mild	None	Drug related
				Sinus Bradycardia	0744	June 15, 1997	1 hr., 48 min.	Mild	None	Drug related
42	HSL	I	A	Sinus Bradycardia	0747	June 15, 1997	1 hr., 47 min.	Mild	None	Drug related
43	DMN	I	A	Headache	0830	June 14, 1997	4 hrs., 30 min.	Mild	None	Probably drug related
44	WP	I	A	Headache	1400	June 14, 1997	7 hrs.	Mild	None	Probably drug related
45	VH	I	A	Cold Symptoms	1810	June 15, 1997	5 hrs., 20 min.	Mild	None	Probably not drug related
48	KAW	I	B	1°AV Block	0012	June 15, 1997	7 hrs., 40 min.	Mild	None	Drug related
				Headache	1300	June 14, 1997	4 hrs.	Mild	None	Probably drug related
				Headache	1700	June 14, 1997	16 hrs., 20 min.	Moderate	Placed in bed on right side with an ice pack	Probably drug related
				Headache	0920	June 15, 1997	55 min.	Mild	None	Probably drug related
49	SB	I	B	Lightheadedness	1030	June 14, 1997	4 hrs., 15 min.	Mild	None	Probably drug related
51	DM	I	A	Headache	1300	June 15, 1997	4 hrs., 30 min.	Mild	None	Probably drug related
56	SG	I	A	Headache	1050	June 14, 1997	12 hrs., 20 min.	Mild	None	Probably drug related
58	RT	I	B	Headache	1715	June 14, 1997	4 hrs., 45 min.	Mild	None	Probably drug related

CODES:

***SEVERITY**

MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.

MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.

SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health.

****REGIMEN**

A: One (1) nifedipine CC 30 mg tablet (Biovail Corporation International, Research and Development Division; Lot Number: 97E003) at 7 AM with 240 mL of water following an overnight fast.

B: One (1) Adalat® CC 30 mg tablet (Bayer Corporation; Lot Number: 6LCT; Expiry Date: 12/98) at 7 AM with 240 mL of water following an overnight fast.

NIFEDIPINE CC 30 mg TABLETS
STUDY # 1866-1 (B97-310PK-NIFB32)
ADVERSE EVENTS (Cont'd)

SUBJECTS NUMBER	SUBJECTS INITIALS	PHASE	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
59	MB	I	A	Sinus Bradycardia	1001	June 14, 1997	3 hrs., 57 min.	Mild	None	Drug related
				Sinus Bradycardia	0804	June 15, 1997	1 hr., 31 min.	Mild	None	Drug related
04	LMY	II	A	Sinus Bradycardia	1107	June 21, 1997	2 hrs.	Mild	None	Drug related
				Headache	1400	June 21, 1997	20 hrs., 5 min.	Mild	None	Probably drug related
08	SK	II	A	Sinus Bradycardia	1113	June 21, 1997	2 hrs.	Mild	None	Drug related
				Sinus Bradycardia	0711	June 22, 1997	2 hrs., 1 min.	Mild	None	Drug related
09	WC	II	A	Headache	1300	June 21, 1997	9 hrs., 30 min.	Mild	None	Probably drug related
11	AHY	II	A	Sinus Bradycardia	0912	June 21, 1997	2 hrs., 3 min.	Mild	None	Drug related
				Sinus Bradycardia	0716	June 22, 1997	1 hr., 52 min.	Mild	None	Drug related
				Headache	1030	June 21, 1997	20 hrs.	Mild	None	Probably drug related
12	ST	II	A	Nausea	1700	June 21, 1997	5 hrs., 30 min.	Mild	None	Probably not drug related
				Vomiting	2230	June 21, 1997	20 min.	Mild	None	Probably not drug related
				Nausea	0630	June 22, 1997	5 hrs., 15 min	Mild	None	Probably not drug related
13	WD	II	B	Headache	1230	June 21, 1997	18 hrs., 15 min.	Mild	None	Probably drug related
14	RG	II	A	VPBs	1115	June 21, 1997	2 hrs.	Mild	None	Probably not drug related
				Sinus Bradycardia	0720	June 22, 1997	1 hr., 50 min.	Mild	None	Drug related

CODES:

***SEVERITY**

MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.

MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.

SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health.

****REGIMEN**

A: One (1) nifedipine CC 30 mg tablet (Biovail Corporation International, Research and Development Division; Lot Number: 97E003) at 7 AM with 240 mL of water following an overnight fast.

B: One (1) Adalat® CC 30 mg tablet (Bayer Corporation; Lot Number: 6LCT; Expiry Date: 12/98) at 7 AM with 240 mL of water following an overnight fast.

NIFEDIPINE CC 30 mg TABLETS
STUDY # 1866-1 (B97-310PK-NIFB32)
ADVERSE EVENTS (Cont'd)

SUBJECTS NUMBER	SUBJECTS INITIALS	PHASE	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
15	RC	II	B	Headache	1200	June 21, 1997	18 hrs., 30 min.	Mild	None	Probably drug related
				Borderline 1°AV Block	0717	June 22, 1997	1 hr., 55 min.	Mild	None	Drug related
16	RW	II	A	Sinus Bradycardia	1120	June 21, 1997	2 hrs.	Mild	None	Drug related
				Headache	1000	June 21, 1997	20 hrs., 30 min.	Mild	None	Probably drug related
18	KL	II	A	Headache	1100	June 21, 1997	8 hrs.	Mild	None	Probably drug related
21	HS	II	B	Headache	1500	June 21, 1997	7 hrs.	Mild	None	Probably drug related
26	GS	II	A	Headache	2000	June 21, 1997	2 hrs.	Mild	None	Probably drug related
28	SM	II	A	Headache	1400	June 21, 1997	9 hrs., 30 min.	Mild	None	Probably drug related
29	AM	II	A	Headache	1700	June 21, 1997	26 hrs.	Mild	None	Probably drug related
32	SA	II	A	Headache	1400	June 22, 1997	1 hr., 30 min.	Mild	None	Probably drug related
37	TL	II	B	Sinus Bradycardia	0938	June 21, 1997	3 hrs., 48 min.	Mild	None	Drug related
				Sinus Bradycardia	0737	June 22, 1997	1 hr., 41 min.	Mild	None	Drug related
38	MGA	II	B	Headache	1200	June 21, 1997	6 hrs., 30 min.	Mild	None	Probably drug related
40	DL	II	A	Sinus Bradycardia	0942	June 21, 1997	6 hrs.	Mild	None	Drug related
				Sinus Bradycardia	2355	June 21, 1977	11 hrs., 22 min.	Mild	None	Drug related
41	RS	II	B	Headache	1230	June 22, 1997	10 min.	Mild	None	Probably drug related
42	HSL	II	B	Sinus Bradycardia	0743	June 22, 1997	1 hr., 49 min.	Mild	None	Drug related
47	VA	II	A	Sinus Bradycardia	1149	June 21, 1997	2 hrs., 1 min.	Mild	None	Drug related

CODES:

***SEVERITY**

MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.

MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.

SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health.

****REGIMEN**

A: One (1) nifedipine CC 30 mg tablet (Biovail Corporation International, Research and Development Division; Lot Number: 97E003) at 7 AM with 240 mL of water following an overnight fast.

B: One (1) Adalat® CC 30 mg tablet (Bayer Corporation; Lot Number: 6LCT; Expiry Date: 12/98) at 7 AM with 240 mL of water following an overnight fast.

NIFEDIPINE CC 30 mg TABLETS
STUDY # 1866-1 (B97-310PK-NIFB32)
ADVERSE EVENTS (Cont'd)

SUBJECTS NUMBER	SUBJECTS INITIALS	PHASE	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
49	SB	II	A	Headache	0400	June 22, 1997	13 hrs.	Mild	None	Probably drug related
50	AH	II	A	Headache	0900	June 21, 1997	15 hrs.	Mild	None	Probably drug related
52	DD	II	A	Sinus Bradycardia	0953	June 21, 1997	1 hr., 58 min.	Mild	None	Drug related
53	TW	II	B	Headache	0530	June 22, 1997	5 hrs.	Mild	None	Probably drug related
59	MB	II	B	Sinus Bradycardia	1159	June 21, 1997	2 hrs.	Mild	None	Drug related
60	EC	I (Group II)	A	Headache	2150	June 21, 1997	1 hr., 55 min.	Mild	None	Probably drug related
61	AS	I (Group II)	A	Headache	1300	June 22, 1997	5 hrs.	Mild	None	Probably drug related
67	PT	I (Group II)	B	Headache	0930	June 21, 1997	3 hrs.	Moderate	None	Probably drug related
				Nausea	0930	June 21, 1997	3 hrs.	Mild	None	Probably drug related
				Sinus Bradycardia	1206	June 21, 1997	2 hrs., 1 min.	Mild	None	Drug related
63	DME	II (Group II)	B	Sinus Bradycardia	1008	June 28, 1997	1 hr., 58 min.	Mild	None	Drug related

CODES:

***SEVERITY**

MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.

MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.

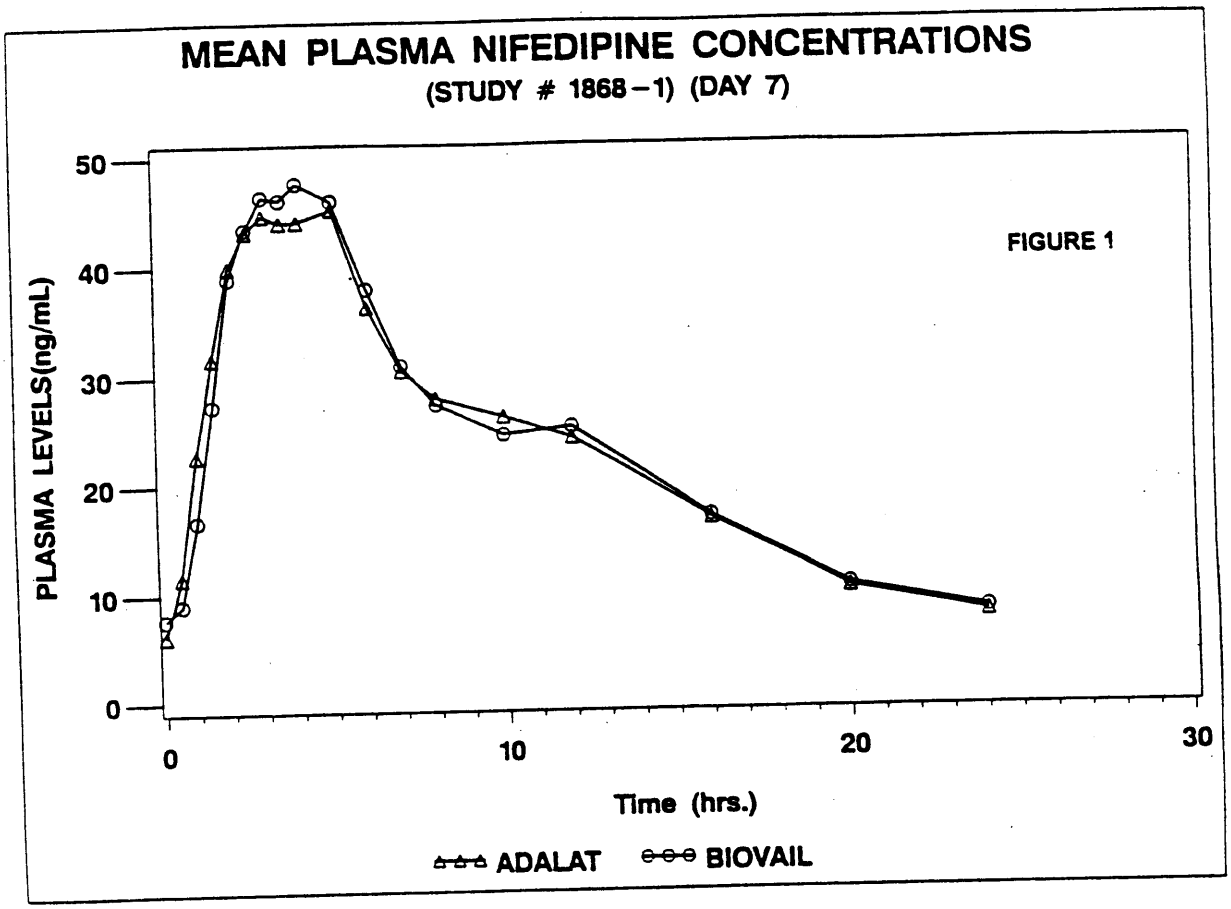
SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health.

****REGIMEN**

A: One (1) nifedipine CC 30 mg tablet (Biovail Corporation International, Research and Development Division; Lot Number: 97E003) at 7 AM with 240 mL of water following an overnight fast.

B: One (1) Adalat® CC 30 mg tablet (Bayer Corporation; Lot Number: 6LCT; Expiry Date: 12/98) at 7 AM with 240 mL of water following an overnight fast.

Mulliple dose Study



NIFEDIPINE CC 30 mg TABLETS
STUDY #1868-1 (B97-312PK-NIFB32)
PROTOCOL DEVIATIONS

PERIOD	DATE	DEVIATION	PROTOCOL STATES
N/A	August 26, 1997	At 9:30 AM, the freezer temperature was recorded as –18.3°C. The temperature incorrectly reflected the room temperature instead of the freezer temperature. The thermometer setting was corrected and within five minutes the temperature read –20.8°C.	[redacted]
I	August 26, 1997	The 0.0 hour (pre-drug) blood draw of Subject #15 was 1 minute late due to sampling difficulty.	A 7 mL blood sample will be collected at exactly 0.0 hour post-drug administration.
I	August 26, 1997	The 2.0 hour blood draw of Subject #15 was 1 minute late due to sampling difficulty.	A 7 mL blood sample will be collected at exactly 2.0 hours post-drug administration.
I	August 26, 1997	The 1.5 hour blood draw of Subject #31 was 1 minute late due to sampling difficulty.	A 7 mL blood sample will be collected at exactly 1.5 hours post-drug administration.
I	August 26, 1997	The 1.5 hour blood draw of Subject #40 was 2 minutes late due to sampling difficulty.	A 7 mL blood sample will be collected at exactly 1.5 hours post-drug administration.
I	August 20, 1997	Subject #37 refused to complete the 4.5 hour post-drug meal. Only 50% of the meal was consumed.	At 4.5 hours post-drug, a standardized xanthine-free meal will be provided to all subjects, with a non-caffeine containing beverage.
I	August 20, 1997	Subject #37 refused to complete the 9.5 hour post-drug meal. Less than 75% of the meal was consumed.	At 9.5 hours post-drug, a standardized xanthine-free meal will be provided to all subjcts, with a non-caffeine containing beverage.
I	August 21, 1997	Subject #13 consumed less than 75% of his 4.5 hour post-drug meal due to nausea.	At 4.5 hours post-drug, a standardized xanthine-free meal will be provided to all subjects, with a non-caffeine containig beverage.

NIFEDIPINE CC 30 mg TABLETS
STUDY #1868-1 (B97-312PK-NIFB32)
PROTOCOL DEVIATIONS (Cont'd)

PERIOD	DATE	DEVIATION	PROTOCOL STATES
II	September 5, 1997	Subject #27 was unable to eat the 9.5 hour post-drug meal at the required time due to nausea. The subject ate the supper five hours late, at 14.5 hours post-drug.	At 9.5 hours post-drug, a standardized, xanthine-free meal will be provided to all subjects, with a non-caffeine containing beverage.
II	September 5, 1997	At 10.0 hours post-drug, Subject #27 drank a can a ginger ale from his supper tray, however he vomited it up soon after.	At 9.5 hours post-drug, a standardized, xanthine-free meal will be provided to all subjects, with a non-caffeine containing beverage.
II	September 5, 1997	Subject #42 began his 9.5 hour post-drug meal 8 minutes late because he was sleeping in an isolated area of the clinic and could not be located by the clinic staff.	At 9.5 hours post-drug, a standardized, xanthine-free meal will be provided to all subjects, with a non-caffeine containing beverage.
II	September 8, 1997	Subject #12 completed his 9.5 hour post-drug meal 15 minutes late because a portion of his meal had to be replaced.	At 9.5 hours post-drug, a standardized, xanthine-free meal will be provided to all subjects, with a non-caffeine containing beverage.
II	September 6, 1997	The 0.0 hour (pre-drug) blood draw of Subject #09 was 1 minute late due to sampling difficulty.	A 7 mL blood sample will be collected at exactly 0.0 hour (pre-drug administration).
II	September 6, 1997	The 0.0 hour (pre-drug) blood draw of Subject #10 was 1 minute late due to sampling difficulty.	A 7 mL blood sample will be collected at exactly 0.0 hour (pre-drug administration).
II	September 9, 1997	The 6.0 hour blood draw of Subject #23 was 2 minutes late due to sampling difficulty.	A 7 mL blood sample will be collected at exactly 6.0 hours post-drug administration.
II	September 9, 1997	The 10.0 hour blood draw of Subject #10 was 2 minutes late due to sampling difficulty.	A 7 mL blood sample will be collected at exactly 10.0 hours post-drug administration.
II	September 9, 1997	The 8.0 hour blood draw of Subject #42 was 1 minute late due to sampling difficulty.	A 7 mL blood sample will be collected at exactly 8.0 hours post-drug administration.

NIFEDIPINE CC 30 mg TABLETS
STUDY # 1868-1 (B97-312PK-NIFB32)
ADVERSE EVENTS

SUBJECT'S NUMBER	SUBJECT'S INITIALS	PERIOD	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET (m/d/y)	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
02	RP	I	B	Headache	0830	08/21/97	12 hrs., 30 min.	Mild	None	Probably drug related
				Headache	1430	08/24/97	2 hrs., 20 min.	Mild	None	Probably drug related
				Headache	1030	08/25/97	5 hrs.	Mild	None	Probably drug related
				Headache	1845	08/26/97	1 hr., 45 min.	Mild	None	Probably drug related
03	RJS	I	B	Sinus Bradycardia	0903	08/20/97	2 hrs.	Mild	None	Drug related
				Sinus Bradycardia	1104	08/22/97	1 hr., 58 min.	Mild	None	Drug related
04	KFC	I	A	Headache	0900	08/20/97	12 hrs.	Mild	None	Probably drug related
				Headache	1030	08/22/97	2 hrs.	Mild	None	Probably drug related
				Borderline 1°AV Block	2308	08/22/97	6 hrs., 16 min.	Mild	None	Drug related
				Tips of ears hot	1230	08/25/97	1 hr.	Mild	None	Probably drug related
05	WC	I	A	Sinus Bradycardia	2306	08/21/97	6 hrs., 18 min.	Mild	None	Drug related
				Sinus Bradycardia	1107	08/22/97	1 hr., 57 min.	Mild	None	Drug related
				Sinus Bradycardia	2310	08/22/97	6 hrs., 16 min.	Mild	None	Drug related
				Sinus Bradycardia	1103	08/24/97	1 hr., 58 min.	Mild	None	Drug related
				Sinus Bradycardia	0905	08/25/97	3 hrs., 59 min.	Mild	None	Drug related
				Sinus Bradycardia	2313	08/26/97	7 hrs., 55 min.	Mild	None	Drug related

CODES:

***SEVERITY**

MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.

MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.

SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health.

****REGIMEN**

A: One nifedipine CC 30 mg tablet (Biovail Corporation International; Lot Number: 97E003) (Test drug) at 7 AM with 240 mL of water, following an overnight fast on Days 1 - 7.

B: One Adalat® CC 30 mg tablet (Bayer Corporation; Lot Number: 61.CT; Expiry Date: 12/98) (Reference drug) at 7 AM with 240 mL of water, following an overnight fast on Days 1 - 7.

NIFEDIPINE CC 30 mg TABLETS
STUDY # 1868-1 (B97-312PK-NIFB32)
ADVERSE EVENTS (Cont'd)

SUBJECT'S NUMBER	SUBJECT'S INITIALS	PERIOD	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET (m/d/y)	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
06	BJ	I	A	Headache	0830	08/22/97	2 hrs., 15 min.	Mild	None	Probably drug related
				Sinus Bradycardia	0906	08/20/97	2 hrs.	Mild	None	Drug related
				Sinus Bradycardia	1506	08/20/97	2 hrs., 31 min.	Mild	None	Drug related
				Sinus Bradycardia	1107	08/21/97	2 hrs., 1 min.	Mild	None	Drug related
				Headache	1050	08/24/97	6 hrs., 50 min.	Mild	None	Probably drug related
				Sinus Bradycardia	0903	08/25/97	2 hrs.	Mild	None	Drug related
07	DC	I	A	Headache	1300	08/20/97	11 hrs.	Mild	None	Probably drug related
08	LB	I	A	Headache	1230	08/23/97	20 hrs., 30 min.	Mild	None	Probably drug related
09	GM	I	A	Headache	1300	08/20/97	3 hrs.	Mild	None	Probably drug related
				Borderline I°AV Block	1109	08/21/97	2 hrs., 8 min.	Mild	None	Drug related
				Sinus Bradycardia	1114	08/22/97	1 hr., 53 min.	Mild	None	Drug related

CODES:

***SEVERITY**
MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.
MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.
SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health

****REGIMEN**
A: One nifedipine CC 30 mg tablet (Biovail Corporation International; Lot Number: 97E003) (Test drug) at 7 AM with 240 mL of water, following an overnight fast on Days 1 - 7.
B: One Adalat® CC 30 mg tablet (Bayer Corporation; Lot Number: 6LCT; Expiry Date: 12/98) (Reference drug) at 7 AM with 240 mL of water, following an overnight fast on Days 1 - 7.

NIFEDIPINE CC 30 mg TABLETS
STUDY # 1868-1 (B97-312PK-NIFB32)
ADVERSE EVENTS (Cont'd)

SUBJECT'S NUMBER	SUBJECT'S INITIALS	PERIOD	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET (m/d/y)	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
10	YP	1	B	Headache	1100	08/20/97	18 hrs.	Mild	None	Probably drug related
11	RS	1	B	Headache	1200	08/20/97	8 hrs., 30 min.	Mild	None	Probably drug related
12	LM	1	B	Sinus Bradycardia	1109	08/20/97	1 hr., 31 min.	Mild	None	Drug related
				Sinus Bradycardia	1112	08/21/97	2 hrs.	Mild	None	Drug related
				1°AV Block	1108	08/24/97	4 hrs., 2 min.	Mild	None	Drug related
				Sinus Bradycardia	2316	08/25/97	6 hrs., 11 min.	Mild	None	Drug related
13	RE	1	B	Lightheadedness	0745	08/20/97	3 hrs., 15 min.	Mild	None	Drug related
				Lightheadedness	0900	08/21/97	3 hrs., 10 min.	Mild	None	Drug related
				Nausea	1210	08/21/97	15 min.	Mild	None	Drug related
				Anxiety	1210	08/21/97	1 hr., 10 min.	Moderate	Placed in bed on right side	Probably not drug related
				Diaphoresis	1210	08/21/97	3 min.	Mild	None	Drug related
17	MP	1	B	Sinus Bradycardia	0916	08/20/97	3 hrs., 28 min.	Mild	None	Drug related
				Sinus Bradycardia	1112	08/23/97	1 hr., 53 min.	Mild	None	Drug related
				Sinus Bradycardia	0912	08/25/97	2 hrs., 3 min.	Mild	None	Drug related

5035

CODES:

***SEVERITY**

MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.

MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.

SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health.

****REGIMEN**

A: One nifedipine CC 30 mg tablet (Biovail Corporation International; Lot Number: 97E003) (Test drug) at 7 AM with 240 mL of water, following an overnight fast on Days 1 - 7.

B: One Adalat® CC 30 mg tablet (Bayer Corporation; Lot Number: 6LCT; Expiry Date: 12/98) (Reference drug) at 7 AM with 240 mL of water, following an overnight fast on Days 1 - 7.

NIFEDIPINE CC 30 mg TABLETS
STUDY # 1868-1 (B97-312PK-NIFB32)
ADVERSE EVENTS (Cont'd)

SUBJECT'S NUMBER	SUBJECT'S INITIALS	PERIOD	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET (m/d/y)	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
18	DL	I	B	Pallor	0716	08/26/97	4 min.	Mild	None	Not drug related
				Dizziness	0716	08/26/97	10 min.	Mild	None	Not drug related
19	AMN	I	B	Headache	1045	08/20/97	36 hrs., 45 min.	Mild	None	Probably drug related
				Headache	1500	08/22/97	44 hrs , 30 min.	Mild	None	Probably drug related
				Headache	0600	08/24/97	8 hrs.	Mild	None	Probably drug related
20	AH	I	A	Sinus Bradycardia	1132	08/22/97	1 hr., 38 min.	Mild	None	Drug related
				Headache	0500	08/25/97	2 hrs.	Mild	None	Probably drug related
				Sinus Bradycardia	1119	08/25/97	1 hr., 47 min.	Mild	None	Drug related
23	JK	I	B	Dizziness	0745	08/22/97	45 min.	Mild	None	Drug related

5036

CODES:

*SEVERITY
MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.
MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.
SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health

**REGIMEN
A: One nifedipine CC 30 mg tablet (Biovail Corporation International; Lot Number: 97E003) (Test drug) at 7 AM with 240 mL of water, following an overnight fast on Days 1 - 7.
B: One Adalat® CC 30 mg tablet (Bayer Corporation; Lot Number: 61LCT; Expiry Date: 12/98) (Reference drug) at 7 AM with 240 mL of water, following an overnight fast on Days 1 - 7.

APPEARS THIS WAY
ON ORIGINAL

023

NIFEDIPINE CC 30 mg TABLETS
STUDY # 1868-1 (B97-312PK-NIFB32)
ADVERSE EVENTS (Cont'd)

SUBJECT'S NUMBER	SUBJECT'S INITIALS	PERIOD	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET (m/d/y)	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
24	TB	I	A	Nausea	1320	08/24/97	5 min.	Mild	None	Probably not drug related
				Vomiting	1320	08/24/97	5 min.	Mild	None	Probably not drug related
				Chest pain	1800	08/24/97	30 min.	Moderate	None	Probably not drug related
				Vomiting	1800	08/24/97	30 min.	Mild	None	Probably not drug related
25	MC	I	A	Diaphoresis	0725	08/23/97	4 min.	Moderate	None	Not drug related
				Pallor	0725	08/23/97	3 min.	Mild	None	Not drug related
				Borderline 1°AV Block	1527	08/22/97	8 hrs., 17 min.	Mild	None	Not drug related
27	JF	I	B	Sinus Bradycardia	1523	08/20/97	2 hrs., 42 min.	Mild	None	Drug related
				Sinus Bradycardia	0925	08/21/97	2 hrs., 1 min.	Mild	None	Drug related
				Sinus Bradycardia	2333	08/21/97	6 hrs., 22 min.	Mild	None	Drug related
				Headache	0845	08/24/97	1 hr.	Mild	None	Probably drug related
28	GF	I	A	Sinus Bradycardia	0925	08/20/97	1 hr., 58 min.	Mild	None	Drug related
				Lightheadedness	0905	08/25/97	40 min.	Mild	None	Probably drug related
				Sinus Bradycardia	0923	08/25/97	2 hrs., 1 min.	Mild	None	Drug related
32	JT	I	B	Sinus Bradycardia	0932	08/23/97	1 hr., 53 min.	Mild	None	Drug related
				Sinus Bradycardia	1132	08/25/97	1 hr., 39 min.	Mild	None	Drug related

CODES:

***SEVERITY**

MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.

MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.

SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health.

****REGIMEN**

A: One nifedipine CC 30 mg tablet (Biovail Corporation International; Lot Number: 97E003) (Test drug) at 7 AM with 240 mL of water, following an overnight fast on Days 1 - 7.

B: One Adalat® CC 30 mg tablet (Bayer Corporation; Lot Number: 61.CT; Expiry Date: 12/98) (Reference drug) at 7 AM with 240 mL of water, following an overnight fast on Days 1 - 7.

NIFEDIPINE CC 30 mg TABLETS
STUDY # 1868-1 (B97-312PK-NIFB32)
ADVERSE EVENTS (Cont'd)

SUBJECT'S NUMBER	SUBJECT'S INITIALS	PERIOD	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET (m/d/y)	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
33	SA	I	B	Nausea	0730	08/23/97	5 min.	Mild	None	Not drug related
				Lightheadedness	0730	08/23/97	8 min.	Moderate	Assisted to lie down on right side	Not drug related
36	FD	I	A	Sinus Bradycardia	1135	08/21/97	1 hr., 45 min.	Mild	None	Drug related
				1°AV Block	0004	08/23/97	6 hrs., 8 min.	Mild	None	Drug related
37	PD	I	A	Headache	0900	08/20/97	34 hrs., 30 min.	Mild	Given Tylenol tablet	Probably not drug related
				Nausea	0900	08/20/97	26 hrs., 20 min.	Mild	None	Probably not drug related
				Lightheadedness	0900	08/20/97	2 min.	Mild	Laid on right side	Probably not drug related
				Vomiting	1217	08/20/97	8 min.	Moderate	None	Probably not drug related
				Vomiting	1600	08/20/97	5 min.	Moderate	None	Probably not drug related
				Sinus Tachycardia	1540	08/20/97	2 hrs., 6 min.	Mild	None	Probably not drug related

CODES:

***SEVERITY**

MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.

MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.

SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health.

****REGIMEN**

A: One nifedipine CC 30 mg tablet (Biovail Corporation International; Lot Number: 97E003) (Test drug) at 7 AM with 240 mL of water, following an overnight fast on Days 1 - 7.

B: One Adalat® CC 30 mg tablet (Bayer Corporation; Lot Number: 61.CT; Expiry Date: 12/98) (Reference drug) at 7 AM with 240 mL of water, following an overnight fast on Days 1 - 7.

NIFEDIPINE CC 30 mg TABLETS
STUDY # 1868-1 (B97-312PK-NIFB32)
ADVERSE EVENTS (Cont'd)

SUBJECT'S NUMBER	SUBJECT'S INITIALS	PERIOD	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET (m/d/y)	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
38	ST	I	B	Headache	1030	08/20/97	23 hrs., 15 min.	Mild	None	Probably not drug related
				Nausea	1030	08/20/97	23 hrs., 15 min.	Mild	None	Probably not drug related
				Vomiting	1730	08/20/97	5 min.	Moderate	None	Probably not drug related
39	VH	I	A	Headache	1300	08/22/97	9 hrs.	Mild	None	Probably drug related
				Headache	1300	08/23/97	10 hrs.	Mild	None	Probably drug related
40	RT	I	A	Headache	0930	08/25/97	30 min.	Mild	None	Probably drug related
				Dizziness	0915	08/26/97	30 min.	Mild	None	Probably drug related
42	PC	I	B	Sore throat	0900	08/25/97	72 hrs.	Mild	None	Not drug related

5039

CODES:

***SEVERITY**

MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.

MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.

SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health.

****REGIMEN**

A: One nifedipine CC 30 mg tablet (Biovail Corporation International; Lot Number: 97E003) (Test drug) at 7 AM with 240 mL of water, following an overnight fast on Days 1 - 7.

B: One Adalat® CC 30 mg tablet (Bayer Corporation; Lot Number: 61.CT; Expiry Date: 12/98) (Reference drug) at 7 AM with 240 mL of water, following an overnight fast on Days 1 - 7.

026

NIFEDIPINE CC 30 mg TABLETS
STUDY # 1868-1 (B97-312PK-NIFB32)
ADVERSE EVENTS (Cont'd)

SUBJECT'S NUMBER	SUBJECT'S INITIALS	PERIOD	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET (m/d/y)	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
43	SK	I	B	Sinus Bradycardia	0940	08/20/97	2 hrs., 1 min.	Mild	None	Drug related
				Dizziness	0845	08/23/97	2 hrs.	Mild	None	Probably not drug related
				Fatigue	0845	08/23/97	2 hrs.	Moderate	None	Probably not drug related
				Right hip pain	1300	08/24/97	2 hrs.	Mild	None	Probably not drug related
				Chest pain	1830	08/24/97	5 hrs., 30 min.	Moderate	None	Probably not drug related
				Palpitations	1830	08/24/97	5 hrs., 30 min.	Moderate	None	Probably not drug related
				Lightheadedness	0940	08/26/97	2 hrs., 20 min.	Moderate	None	Probably not drug related
44	BP	I	B	Headache	1000	08/20/97	11 hrs.	Mild	None	Probably drug related
				Headache	1100	08/21/97	4 hrs.	Mild	None	Probably drug related
				Borderline 1°AV Block	2346	08/21/97	6 hrs., 29 min.	Mild	None	Drug related
				Borderline 1°AV Block	0016	08/23/97	6 hrs., 45 min.	Mild	None	Drug related
				Headache	1015	08/24/97	11 hrs., 15 min.	Mild	None	Probably drug related
				Headache	1030	08/25/97	1 hr.	Mild	None	Probably drug related
				Headache	0915	08/26/97	9 hrs., 45 min.	Mild	None	Probably drug related

CODES:

***SEVERITY**

MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.

MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.

SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health.

****REGIMEN**

A: One nifedipine CC 30 mg tablet (Biovail Corporation International; Lot Number: 97E003) (Test drug) at 7 AM with 240 mL of water, following an overnight fast on Days 1 - 7.

B: One Adalat® CC 30 mg tablet (Bayer Corporation; Lot Number: 6LCT; Expiry Date: 12/98) (Reference drug) at 7 AM with 240 mL of water, following an overnight fast on Days 1 - 7.

NIFEDIPINE CC 30 mg TABLETS
STUDY # 1868-1 (B97-312PK-NIFB32)
ADVERSE EVENTS (Cont'd)

SUBJECT'S NUMBER	SUBJECT'S INITIALS	PERIOD	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET (m/d/y)	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
45	III	I	B	Sinus Bradycardia	0940	08/21/97	2 hrs., 6 min.	Mild	None	Drug related
				Sinus Bradycardia	2349	08/21/97	6 hrs., 29 min.	Mild	None	Drug related
				Sinus Bradycardia	1019	08/22/97	2 hrs., 57 min.	Mild	None	Drug related
				Sinus Bradycardia	0944	08/23/97	3 hrs., 23 min.	Mild	None	Drug related
				Sinus Bradycardia	2334	08/23/97	7 hrs., 9 min.	Mild	None	Drug related
				Sinus Bradycardia	1129	08/24/97	1 hr., 36 min.	Mild	None	Drug related
				Sinus Bradycardia	2347	08/24/97	6 hrs., 20 min.	Mild	None	Probably drug related
				Headache	1135	08/25/97	3 hrs., 25 min.	Mild	None	Drug related
				Sinus Bradycardia	1141	08/25/97	1 hr., 23 min.	Mild	None	Drug related
				Sinus Bradycardia	2351	08/26/97	8 hrs.	Mild	None	Probably drug related
46	JR	I	A	Headache	1800	08/20/97	11 hrs., 30 min.	Mild	None	Probably drug related
47	DM	I	A	Headache	1100	08/20/97	8 hrs.	Mild	None	Probably drug related
48	DBZ	I	B	Headache	0915	08/20/97	10 hrs., 45 min.	Mild	None	Probably drug related
				Headache	0945	08/21/97	1 hr., 35 min.	Mild	None	Probably drug related
				Headache	1120	08/21/97	4 hrs., 10 min.	Moderate	Ice pack given & placed in bed on right side	Probably drug related
				Lightheadedness	0900	08/22/97	1 hr.	Mild	None	Probably drug related
				Headache	0900	08/22/97	1 hr., 15 min.	Mild	None	Probably drug related

CODES:

***SEVERITY**

MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.

MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.

SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health.

****REGIMEN**

A: One nifedipine CC 30 mg tablet (Biovail Corporation International; Lot Number: 97E003) (Test drug) at 7 AM with 240 mL of water, following an overnight fast on Days 1 - 7.

B: Adalat® CC 30 mg tablet (Bayer Corporation; Lot Number: 6LCT; Expiry Date: 12/98) (Reference drug) at 7 AM with 240 mL of water, following an overnight fast on Days 1 - 7.

NIFEDIPINE CC 30 mg TABLETS
STUDY # 1868-1 (B97-312PK-NIFB32)
ADVERSE EVENTS (Cont'd)

SUBJECT'S NUMBER	SUBJECT'S INITIALS	PERIOD	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET (m/d/y)	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
48 (cont'd)	DBZ	I	B	Headache	1015	08/22/97	5 hrs., 15 min.	Moderate	Ice pack given	Probably drug related
				Lightheadedness	0915	08/23/97	45 min.	Mild	None	Probably drug related
				Headache	1000	08/23/97	5 hrs.	Mild	None	Not drug related
				Headache	0930	08/25/97	9 hrs.	Mild	None	Not drug related
				Lightheadedness	0930	08/25/97	2 hrs.	Mild	None	Not drug related
				Pallor	1117	08/25/97	4 min.	Mild	Assisted to lie in bed	Not drug related
				Diaphoresis	1117	08/25/97	5 min.	Mild	Assisted to lie in bed	Not drug related
02	RP	II	A	Headache	1610	09/05/97	12 hrs., 50 min.	Mild	None	Probably drug related
				Nausea	2300	09/05/97	6 hrs.	Mild	None	Probably not drug related
03	RJS	II	A	Sinus Bradycardia	0903	09/04/97	1 hr., 58 min.	Mild	None	Drug related
04	KFC	II	B	Headache	0900	09/03/97	9 hrs.	Mild	None	Probably drug related
05	WC	II	B	Sinus Bradycardia	0906	09/03/97	1 hr., 58 min.	Mild	None	Drug related
				Sinus Bradycardia	0903	09/04/97	4 hrs., 6 min.	Mild	None	Drug related
				Sinus Bradycardia	0903	09/05/97	2 hrs., 2 min.	Mild	None	Drug related
				Sinus Bradycardia	2255	09/05/97	6 hrs., 30 min.	Mild	None	Drug related

CODES:

***SEVERITY**

MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.

MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.

SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health.

****REGIMEN**

A: One nifedipine CC 30 mg tablet (Biovail Corporation International; Lot Number: 97E003) (Test drug) at 7 AM with 240 mL of water, following an overnight fast on Days 1 - 7.

B: One Adalat® CC 30 mg tablet (Bayer Corporation; Lot Number: 61CT; Expiry Date: 12/98) (Reference drug) at 7 AM with 240 mL of water, following an overnight fast on Days 1 - 7.

NIFEDIPINE CC 30 mg TABLETS
STUDY # 1868-1 (B97-312PK-NIFB32)
ADVERSE EVENTS (Cont'd)

SUBJECT'S NUMBER	SUBJECT'S INITIALS	PERIOD	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET (m/d/y)	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
07	DC	II	B	Sinus Bradycardia	0906	09/03/97	2 hrs., 2 min.	Mild	None	Drug related
				Headache	1200	09/03/97	11 hrs.	Mild	None	Probably drug related
				Headache	2200	09/09/97	9 hrs.	Mild	None	Probably drug related
09	GM	II	B	Chest pain	0100	09/09/97	5 hrs.	Mild	None	Probably not drug related
10	YP	II	A	Headache	1130	09/03/97	12 hrs.	Mild	None	Probably drug related
11	RS	II	A	Headache	1230	09/03/97	8 hrs.	Mild	None	Probably drug related
12	LM	II	A	Sinus Bradycardia	0910	09/03/97	3 hrs., 52 min.	Mild	None	Drug related
				Sinus Bradycardia	0909	09/05/97	2 hrs., 2 min.	Mild	None	Drug related
				Nausea	0800	09/05/97	24 hrs., 30 min.	Mild	None	Probably drug related
				Sinus Bradycardia	1110	09/08/97	1 hr., 57 min.	Mild	None	Drug related
				Lightheadedness	0740	09/09/97	14 hrs., 20 min.	Mild	Lied on right side	Probably drug related
				Nausea	0740	09/09/97	14 hrs., 20 min.	Mild	Lied on right side	Probably drug related

CODES:

***SEVERITY**

MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.

MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.

SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health

****REGIMEN**

A: One nifedipine CC 30 mg tablet (Biovail Corporation International; Lot Number: 97E003) (Test drug) at 7 AM with 240 mL of water, following an overnight fast on Days 1 - 7.

B: One Adalat® CC 30 mg tablet (Bayer Corporation; Lot Number: 61LCT; Expiry Date: 12/98) (Reference drug) at 7 AM with 240 mL of water, following an overnight fast on Days 1 - 7.

NIFEDIPINE CC 30 mg TABLETS
STUDY # 1868-1 (B97-312PK-NIFB32)
ADVERSE EVENTS (Cont'd)

SUBJECT'S NUMBER	SUBJECT'S INITIALS	PERIOD	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET (m/d/y)	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
15	CK	II	A	Itchiness	2200	09/04/97	15 hrs.	Mild	None	Probably not drug related
				Headache	1200	09/09/97	5 hrs.	Mild	None	Probably drug related
16	PG	II	A	Headache	1500	09/03/97	5 min.	Mild	None	Probably drug related
17	MP	II	A	Borderline 1°AV Block	0912	09/03/97	2 hrs.	Mild	None	Drug related
19	AMN	II	A	Headache	1200	09/03/97	11 hrs., 30 min.	Moderate	Instructed to lie down; refused ice pack	Probably drug related
				Headache	1430	09/08/97	14 hrs., 45 min.	Mild	None	Probably drug related
20	AH	II	B	Chest pressure	2100	09/05/97	72 hrs.	Mild	None	Not drug related
				Sinus Bradycardia	1114	09/06/97	1 hr., 48 min.	Mild	None	Not drug related
22	KS	II	B	Itchiness	1000	09/03/97	50 hrs.	Mild	None	Probably not drug related

CODES:

***SEVERITY**

MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.
MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.
SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health.

****REGIMEN**

A: One nifedipine CC 30 mg tablet (Biovail Corporation International; Lot Number: 97E003) (Test drug) at 7 AM with 240 mL of water, following an overnight fast on Days 1 - 7.
B: One Adalat® CC 30 mg tablet (Bayer Corporation; Lot Number: 61.CT; Expiry Date: 12/98) (Reference drug) at 7 AM with 240 mL of water, following an overnight fast on Days 1 - 7.

NIFEDIPINE CC 30 mg TABLETS
STUDY # 1868-1 (B97-312PK-NIFB32)
ADVERSE EVENTS (Cont'd)

SUBJECT'S NUMBER	SUBJECT'S INITIALS	PERIOD	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET (m/d/y)	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
27	JF	II	A	Sinus Bradycardia	1119	09/03/97	1 hr., 47 min.	Mild	None	Drug related
				Sinus Bradycardia	1518	09/05/97	2 hr., 18 min.	Mild	None	Drug related
				Headache	1300	09/05/97	22 hrs.	Mild-Moderate	None	Possibly drug related
				Dizziness	1300	09/05/97	18 hrs.	Mild	None	Possibly drug related
				Nausea	1500	09/05/97	16 hrs.	Mild	None	Possibly drug related
				Chills	1710	09/05/97	13 hrs., 50 min.	Mild	None	Possibly drug related
				Vomiting	1710	09/05/97	2 min.	Mild	None	Possibly drug related
				Sinus Bradycardia	1130	09/09/97	1 hr., 33 min.	Mild	None	Drug related
28	GF	II	B	Sinus Bradycardia	0919	09/03/97	3 hrs., 51 min.	Mild	None	Drug related
				Sinus Bradycardia	1123	09/05/97	1 hr., 44 min.	Mild	None	Drug related
				Sinus Bradycardia	2318	09/05/97	6 hrs., 35 min.	Mild	None	Drug related
32	JT	II	A	Sinus Bradycardia	1123	09/03/97	1 hr., 52 min.	Mild	None	Drug related
				Sinus Bradycardia	0925	09/04/97	2 hrs.	Mild	None	Drug related
				Sinus Bradycardia	0922	09/05/97	2 hrs., 7 min.	Mild	None	Drug related
				Sinus Bradycardia	0924	09/06/97	2 hrs., 1 min.	Mild	None	Drug related
34	GH	II	A	Sore throat	0700	09/03/97	72 hrs.	Mild	None	Not drug related
35	SW	II	B	Borderline 1°AV Block	2354	09/09/97	7 hrs., 48 min.	Mild	None	Drug related

CODES:

***SEVERITY**

MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.

MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.

SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health

****REGIMEN**

A: One nifedipine CC 30 mg tablet (Biovail Corporation International; Lot Number: 97E003) (Test drug) at 7 AM with 240 mL of water, following an overnight fast on Days 1 - 7.

B: One Adalat® CC 30 mg tablet (Bayer Corporation; Lot Number: 6LCT; Expiry Date: 12/98) (Reference drug) at 7 AM with 240 mL of water, following an overnight fast on Days 1 - 7.

NIFEDIPINE CC 30 mg TABLETS
STUDY # 1868-1 (B97-312PK-NIFB32)
ADVERSE EVENTS (Cont'd)

SUBJECT'S NUMBER	SUBJECT'S INITIALS	PERIOD	REGIMEN**	SYMPTOMS	TIME OF ONSET (24 hour clock)	DATE OF ONSET (m/d/y)	DURATION	SEVERITY*	TREATMENT	RELATIONSHIP TO STUDY DRUG
36	FD	II	B	Sinus Bradycardia	0925	09/03/97	3 hrs., 53 min.	Mild	None	Drug related
				Sinus Bradycardia	0928	09/04/97	1 hr., 55 min.	Mild	None	Drug related
				Sinus Bradycardia	1129	09/08/97	1 hr., 42 min.	Mild	None	Drug related
39	VH	II	B	Headache	1300	09/03/97	10 hrs.	Mild	None	Probably drug related
40	RT	II	B	Headache	0925	09/06/97	2 hrs.	Mild	None	Not drug related
				Swelling	0200	09/07/97	23 hrs.	Mild	None	Not drug related
				Chest pain	0613	09/09/97	2 min.	Mild	None	Not drug related
44	BP	II	A	Headache	1100	09/03/97	18 hrs., 45 min.	Mild	None	Probably drug related
				Borderline 1°AV Block	2338	09/03/97	6 hrs., 48 min.	Mild	None	Drug related
				Sinus Bradycardia	0929	09/06/97	2 hrs., 3 min.	Mild	None	Drug related
45	HI	II	A	Sinus Bradycardia	0932	09/03/97	3 hrs., 49 min.	Mild	None	Drug related
				Sinus Bradycardia	1128	09/04/97	1 hr., 48 min.	Mild	None	Drug related
				Sinus Bradycardia	2331	09/04/97	6 hrs., 48 min.	Mild	None	Drug related
				Sinus Bradycardia	2329	09/05/97	6 hrs., 47 min.	Mild	None	Drug related
				Sinus Bradycardia	2341	09/07/97	6 hrs., 37 min.	Mild	None	Drug related
				Sinus Bradycardia	1534	09/08/97	1 hr., 42 min.	Mild	None	Drug related
				Sinus Bradycardia	0948	09/09/97	2 hrs.	Mild	None	Drug related
47	DM	II	B	Headache	1200	09/04/97	6 hrs.	Mild	None	Probably drug related

CODES:

***SEVERITY**

MILD: Any event that is an annoyance to the patient but does not hinder normal daily functioning; intermittent or continuous.

MODERATE: Any event that produces some interference with normal daily functioning; prescription drug may have been given.

SEVERE/SERIOUS: Any event that is fatal, life threatening, and/or permanently disabling; requires in-patient or prolonged hospitalization; has permanent residual effects; a definite hazard to health

****REGIMEN**

A: One nifedipine CC 30 mg tablet (Biovail Corporation International; Lot Number: 97F003) (Test drug) at 7 AM with 240 mL of water, following an overnight fast on Days 1 - 7

B: One Adalat® CC 30 mg tablet (Bayer Corporation; Lot Number: 61.CT; Expiry Date: 12/98) (Reference drug) at 7 AM with 240 mL of water, following an overnight fast on Days 1 - 7

BIOVAIL TECHNOLOGIES LTD.

Fax Transmittal Sheet

14555 AVION PARKWAY
CHANTILLY, VA 20151

NDA ORIG AMENDMENT
N/FA

TO: Document Control Room

FROM:

COMPANY: FDA, Office of Generic Drugs

DATE: Nov. 27/00

FAX NUMBER: (301) 827-4337

TOTAL NO. OF PAGES INCLUDING COVER: 17

PHONE NUMBER:

SENDER'S FAX NUMBER: (703) 995-2444

RE: ANDA 75-269

SENDER'S PHONE NUMBER: (703) 995-2400

☐ URGENT ☐ FOR REVIEW ☐ PLEASE COMMENT ☐ PLEASE REPLY ☐ PLEASE RECYCLE

FAX AMENDMENT

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-269

ADMINISTRATIVE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Biovail Laboratories Incorporated	November 27, 2000
TELEPHONE NO. *(Include Area Code)* (703) 995-2400	**FACSIMILE (FAX) Number** *(Include Area Code)* (703) 995-2444

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*

Chelston Park, Building 2
Collymore Rock
St. Michael, BHI
Barbados, WI

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

John Dubeck, Agent for Biovail Laboratories Inc.
Keller and Heckman
1001 G Street, N.W., Suite 500 West
Washington, D.C. 20001

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Nifedipine Extended Release Tablets 30 mg and 60mg	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*: Dimethyl 1,4-dihydro-2, 6-dimethyl-4-(o-nitrophenyl)-3,5-pyridinedicarboxylate

CODE NAME *(If any)*: B32

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	30 mg and 60 mg	Oral

(PROPOSED) INDICATION(S) FOR USE: Please see Attachment A

APPLICATION INFORMATION

ATION TYPE (one)
☐ NEW DRUG APPLICATION (21 CFR 314.50) ☒ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug	Holder of Approved Application
Adalat CC	Bayer Corporation, Pharmaceutical Division

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☒ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION: Response to Fax Amendment of November 27, 2000

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED: 1

THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Please see Attachment A.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

e see Attachment B.

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☒	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (k)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

:RTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
John B. Dubeck	John B. Dubeck (U.S. Agent)	November 27/00

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
Keller and Heckman LLP, 1001 G Street, NW, Ste 500-W, Washington, DC 20001	(202) 434-4125

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Dr., Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

FORM FDA 356h – ATTACHMENT A

Nifedipine Extended-Release Tablets, 30 mg and 60 mg

[redacted]

[redacted]

[redacted]	**Contact:** [redacted] **Telephone:** [redacted]

[redacted]

Manufacturer:

[redacted]

Biovail Corporation International 100 Lifesciences Parkway P.O. Box 21390 Steinbach, Manitoba Canada R0A 2T3	**Contact:** Larry Thiessen **Telephone:** (204) 326-9000 **Inspection:** Ready

Outside Testing Facilities:

[redacted]	**Contact:** [redacted] **Telephone:** [redacted] **Inspection:** Ready
[redacted]	**Contact:** [redacted] **Telephone:** [redacted] **Inspection:** Ready
[redacted]	**Contact:** [redacted] **Telephone:** [redacted] **Inspection:** Ready
[redacted]	**Contact:** [redacted] **Telephone:** [redacted] **Inspection:** Ready

FORM FDA 356h – ATTACHMENT B

Nifedipine Extended-Release Tablets, 30 mg and 60 mg

[redacted]

Nifedipine USP	[redacted]
[redacted]	[redacted]
Hydroxyethyl Cellulose (NF)	[redacted]
Hydroxypropyl Methylcellulose	[redacted]
Microcrystalline Cellulose NF	[redacted]
Polyethylene Glycol 600 NF	[redacted]

[redacted]

[redacted]

APPEARS THIS WAY ON ORIGINAL

Current Quality Standard Specification Form for Nifedipine CC ER ——, Tablets, 30 mg

List No. B32B106

Effective Date: November 21, 1999

APPEARS THIS WAY
ON ORIGINAL

QUALITY STANDARD SPECIFICATION FORM - IN-PROCESS PRODUCT

FORM REVIEW: G. Bédard	DATE: Apr 20/99
FORM APPROVAL (QA): M Smith	EFFECTIVE DATE: Apr. 21/99
FORM #: FQA-0107.E/B32B106 REV #: 03	SUPERSEDES DATE: JAN 21, 1999

Lab #

MATERIAL:	Nifedipine CC ER Coated Tablets, 30mg			LIST NO:	B32B106
LOT NO.:		BATCH SIZE:		EXPIRY DATE:	
ACTIVE INGREDIENT:		VENDOR:		PMF DATE:	
MFR SITE:		MFG LOT NO.:		MFG START DATE:	
				MFG FINISH DATE:	

#	TESTS AND METHODS	SPECIFICATIONS	RESULTS	LAB ANALYST/ REFERENCES
1.	DESCRIPTION <0006.00> Rev ____	Round film coated mustard yellow tablets engraved with "B" on one side and "30" on the other side		
2.	POTENCY <0022.07> Rev	____		
3.	IDENTIFICATION <0022.07> Rev	Meets retention time of standard		
4.	IMPURITIES <0022.07> Rev ____	____ NMT ____ ____ NMT ____ Total Impurities: NMT ____ NMT ____ for any unspecified impurity		
	CONTENT UNIFORMITY USP <905>	Min: ____ of LC Max: ____ of LC % RSD ≤ ____		
6.	DISSOLUTION <0021.11> Rev ____ USP <724> Acceptance Table 1	1 hour: ____ Range 4 hours: ____ Range 12 hours: NLT ____ (Avg) Range		
7.	____ CONTENT <0009.01> Rev	NMT ____		
8.	____ CONTENT <0029.05> Rev	NMT ____		

Comments: _____

Reviewed by (QC): _____ Date: _____

Approved by (QA): _____ Date: _____

Current Interim Stability Report
for
Nifedipine CC Extended Release 30 mg Tablets in 100's
List No. B32B1SF

Project:		Product: Nifedipine CC Extended Release 30 mg Tablets in 100's	List No.: B32B1SF	Lot No:
	Mfg / Test Site	Start Date	Active Drug Sub. Mfr: ~	Bulk Tablet Lot No:	Coated Tablet Lot No:
Manufacturing Information:			Active Drug Sub. Lot#:		Coated Tablet Batch Size:
Tableting Information :			Tablet Description: Round mustard yellow film coated tablets with "B" on one side and "30" on the other		Stability Program: Room Temperature
Packaging Information :			Container: ~		Schedule: 0, 3, 6, 9, 12, 18, 24, 36 mos.
Stability Testing Information:			Closure/Innerseal: ~		Storage Conditions: 25 ± 2°C / 60 ± 5% R.H.
Project Purpose:			Filler: HIA Desiccant: ~	Temperbond: Present	Station ID: ECC 10 Samples: UP

TEST & METHODS	SPECIFICATIONS	INITIAL Date:		MONTH Date:		MONTH Date:		MONTH Date:	
Tablet Appearance <0006.00>	Mustard yellow, film coated tablets with no discoloration and "B" on one side and "30" on the other side								
Potency <0022.07>	~								
~	NMT ~								
~	NMT ~								
Individual Impurities <0022.07>	NMT ~ % for any unspecified impurity								
Total Impurities <0022.07>	NMT ~								
Dissolution <0021.11>	1 hours: ~								
	Range								
	4 hours: ~								
	Range								
	12 hours: NLT ~								
	Range								
Moisture content <0009.01>	NMT ~								

Reviewed by: Date:

APPEARS THIS WAY
ON ORIGINAL

Project:		Product: Nifedipine CC Extended Release 30 mg Tablets in 100's		List No.: 832B1SF	Lot No:
	Mfg / Test Site	Start Date	Active Drug Sub. Mfr:	Bulk Tablet Lot No.:	Coated Tablet Lot No.:
Manufacturing Information:			Active Drug Sub. Lot#:		Coated Tablet Batch Size:
Tableting Information :			Tablet Description: Round mustard yellow film coated tablets with "8" on one side and "10" on the other		Stability Program: Room Temperature
Packaging Information :			Container:		Schedule: 0, 3, 6, 9, 12, 18, 24, 36 mos.
Stability Testing Information:			Closure/Innerseal:		Storage Conditions: 25 ± 2°C / 60 ± 5% R.H.
Project Purpose:			Filler: N/A Desiccant:	Tamperband: Present	Station ID: ECC 10 Samples: UP

TEST & METHODS	SPECIFICATIONS	INITIAL Date: RESULTS 1 2 3 4 5 6	MONTH Date: RESULTS 1 2 3 4 5 6	MONTH Date: RESULTS 1 2 3 4 5 6	MONTH Date: RESULTS 1 2 3 4 5 6
Dissolution <0021 11>	1 hours: —				
	Range				
	4 hours: —				
	Range				
	12 hours: NLT —				
	Range				

Reviewed by: Date:

APPEARS THIS WAY
ON ORIGINAL

Current Interim Stability Report
for
Nifedipine CC Extended Release 30 mg Tablets in 300's
List No. B32B1SV

Project:		Product: Nifedipine CC Extended Release 30 mg Tablets in 300's	List No.: B3281SV	Lot No:
	Mfg / Test Site	Start Date	Active Drug Sub. Mfr: ~	Bulk Tablet Lot No.:
Manufacturing Information:			Active Drug Sub. Lot#:	Coated Tablet Lot No.:
Tableting Information :			Tablet Description: Mustard yellow film coated tablets with no discoloration and "8" on one side and "30" on the other	Coated Tablet Batch Size:
Packaging Information :			Container: ~	Stability Program: Room Temperature
Stability Testing Information:			Closure/Innerseal: ~	Schedule: 0, 3, 6, 9, 12, 18, 24, 36 mos.
Project Purpose:			Filler: N/A Desiccant: ~ Tempertrend: Present	Storage Conditions: 25 ± 2°C / 60 ± 5% R.H.
				Station ID: ECC 10 Samples: UP

TEST & METHODS	SPECIFICATIONS	INITIAL Date:	MONTH Date:	MONTH Date:	MONTH Date:
Tablet Appearance <0006.00>	Mustard yellow, film coated tablets with no discoloration and "8" on one side and "30" on the other side				
Potency <0022.07>	~				
~	NMT ~				
~	NMT ~				
Individual Impurities <0022.07>	NMT ~ for any unspecified impurity				
Total Impurities <0022.07>	NMT ~				
Dissolution <0021.11>	1 hours: ~	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
	Range				
	4 hours: ~	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
	Range				
	12 hours: NLT ~	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
	Range				
Moisture content <0009.01>	NMT ~				

Reviewed by: Date:

APPEARS THIS WAY
ON ORIGINAL

Project:		Product: Nifedipine CC Extended Release 30 mg Tablets in 300's	List No.: 83281SV	Lot No:
	Mfg / Test Site	Start Date	Active Drug Sub. Mfr: ~~~	Bulk Tablet Lot No.:	Coated Tablet Lot No.:
Manufacturing Information:			Active Drug Sub. Lot#:		Coated Tablet Batch Size:
Tabletting Information :			Tablet Description: Mustard yellow film coated tablets with no discolorations and "9" on one side and "30" on the other		Stability Program: Room Temperature
Packaging Information :			Container: ~~~		Schedule: 0, 3, 6, 9, 12, 18, 24, 36 mos.
Stability Testing Information:			Closure/Liner: ~~~		Storage Conditions: 25 ± 2°C / 60 ± 5% R.H.
Project Purpose:			Filler: N/A Desiccant: ~~~ Temperbond: Present		Station ID: ECC 10 Samples: UP

TEST & METHODS	SPECIFICATIONS	INITIAL Date: RESULTS 1 2 3 4 5 6	MONTH Date: RESULTS 1 2 3 4 5 6	MONTH Date: RESULTS 1 2 3 4 5 6	MONTH Date: RESULTS 1 2 3 4 5 6
Dissolution <0021.11>	1 hours: ~~~				
	Range				
	4 hours: ~~~				
	Range				
	12 hours: NLT ~~~				
	Range				

Reviewed by: Date:

APPEARS THIS WAY
ON ORIGINAL

Current Interim Stability Report
for
Nifedipine CC Extended Release 30 mg Tablets in 1000's
List No. B32B1SH

Project:		Product: Nifedipine CC Extended Release 30 mg Tablets in 1000's	List No.: B32B1SH	Lot No:
	Mfg / Test Site	Start Date	Active Drug Sub. Mfr: ~	Bulk Tablet Lot No.:	Coated Tablet Lot No.:
Manufacturing Information:			Active Drug Sub. Lot#:		Coated Tablet Batch Size:
Tabletting Information :			Tablet Description: Mustard yellow film coated tablets with no discoloration and "B" on one side and "30" on the other		Stability Program: Room Temperature
Packaging Information :			Container: ~		Schedule: 0, 3, 6, 9, 12, 18, 24, 36 mos.
Stability Testing Information:			Closure/Liner/Seal ~		Storage Conditions: 25 ± 2°C / 60 ± 5% R.H.
Project Purpose:			Film: N/A Desiccant: ~	Temperbead: Present	Station ID: ECC 10 Samples: UP

TEST & METHODS	SPECIFICATIONS	INITIAL Date:	MONTH Date:	MONTH Date:	MONTH Date:
Tablet Appearance <0006.00>	Mustard yellow, film coated tablets with no discoloration and "B" on one side and "30" on the other side				
Potency <0022.07>	~				
~	NMT ~				
~	NMT ~				
Individual Impurities <0022.07>	NMT ~ for any unspecified impurity				
Total Impurities <0022.07>	NMT ~				
Dissolution <0021.11>	1 hours: ~				
	Range				
	4 hours: ~				
	Range				
	12 hours: NLT ~				
	Range				
Moisture content <0009.01>	NMT ~				

Reviewed by: Date:

THIS WAY
ON ORIGINAL

Project:		Product: Nifedipine CC Extended Release 30 mg Tablets in 1000's		List No.: B32B1SH	Lot No:
	Mfg / Test Site	Start Date	Active Drug Sub. Mfr: ~~~	BMB Tablet Lot No:	Coated Tablet Lot No.:
Manufacturing Information:			Active Drug Sub. Lot#:		Coated Tablet Batch Size:
Tabletting Information:			Tablet Description: Mustard yellow film coated tablets with no discoloration and '6' on one side and '30' on the other		Stability Program: Room Temperature
Packaging Information:			Container: ~~~		Schedule: 0, 3, 6, 9, 12, 18, 24, 36 mos.
Stability Testing Information:			Closure/liner/seal: ~~~		Storage Conditions: 25 ± 2°C / 40 ± 5% RH
Project Purpose:			Filler: N/A Desiccant: ~~~	Temperband: Present	Station ID: ECC 10 Samples: UP

TEST & METHODS	SPECIFICATIONS	INITIAL Date: RESULTS						MONTH Date: RESULTS						MONTH Date: RESULTS						MONTH Date: RESULTS					
		1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6
Dissolution <0021.11>	1 hours: ~~~																								
	Range																								
	4 hours: / ~~~																								
	Range																								
	12 hours: NLT ~~~																								
	Range																								

Reviewed by: Date:

APPEARS THIS WAY
ON ORIGINAL

(this approval summary supersedes the approval summary dated 8-30-00)

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

ANDA Number: **75-269** Date of Submission: **November 22, 2000**

Applicant's Name: **Biovail Laboratories Incorporated**

Established Name: **Nifedipine Extended-release Tablets USP, 30 mg and 60 mg**

APPROVAL SUMMARY

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: 100s, 300s, 1000s
Satisfactory, in FPL, as of November 22, 2000 submission. (30 mg)
Satisfactory in FPL as of July 31, 2000 submission. (60 mg)

Professional Package Insert Label:
Satisfactory, in FPL, as of November 22, 2000 submission. (30 mg)
Satisfactory in FPL as of July 31, 2000 submission. (60 mg)

Revisions Needed Post Full Approval: May add "USP" to the established name; add "The USP Drug Release Test number is pending." as the last sentence of the DESCRIPTION section (the firm has done this for the 30 mg PI). **These changes can be done and reported in an annual report. The firm has committed to make these changes after 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) Tablet

NDA Firm: Bayer Corporation, Pharmaceutical Division

Date of Approval of NDA Insert and supplement # 3/29/96 (S-005)

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: Adalat CC approved container labels in folder.

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured.			

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

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

FOR THE RECORD: (portions taken from previous review)

1. Review based on the labeling of the listed drug Adalat® CC which was approved March 29, 1996 and revised February 1996. (Note: that for the record, the last SLP was listed as July 7, 1994, however, a SCP was done on March 29, 1996 concerning efficacy and apparently a labeling review was completed and approved at that same time.)

2. Patent expires on Adalat® CC Tablets patent (#4892741) on June 8, 2008 and patent (#5264446) on November 23, 2010. Biovail Laboratories Incorporated filed paragraph 4. For these patents, there is no exclusivity listed.

3. Storage/Dispensing Conditions:

   NDA: Store below 86°F(30°C)
   ANDA: Store below 30°C(86°F)
   USP: Not applicable

4. Scoring:

   NDA: Not specified.
   ANDA: Unscored.

5. Product Line:

   The innovator markets their product in bottles of 100s, 1000s, 5000s and unit dose packages of 100 tablets.

   The applicant proposes to market their product in bottles of 100s, 300s and 1000s tablets.

6. The tablet imprintings have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). Page 10745 of vol 1.31.

7. Inactive Ingredients:

   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 10226, vol 1.2.

8. All manufacturing will be performed by Biovail Corporation International. Manufactured for Biovail Laboratories Incorporated. See pages 10278, volume 1.2.

9. Container/Closure:

Container used is —— Closure system used for bottles of 100 and 300 is (CRC). Closure system used for bottles of 1000 is (non-CRC). See pages 10678 of volume 1.31.

10. [redacted]

11. We will be approving both the 30 mg and the 60 mg strengths. The 30 mg and 60 mg tablets have separate inserts and initially the firm will only be marketing the 60 mg strength.

Date of Review: 11-27-00 **Date of Submission:** 11-22-00

Primary Reviewer: Adolph Vezza /S/ **Date:** 11/27/00

Team Leader: Charlie Hoppes /S/ **Date:** 11/27/00

cc:

ANDA: 75-269
DUP/DIVISION FILE
HFD-613/AVezza/CHoppes (no cc)
aev/11/27/00|V:\FIRMSAM\BIOVAIL\LTRS&REV\75269.APL2
Review

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Biovail Laboratories Incorporated	November 9, 2000
TELEPHONE NO. *(Include Area Code)* (703) 995-2400	**FACSIMILE (FAX) Number** *(Include Area Code)* (703) 995-2444

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*

Chelston Park, Building 2
Collymore Rock
St. Michael, BHI
Barbados, WI

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

John Dubeck, Agent for Biovail Laboratories Inc.
Keller and Heckman
1001 G Street, N.W., Suite 500 West
Washington, D.C. 20001

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Nifedipine Extended Release Tablets 30 mg and 60mg	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*: Dimethyl 1,4-dihydro-2, 6-dimethyl-4-(o-nitrophenyl)-3,5-pyridinedicarboxylate

CODE NAME *(If any)*: B32

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	30 mg and 60 mg	Oral

(PROPOSED) INDICATION(S) FOR USE: Please see Attachment A

APPLICATION INFORMATION

APPLICATION TYPE (check one)
- ☐ NEW DRUG APPLICATION (21 CFR 314.50)
- ☒ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
- ☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE
- ☐ 505 (b) (1)
- ☐ 505 (b) (2)
- ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug: Adalat CC

Holder of Approved Application: Bayer Corporation, Pharmaceutical Division

TYPE OF SUBMISSION (check one)
- ☐ ORIGINAL APPLICATION
- ☒ AMENDMENT TO A PENDING APPLICATION
- ☐ RESUBMISSION
- ☐ PRESUBMISSION
- ☐ ANNUAL REPORT
- ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT
- ☐ SUPAC SUPPLEMENT
- ☐ EFFICACY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☒ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT
- ☐ OTHER

REASON FOR SUBMISSION: Response to Fax Amendment of November 6, 2000

PROPOSED MARKETING STATUS (check one)
- ☒ PRESCRIPTION PRODUCT (Rx)
- ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED: 1

THIS APPLICATION IS
- ☒ PAPER
- ☐ PAPER AND ELECTRONIC
- ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Please see Attachment A.

References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

Please see Attachment B.

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☒	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (k)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
John B. Dubeck	John B. Dubeck (U.S. Agent)	November 9, 2000.

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
Keller and Heckman LLP, 1001 G Street, NW, Ste 500-W, Washington, DC 20001	(202) 434-4125

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Dr., Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

FORM FDA 356h (4/00)

19 Pages

BIOVAIL TECHNOLOGIES LTD.

Fax Transmittal Sheet

14555 AVION PARKWAY
CHANTILLY, VA 20151

TO: Document Control Room.

FROM:

COMPANY: FDA Office of Generic Drugs

DATE: Nov 9/00

FAX NUMBER: (301) 827-4337

TOTAL NO. OF PAGES INCLUDING COVER: 18

PHONE NUMBER:

SENDER'S FAX NUMBER: (703) 995-

RE: ANDA 75-269

SENDER'S PHONE NUMBER: (703) 995-

☐ URGENT ☐ FOR REVIEW ☐ PLEASE COMMENT ☐ PLEASE REPLY ☐ PLEASE RECYCLE

FAX AMENDMENT.

FORM FDA 356h – ATTACHMENT A

Nifedipine Extended-Release Tablets, 30 mg and 60 mg

[redacted]

[redacted]	**Contact:** See Supplier below **Telephone:** See Supplier below **DMF No.:** [redacted] **Inspection:** Ready
[redacted]	**Contact:** [redacted] **Telephone:** [redacted]

[redacted]

Manufacturer:

Biovail Corporation International 100 Lifesciences Parkway P.O. Box 21390 Steinbach, Manitoba Canada R0A 2T3	**Contact:** Larry Thiessen **Telephone:** (204) 326-9000 **Inspection:** Ready

Outside Testing Facilities:

[redacted]	**Contact:** [redacted] **Telephone:** [redacted] **Inspection:** Ready
[redacted]	**Contact:** [redacted] **Telephone:** [redacted] **Inspection:** Ready
[redacted]	**Contact:** [redacted] **Telephone:** [redacted] **Inspection:** Ready
[redacted]	**Contact:** [redacted] **Telephone:** [redacted] **Inspection:** Ready

FORM FDA 356h – ATTACHMENT B

Nifedipine Extended-Release Tablets, 30 mg and 60 mg

[redacted]

Nifedipine USP	
[redacted]	
Hydroxyethyl Cellulose (NF)	
Hydroxypropyl Methylcellulose	
Microcrystalline Cellulose NF	
Polyethylene Glycol 600 NF	

[redacted]

[redacted]	

APPEARS THIS WAY
ON ORIGINAL

Current Quality Standard Specification Form
for
Nifedipine ER Coated Tablets, 60 mg
List No. B32C106
Effective Date: November 9, 2000

APPEARS THIS WAY
ON ORIGINAL

BIOVAIL CORPORATION

QUALITY STANDARD SPECIFICATION FORM - TEST METHODS

FORM REVIEW: D Beddall	DATE: NOV 09/00
FORM APPROVAL (QA): [signature]	DATE: Nov. 9/00
FORM #: FQA-0107.H/B32C106	REV #: 08
SUPERSEDES DATE: SEP 18/00	

Lab #

MATERIAL:	Nifedipine ER Coated Tablets, 60mg			LIST NO:	B32C106
LOT NO.:		BATCH SIZE:		EFFECTIVE DATE:	NOV 0 9 2000
ACTIVE INGREDIENT:	Nifedipine	VENDOR:	TEVA	EXPIRY DATE:	
MFR SITE:		MFG START DATE		MFG FINISH DATE:	

#	TESTS AND METHODS	SPECIFICATIONS	RESULTS	LAB ANALYST/ REFERENCES
1.	DESCRIPTION <0006.00> Rev # ____	Round film coated mustard yellow tablets engraved with "B" on one side and "60" on the other side		
2.	PHYSICAL DEFECTS * <0006.00> Rev # ____	Critical: ____ Major: ____ Minor: ____		
3	POTENCY <0022.07> Rev #	____		
4.	IDENTIFICATION <0022.07> Rev #	Meets retention time of standard		
5.	IMPURITIES <0022.07> Rev # ____	____ NMT ____ ____ NMT ____ Total Impurities: NMT ____ NMT ____ for any unspecified impurity		
6.	CONTENT UNIFORMITY USP <905> <0022.07>	Min: ____ of LC Max: ____ of LC % RSD <		
7	DISSOLUTION <0021.11> Rev # ____ USP <724> Acceptance Table 1	1 Hour (60 mins): ____ Range 4 Hours (240 mins): ____ Range 12 Hours (720 mins): NLT ____ Range		
8.	____ CONTENT <0009.01> Rev #	NMT ____		
9.	____ CONTENT <0029.05> Rev #	NMT ____		

Comments: _____

Reviewed by (QC): _____ Date: _____

Approved by (QA): _____ Date: _____

BIOVAIL CORPORATION

QUALITY STANDARD SPECIFICATION FORM - TEST METHODS

FORM REVIEW: D.Beddall		DATE: NOV09/00	
FORM APPROVAL (QA):		DATE: Nov. 9/00	
FORM #: FQA-0107.H/B32C106	REV #: 08	SUPERSEDES DATE:	SEP 18/00

Lab #

MATERIAL:	Nifedipine ER Coated Tablets, 60mg			LIST NO:	B32C106
LOT NO.:		BATCH SIZE:		EFFECTIVE DATE:	NOV 0 9 2000
ACTIVE INGREDIENT:	Nifedipine	VENDOR:	TEVA	EXPIRY DATE:	
TYPE OF TESTING.	Full Testing ✓	Reduced Testing ☐	Re-Assay Testing ☐		
	BIOVAIL TESTING ✓	CONTRACT TESTING ☐			

Check one below	Lot or Batch Size	Sample Size	Critical: 0.01%		Major: 1.0%		Minor: 4.0%	
			Ac	Re	Ac	Re	Ac	Re
☐	10001 – 35000	315	0	1	7	8	21	22
☐	35001 – 150000	500	0	1	10	11	21	22
☐	150001- 500000	800	0	1	14	15	21	22
☐	500001 & over	1250	0	1	21	22	21	22
Sum of defects at 0.01% AQL								
Sum of defects at 1.0% AQL								
Sum of defects at 4.0% AQL								

If more than one defect is found on any individual tablet, identify below as per STM QC-0006.00

APPEARS THIS WAY
ON ORIGINAL

LAB ANALYST / REFERENCES	

Reviewed by (QC): _____ Date: _____

Approved by (QA): _____ Date: _____

Current Interim Stability Report
for
Nifedipine CC Extended Release 60 mg Tablets in 100's
List No. B32C1SF

BIOVAIL CORPORATION - Manufacturing Division

INTERIM STABILITY REPORT

Project:		Product: Nifedipine CC Extended Release 60 mg Tablets in 100's	List No.: B32C1SF	Lot No:
	Mfg / Test Site	Start Date	Active Drug Sub. Mfr: / Active Drug Sub. Lot#:	Bulk Tablet Lot No.:	Coated Tablet Lot No.:
Manufacturing Information:				Coated Tablet Batch Size:
Tableting Information :			Tablet Description: Mustard yellow film coated tablets with "B" on one side and "60" on the other	Stability Program: Room Temperature
Packaging Information :			Container:	Schedule: 0, 3, 6, 9, 12, 18, 24, 36 mos.
Stability Testing Information:			Closure/liner/seal:	Storage Conditions: 25 ± 2°C / 60 ± 5% R.H.
Project Purpose:			Filler: NA Desiccant: Tamper band: Present	Station ID: ECC 10 Samples: UP

TEST & METHODS	SPECIFICATIONS	INITIAL Date:	MONTH Date:	MONTH Date:	MONTH Date:
Tablet Appearance <0005.00>	Mustard yellow, film coated tablets with no discoloration and "B" on one side and "60" on the other side				
Potency <0022.07>					
	NMT				
	NMT				
Individual Impurities <0022.07>	NMT , for any unspecified impurity				
Total Impurities <0022.07>	NMT				
Dissolution <0021.11>	1 hours:				
	Range				
	4 hours:				
	Range				
	12 hours: NLT				
	Range				
content <0009.01>	NMT				

Reviewed by: Date:

APPEARS THIS WAY
ON ORIGINAL

BIOVAIL CORPORATION - Manufacturing Division

INTERIM STABILITY REPORT

Project:		Product: Nifedipine CC Extended Release 60 mg Tablets in 100's	List No.: B32C1SF	Lot No:
	Mfg / Test Site	Start Date	Active Drug Sub. Mfr.:	Bulk Tablet Lot No.:
Manufacturing Information:			Active Drug Sub. Lot#:	Coated Tablet Lot No.:
Tableting Information:			Tablet Description: Mustard yellow film coated tablets with "B" on one side and "60" on the other	Coated Tablet Batch Size:
Packaging Information:			Container:	Stability Program: Room Temperature
Stability Testing Information:			Closure/Inner seal:	Schedule: 0, 3, 6, 9, 12, 18, 24, 36 mos.
Project Purpose:			Filler: N/A Desiccant:	Storage Conditions: 25 ± 2°C / 60 ± 5% R.H.
			Impermeant: Present	Station ID: ECC 10 Samples: UP

TEST & METHODS	SPECIFICATIONS	INITIAL Date: RESULTS						MONTH Date: RESULTS						MONTH Date: RESULTS						MONTH Date: RESULTS					
		1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6
Dissolution <0021.11>	1 hours:																								
	Range																								
	4 hours:																								
	Range																								
	12 hours: NLT																								
	Range																								

Reviewed by: Date:

APPEARS THIS WAY
ON ORIGINAL

Current Interim Stability Report
for
Nifedipine CC Extended Release 60 mg Tablets in 300's
List No. B32C1SV

BIOVAIL CORPORATION - Manufacturing Division

INTERIM STABILITY REPORT

Project:		Product: Nifedipine CC Extended Release 60 mg Tablets In 300's	List No.: B32C1SV	Lot No:
	Mfg / Test Site	Start Date	Active Drug Sub. Mfr.:	Bulk Tablet Lot No.:	Coated Tablet Lot No.:
Manufacturing Information:			Active Drug Sub. Lot#:		Coated Tablet Batch Size:
Tabletting Information :			Tablet Description: Mustard yellow film coated tablets with "B" on one side and "60" on the other		Stability Program: Room Temperature
Packaging Information :			Container:		Schedule: 0, 3, 6, 9, 12, 18, 24, 36 mos.
Stability Testing Information:			Closure/Innerseal:		Storage Conditions: 25 ± 2°C / 60 ± 5% RH
Project Purpose:			Filler: N/A Desiccant:	Tamperband: Present	Station ID: ECC 10 Samples: UP

TEST & METHODS	SPECIFICATIONS	INITIAL Date:	MONTH Date:	MONTH Date:	MONTH Date:
Tablet Appearance <0006.00>	Mustard yellow, film coated tablets with no discoloration and "B" on one side and "60" on the other side				
Potency <0022.07>					
	NMT				
	NMT				
Individual Impurities <0022.07>	NMT for any unspecified impurity				
Total Impurities <0022.07>	NMT				
Dissolution <0021.11>	1 hours:	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
	Range				
	4 hours:	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
	Range				
	12 hours: NLT	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
	Range				
content <0009.01>	NMT				

Reviewed by: Date:

BIOVAIL CORPORATION - Manufacturing Division

INTERIM STABILITY REPORT

Project:		Product: Nifedipine CC Extended Release 60 mg Tablets in 300's			List No.: B32C1SV	Lot No:
	Mfg / Test Site	Start Date	Active Drug Sub. Mfr.:	Bulk Tablet Lot No.:		Coated Tablet Lot No.:
Manufacturing Information:			Active Drug Sub. Lot#:			Coated Tablet Batch Size:
Tableting Information :			Tablet Description: Mustard yellow film coated tablets with "B" on one side and "60" on the other			Stability Program: Room Temperature
Packaging Information :			Container:			Schedule: 0, 3, 6, 9, 12, 18, 24, 36 mos.
Stability Testing Information:			Closure/Innerseal:			Storage Conditions: 25 ± 2°C / 60 ± 5% R.H.
Project Purpose:			Filler: N/A	Desiccant:	Tamperband: Present	Station ID: ECC 10 Samples: UP

TEST & METHODS	SPECIFICATIONS	INITIAL Date: RESULTS						MONTH Date: RESULTS						MONTH Date: RESULTS						MONTH Date: RESULTS					
		1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6
Dissolution <0021.11>	1 hours:																								
	Range																								
	4 hours:																								
	Range																								
	12 hours: NLT																								
	Range																								

Reviewed by: Date:

1.3

Current Interim Stability Report
for
Nifedipine CC Extended Release 60 mg Tablets in 1000's
List No. B32C1SH

BIOVAIL CORPORATION - Manufacturing Division

INTERIM STABILITY REPORT

Project:		Product: Nifedipine CC Extended Release 60 mg Tablets in 1000's		List No.: B32C1SH	Lot No:
	Mfg / Test Site	Start Date	Active Drug Sub. Mfr:	Bulk Tablet Lot No.:	Coated Tablet Lot No.:
Manufacturing Information:			Active Drug Sub. Lot#:		Coated Tablet Batch Size:
Tabletting Information:			Tablet Description: Mustard yellow film coated tablets with "B" on one side and "60" on the other		Stability Program: Room Temperature
Packaging Information:			Container:		Schedule: 0, 3, 6, 9, 12, 18, 24, 36 mos.
Stability Testing Information:			Closure/Immersal:		Storage Conditions: 15 ± 2°C / 60 ± 5% R.H
Project Purpose:			Filler: N/A Desiccant:	Temperband: Present	Station ID: EOC 10 Samples: UP

TEST & METHODS	SPECIFICATIONS	INITIAL Date:		MONTH Date:		MONTH Date:		MONTH Date:	
Tablet Appearance <0006.00>	Mustard yellow, film coated tablets with no discoloration and "B" on one side and "60" on the other side								
Potency <0022.07>									
	NMT								
	NMT								
Individual Impurities <0022.07>	NMT any unspecified impurity								
Total Impurities <0022.07>	NMT								
Dissolution <0021.11>	1 hours: 10								
	Range								
	4 hours:								
	Range								
	12 hours: NLT								
	Range								
content <0009.01>	NMT								

Reviewed by: Date:

APPEARS THIS WAY
ON ORIGINAL

BIOVAIL CORPORATION - Manufacturing Division

INTERIM STABILITY REPORT

Project:		Product: Nifedipine CC Extended Release 60 mg Tablets in 1000's	List No.: B32C1SH	Lot No:
	Mfg / Test Site	Start Date	Active Drug Sub. Mfr: / Bulk Tablet Lot No.:	Coated Tablet Lot No.:
Manufacturing Information:			Active Drug Sub. Lot#:	Coated Tablet Batch Size:
Tabletting Information :			Tablet Description: Mustard yellow film coated tablets with '8' on one side and '60' on the other	Stability Program: Room Temperature
Packaging Information :			Container:	Schedule: 0, 3, 6, 9, 12, 18, 24, 36 mos.
Stability Testing Information:			Closure/Innerseal:	Storage Conditions: 25 ± 2°C / 60 ± 5% R.H.
Project Purpose:			Filler: N/A Desiccant: Temperband: Present	Station ID: ECC 10 Samples: UP

TEST & METHODS	SPECIFICATIONS	INITIAL Date: RESULTS						1 MONTH Date: RESULTS						2 MONTH Date: RESULTS						3 MONTH Date: RESULTS					
		1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6
Dissolution <0021.1I>	1 hours:																								
	Range																								
	4 hours:																								
	Range																								
	12 hours: NLT																								
	Range																								

Reviewed by: Date:

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY

RECORD OF TELEPHONE CONVERSATION

Called Mr. Kreppner to request that they update the release and stability specifications for the 60 mg product to include Bio recommended dissolution specifications. He said they had submitted such an amendment recently per telephone request from T. Ames. I told him that the amendment did not include the range for the 1 hour time point. He was not very happy about this. We discussed the results and I pointed out the results fall within the proposed range. He said he will have to discuss this with the production department as they have already implemented these changes.

He called back and left a message that they would like to receive a deficiency letter to confirm what the Agency requires.

DATE
October 25, 2000

ANDA NUMBER
75-269

IND NUMBER

TELECON

INITIATED BY	**MADE**
APPLICANT/ SPONSOR	X **BY TELE.**
X FDA	_ **IN PERSON**

PRODUCT NAME
Nifedipine ER Tablets USP

FIRM NAME
Biovail

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Wayne Kreppner
Reg. Affairs

TELEPHONE NUMBER
(703) 995-2280

SIGNATURE
Ubrani V. Venkataram

DIVISION OF Chemistry

/S/

10/27/00

cc: ANDA 75-269
Div. File

(this approval summary supersedes the review dated 8-25-00)
APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-269** Date of Submission: **July 31, 2000**

Applicant's Name: **Biovail Laboratories Incorporated**

Established Name: **Nifedipine Extended-release Tablets USP, 30 mg and 60 mg**

APPROVAL SUMMARY

Do you have 12 Final Printed Labels and Labeling? Yes/No - of the 60 mg strength only - which is up for full approval 11-29-00

Container Labels: 100s, 300s, 1000s
Satisfactory, in draft, as of April 22, 1999 submission. (30 mg)
Satisfactory in FPL as of July 31, 2000 submission. (60 mg)

Professional Package Insert Label:
Satisfactory, in draft, as of April 22, 1999 submission. (30 mg)
Satisfactory in FPL as of July 31, 2000 submission. (60 mg)

Revisions Needed Post Full Approval: Add "USP" to the established name; add "The USP Drug Release Test number is pending." as the last sentence of the DESCRIPTION section. **These changes can be done and reported in an annual report. The firm has committed to make these changes after 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) Tablet

NDA Firm: Bayer Corporation, Pharmaceutical Division

Date of Approval of NDA Insert and supplement # 3/29/96 (S-005)

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: Adalat CC approved container labels in folder.

Other Comments: The 30 mg strength is subject to unexpired "first-to-file" market exclusivity so we will be approving only the 60 mg strength for now.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.

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

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

FOR THE RECORD: (portions taken from previous review)

1. Review based on the labeling of the listed drug Adalat® CC which was approved March 29, 1996 and revised February 1996. (Note: that for the record, the last SLP was listed as July 7, 1994, however, a SCP was done on March 29, 1996 concerning efficacy and apparently a labeling review was completed and approved at that same time.)

2. Patent expires on Adalat® CC Tablets patent (#4892741) on June 8, 2008 and patent (#5264446) on November 23, 2010. Biovail Laboratories Incorporated filed paragraph 4. For these patents, there is no exclusivity listed.

3. Storage/Dispensing Conditions:

   NDA: Store below 86°F(30°C)
   ANDA: Store below 30°C(86°F)
   USP: Not applicable

4. Scoring:

   NDA: Not specified.
   ANDA: Unscored.

5. Product Line:

   The innovator markets their product in bottles of 100s, 1000s, 5000s and unit dose packages of 100 tablets.

   The applicant proposes to market their product in bottles of 100s, 300s and 1000s tablets.

6. The tablet imprintings have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). Page 10745 of vol 1.31.

7. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 10226, vol 1.2.

8. All manufacturing will be performed by Biovail Corporation International. Manufactured for Biovail Laboratories Incorporated. See pages 10278, volume 1.2.

9. Container/Closure:

Container used is —. Closure system used for bottles of 100 and 300 is (CRC). Closure system used for bottles of 1000 is (non-CRC). See pages 10678 of volume 1.31.

10. [redacted]

11. We will be approving only the 60 mg strength (on 11-29-00) because the 30 mg strength is subject to unexpired "first-to-file" market exclusivity. Both the 30 mg and the 60 mg strength tablets are the subject of this ANDA 75-269.

Date of Review: 8-29-00 **Date of Submission:** 7-31-00

Primary Reviewer: Adolph Vezza /S/ **Date:** 8/29/00

Team Leader: Charlie Hoppes /S/ **Date:** 8/30/00

cc:

ANDA: 75-269
DUP/DIVISION FILE
HFD-613/AVezza/CHoppes (no cc)
aev//8/29/00|V:\FIRMSAM\BIOVAIL\LTRS&REV\75269.APL
Review

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

ANDA Number: **75-269** Date of Submission: **July 31, 2000**

Applicant's Name: **Biovail Laboratories Incorporated**

Established Name: **Nifedipine Extended-release Tablets USP, 30 mg and 60 mg**

Labeling Deficiencies:

1. GENERAL COMMENT

   We encourage you to add "USP" to the established name on your container labels and insert labeling. This may be done in an annual report after approval of your drug product.

2. INSERT

   DESCRIPTION

   Add the statement "The USP Drug Release Test number is pending." as the last sentence of this section.

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

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

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

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

/S/

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

ANDA APPROVAL SUMMARY

ANDA: 75-269 DRUG PRODUCT: Nifedipine Tablets

FIRM: Biovail
#34 Iturregui Avenue
Carolina, Puerto Rico
USA 00983

DOSAGE FORM: Extended Release Tablets

STRENGTHS: 30 mg
60 mg

CGMP STATEMENT/EIR UPDATE STATUS:

CGMP statement (p. 10279) in original submission. Paragraph 306(k) certification submitted (p. 15).

EIR acceptable for drug product manufacturer and [redacted] 4/9/99.

Facilities included:

Manufacturing, testing, packaging, labeling, and stability testing:

Biovail Corporation International
Manufacturing Division
100 Life Science Parkway
Steinbach, Manitoba
Canada ROA 2T3

[redacted]

BIO STUDY:

Bioequivalence study conducted on 60 mg tablet Lot #97D052, batch size [redacted] tablets, was found acceptable by the Division of Bioequivalence per S. Pradhan, 11/6/98.

Waiver granted for the 30 mg product as it has been shown to be proportional to the 60 mg product.

In-vitro dissolution study was found acceptable. Firm's drug release specifications consistent with those of the Office of Bioequivalence.

VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

Drug substance is compendial. Drug product noncompendial. Methods for drug product found acceptable by the Northeast Regional Laboratory, APPEARS THIS WAY ON ORIGINAL Laboratory description of dosage form was the same as firm's.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?:

Stability for the following included:

Lot #	Batch Size	Sample	Test Conditions
97D052	——— tablets	100's	40°C/75% RH/3 months
		300's	25°C/60% RH/3 months
		1000's	
97D042	——— tablets	100's	40°C/75% RH/3 months
		300's	25°C/60% RH/3 months
		1000's	

Container/Closure system:

100's in ——— bottle, ———
plastic child resistant cap, ———

300's in ——— bottle, ———
plastic child resistant cap, ———

1000's in ——— bottle, ———

All container/closure systems are as described in the Container/Closure section.

Expiration date: 24 months based on accelerated stability data.

LABELING:

Description in package insert satisfactory for molecular structure, molecular formula, formula weight, inactive ingredients, product description and package size.

Professional labeling - satisfactory, A. Vezza, 5/5/99.

STERILIZATION VALIDATION (IF APPLICABLE):

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):

Bio batch: 60 mg product, Lot #97D052, batch size [redacted] tablets, stability data included.

DMF [redacted] satisfactory, G.J. Smith, 11/13/98, no amendments since then.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):

See above.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?:

Executed batch records for the 60 mg x [redacted] tablet batch Lot #97D052 and the 30 mg x [redacted] tablet batch Lot #97D042 (bio/stability batches) included. Blank batch records were submitted in the application for [redacted] for 30 mg x [redacted] tablets and 60 mg x [redacted] tablets. All scale-ups consistent with current Office policy. Proposed manufacturing processes are the same as the bio/stability batches.

CHEMIST: Glen Jon Smith /S/ 6/3/99 DATE: 5/11/99

SUPERVISOR: Ubrani Venkataram DATE: 5/18/99

F/T by pah/6/2/99
V:\firmsam\biovail\ltrs&rev\75269no3.sum

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

ANDA Number: **75-269** Date of Submission: **September 24, 1998**

Applicant's Name: **Biovail Laboratories Incorporated.**

Established Name: **Nifedipine Extended-release Tablets, 30mg**

Labeling Deficiencies:

1. GENERAL COMMENT:

   Please note that since [redacted] is being collapsed into this ANDA (75-269) all submissions addressing deficiencies relating to ANDA [redacted] must be submitted to ANDA 75-269. We refer you to our letter dated October 7, 1998, for further guidance.

2. CONTAINER 100s, 300s and 1000s.

   a. Satisfactory, in draft.

   b. We encourage you to differentiate your product strengths (30 mg and 60 mg) by boxing, contrasting colors, or some other means.

3. INSERT

   a. GENERAL

      We encourage you to locate the symbol "Rx only" to immediately below the title of the insert.

   b. DESCRIPTION

      "polyacrylic dispersion" rather than "[redacted]

Please revise your insert labeling, as instructed above, and submit container labels and insert labeling in final print, or in draft if you prefer.

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.

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.

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

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

ANDA Number: 75-359 Date of Submission: April 15, 1998

Applicant's Name: Biovail Laboratories Incorporated

Established Name: Nifedipine Extended-release Tablets, 60 mg

Labeling Deficiencies:

1. GENERAL COMMENTS:

   a. Section 126 of Title I of the FDA Modernization Act of 1997, amends Section 503(b)(4) of the Federal Food, Drug, and Cosmetic Act to require, at a minimum, that prior to dispensing, the label of prescription products contain the symbol "Rx only". A GUIDANCE FOR INDUSTRY entitled "Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 Elimination of Certain Labeling Requirements", was revised July 1998 and posted at Internet site: **http://www.fda.gov/cder/guidance/index.htm.** Please note that Section IV, "Frequently Asked Questions" offers guidance on placement of the symbol on all labels and labeling.

   b. "30°C (86°F)" rather than ——— throughout your labels and labeling.

2. CONTAINER 100s, 300s and 1000s

   a. See GENERAL COMMENTS above.

   b. Delete ———.

3. INSERT

   a. GENERAL COMMENTS

      i. There is no need to capitalize the established name unless required to by sentence structure.

ii. We encourage the use of "to" rather than a —— when expressing a range of values .

b. DESCRIPTION

i. First sentence - Nifedipine extended-release tablets are an ...

ii. ...-4-(*o*-nitrophenyl)... (italic "*o*").

iii. You may delete "— and "—— after the inactive ingredients.

iv. Please list the ingredient(s) of ——— —

v. Center the section title as seen in the other sections of the insert.

c. CLINICAL PHARMACOLOGY

Table - "—— rather than " —

d. INDICATIONS AND USAGE

Revise the section title as seen above.

e. PRECAUTIONS

i. General -- Hypotension, first sentence - ... of nifedipine extended-release tablets is ...

ii. Information for Patients - Nifedipine extended-release tablets are an ...

f. ADVERSE REACTIONS

i. Revise the section title as seen above.

ii. Last paragraph - ... alopecia, anemia ... (add comma).

iii. Add the following text as the last paragraph:

There have been rare reports of exfoliative or bullous skin adverse events (such as erythema multiforme, Stevens-Johnson Syndrome, and toxic epidermal necrolysis) and photosensitivity reactions.

g. HOW SUPPLIED

See GENERAL COMMENT (1)(b) above.

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

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.

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.

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

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

ANDA Number: 75-269 Date of Submission:12/9/97

Applicant's Name: Biovail Laboratories Incorporated.

Established Name: Nifedipine Extended-release Tablets, 30mg

Labeling Deficiencies:

1. GENERAL COMMENTS:

   Replace the [redacted] statement with the symbol "Rx only" or "℞ only". We refer you to the Guidance For Industry, "Implementation of Section 126, Elimination of Certain Labeling Requirements...", at the internet site, **http://www.fda.gov/cder/guidance/index.htm** for guidance.

2. CONTAINER- 100s, 300s and 1000s.

   a. Please note that "Extended-release Tablets" is a part of the established name. We encourage you to increase the prominence to be relatively comparable to the shaded "Nifedipine".

   b. Delete " [redacted] , which appears directly below established name, from principal display panel.

   c. ...below 30°C(86°F).

3. INSERT

   a. GENERAL

      i. It is preferable to use the term "to" rather than a ' [redacted] when expressing a range.

      ii. Please note that USAN names are common nouns and should be treated as such in the text of labeling (i.e., lower case). Upper case may be used when the USAN name stands alone as on

labels or on the title of the package insert.

b. DESCRIPTION

i. First paragraph, third sentence: The molecular formula is...

ii. Second paragraph, first sentence: Revise to be the same as the reference listed drug.

iii. Third paragraph: delete —and ~ throughout the text.

iv. Third paragraph, first sentence: In addition, each capsule contains the following inactive ingredients:...

v. Alphabetize the listing of inactive ingredients.

c. CLINICAL PHARMACOLOGY

i. (Sub-section: Pharmacokinetics and Metabolism), third paragraph:

....result in substantially higher... [delete'—,

ii. (Sub-section: Clinical Studies), Title of the Table:

...(mmHg)..[no space after "mm"]

d. PRECAUTIONS

Fifth paragraph, last sentence:

....positivity of this laboratory test,...[add the word "of"]

e. ADVERSE EXPERIENCES

i. Revise the section title to read "ADVERSE REACTIONS". We refer you to 21 CFR 201.57 (g).

ii. Last paragraph:

...alopecia, anemia...[add a comma after "alopecia"]

f. OVERDOSAGE

First paragraph, last sentence: please revise to read ...is not likely to be of any benefit. [add the word "of"]

e. HOW SUPPLIED

i. Revise " ——— to read "color".[note: it is preferable not to use British variants.]

ii. We ask you to specify "Markings" of your products as stipulated in 21 CFR 206.3.

iii. Please describe your drug products as "unscored".[i.e., ...as 30mg unscored, round film coated tablets.]

iv. See comment (c.) Under CONTAINER.

Please revise your labels and labeling, as instructed above, and submit in final print, or in draft if you prefer.

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.

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.

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

JUN 9 1998

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-269 APPLICANT: Biovail Lab., Inc.

DRUG PRODUCT:Nifedipine ER Tablet

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. The validation of assay method, without any stability data for nifedipine samples, standard and QC samples at -25°C and at room temperature, is incomplete.

2. The stability report should also contain the long-term stability data of samples covering at least a period equivalent to the actual sample storage duration. The study is considered incomplete until the stability data are found acceptable.

3. You should provide the first and last dates of sample analysis, and dates of nifedipine QC samples preparation.

4. In the single dose fasting study, subjects were enrolled on two separate occasions
(Study Dates of Group I: Period 1 dosing, 6/14/97;
Period 2 dosing, 6/21/97; and
Study Dates of Group II: Period 1 dosing, 6/21/97;
Period 2 dosing, 6/28/97), and therefore, an additional ANOVA model should be used to determine if the makeup group was significantly different from the first group with respect to the pharmacokinetic parameters of nifedipine. This model should include, group, sequence, sequence*group, subject(sequence*group), period(group), treatment, treatment*group.

5. Lot size of the test product used in the bioequivalence study should be provided.

6. The dissolution testing is acceptable. However, you should be advised to conduct in vitro comparative dissolution testing on the test and reference products of same lots used in the in

vivo bioequivalence study in the future. Your proposed dissolution specifications are acceptable.

Sincerely yours,

/S/

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-269

CORRESPONDENCE

ANDA 75-269 (30 mg)
ANDA ——— (60 mg)
ANDA 75-289 (60 mg)
ANDA ——— (30 mg)

Keller & Heckman
Attention: John Dubeck
U.S. Agent for: Biovail Laboratories Inc.
1001 G Street N.W.
Suite 500 West
Washington, DC 20001

OCT 7 1998

Dear Sir:

Reference is made to your abbreviated new drug applications (ANDAs) dated December 9, 1997, December 24, 1997, February 11, 1998 and April 15, 1998 for Nifedipine Extended-release Tablets.

It has been the Office of Generic Drugs (OGD) policy to collapse variations of certain drug products into a single application. OGD Policy and Procedure Guide (P&PG) #20-90 lays out the framework for collapsed submissions and describes the benefits to both FDA and the industry. This policy applies to solid oral dosage forms and injectable dosage forms and has been consistently followed since it became effective on October 1, 1990.

Biovail submitted four separate ANDAs for two different reference listed products of Nifedipine Extended-release Tablets. This was not in conformance with OGD P&PG #20-90. These submissions occurred on four different dates ranging from December 9, 1997 to April 15, 1998. All four ANDAs were accepted and filed as individual applications since it was not recognized that other strengths for these drug products had already been filed. Based on OGD P&PG #20-90 and to keep consistency in our filing process, the four ANDAs will be administratively collapsed into two ANDAs as outlined below.

ANDA ——— will be collapsed into ANDA 75-269 and will be given a filing date of December 11, 1997. All data from ANDA ——— will be considered a major amendment to ANDA 75-269.

ANDA ——— will be collapsed into ANDA 75-289 and will be given a filing date of February 5, 1998. All data from ANDA ———

The information in ANDAs [redacted] and [redacted] shall be merged into their respective ANDAs as outlined above. ANDA numbers [redacted] and [redacted] will be retired in accord with agency procedures.

For purposes of complying with the regulatory requirements related to paragraph IV patent certifications and subsequent 180 day exclusivity provisions, each product strength will retain its date of receipt from the individual submission as listed below.

ANDA 75-269 - December 11, 1997
ANDA [redacted] - April 17, 1998
ANDA 75-289 - February 5, 1998
ANDA [redacted] - February 12, 1998

If you have any questions, please contact Mr. Peter Rickman, Chief, Regulatory Support Branch at 301-827-5862.

Sincerely yours,

/S/ 10/7/98

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug and Evaluation and Research

ANDA 75-269

Biovail Laboratories Incorporated
Attention: Carmen Reyes
#34 Iturregui Ave.
Carolina, Puerto Rico
U.S.A 00983

JAN 9 1998

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Nifedipine Extended-release Tablets, 30 mg

DATE OF APPLICATION: December 9, 1997

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 11, 1997

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(I)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

  1) Each owner of the patent or the representative designated by the owner to receive the notice;

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a 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. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Peter Rickman, Chief Regulatory Support Branch, at (301)827-5862.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Tim Ames
Project Manager
(301) 827-5849

Sincerely yours,

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-269
DUP/Jacket
Division File
Field Copy
HFD-600/Reading File
HFD-610/J.Phillips
HFD-92
HFD-615/M.Bennett
HFD-324/M.Lynch

Endorsements:
HFD-615/P.Rickman, Chief, RSB/ /S/ date 1/8/98
HFD-615/D.Huie/PM/ /S/ date 1/6/98
HFD-647/UVenkataram date
x:\new\firmsam\biovail\ltrs&rev\75269.ack
FT/njg/1/6/98
ANDA Acknowledgment Letter!

BIOVAIL
BIOVAIL
BIOVAIL
BIOVAIL
BIOVAIL

09 December 1997

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855
USA

VIA FEDEX

Attention: Dr. Douglas Sporn
Office of Generic Drugs, CDER, FDA

RECEIVED
DEC 1 1 1997
GENERIC DRUGS

Re: Nifedipine Extended-release Tablets, 30 mg - ANDA (Code Name B32-30mg)

Dear Dr. Sporn,

In accordance with the provisions of Section 505(j) of the Federal Food, Drug and Cosmetic Act and Section 314.94 of 21 CFR, enclosed please find an Abbreviated New Drug Application for Nifedipine Extended-release Tablets, 30 mg for once daily administration. The listed drug used in the bioavailability / bioequivalence studies is the Adalat® CC manufactured by Bayer in USA. This product contains nifedipine, a calcium ion influx inhibitor (slow-channel blocker or calcium ion antagonist), and is indicated for the treatment of hypertension.

Biovail Laboratories Incorporated (BLI) in Barbados has sponsored the development of this product and is the ANDA holder. Biovail Laboratories Incorporated (BLI) in Puerto Rico is the US Agent for this application. Biovail Corporation International (BCI), Manufacturing Division, will manufacture the commercial product. Upon approval, BLI will market the product in the USA under the BLI labeling which is submitted in this ANDA. This ANDA submission has been prepared by BCI (Corporate) on behalf of BLI.

Biovail Laboratories Incorporated is the subsidiary of Biovail Corporation International. Biovail Laboratories Incorporated has its head office at Chelston Park, Building 2, Collymore Rock, St. Michael, BH1, Barbados, W.I., and its manufacturing site at Ave. Iturregui Street B Lot # 34, Sabana Abajo Industrial Park, Carolina, Puerto Rico, 00984, USA.

Biovail Corporation International (Corporate) is located at 2488 Dunwin Drive, Mississauga, Ontario, Canada L5L 1J9. Its manufacturing site is at 100 LifeSciences Parkway, Box 21390, Steinbach, Manitoba, Canada R0A 2T3.

BIOVAIL CORPORATION INTERNATIONAL
I:\projects\Nif-B32 (CC)\us\submission\ANDA\Original\30mg\cov
2488 DUNWIN DRIVE, MISSISSAUGA, ONTARIO, CANADA L5L 1J9 • TEL (416) 285-6000 FAX (416) 285-6499

/S/ 1/5/98
505(j)(2)(a)
acceptable for
filing

BIOVAIL
BIOVAIL
BIOVAIL
BIOVAIL
BIOVAIL

09 December 1997

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855
USA

VIA FEDEX

Attention: Dr. Douglas Sporn
Office of Generic Drugs, CDER, FDA

RECEIVED
DEC 11 1997
GENERIC DRUGS

Re: Nifedipine Extended-release Tablets, 30 mg - ANDA (Code Name B32-30mg)

Dear Dr. Sporn,

In accordance with the provisions of Section 505(j) of the Federal Food, Drug and Cosmetic Act and Section 314.94 of 21 CFR, enclosed please find an Abbreviated New Drug Application for Nifedipine Extended-release Tablets, 30 mg for once daily administration. The listed drug used in the bioavailability / bioequivalence studies is the Adalat® CC manufactured by Bayer in USA. This product contains nifedipine, a calcium ion influx inhibitor (slow-channel blocker or calcium ion antagonist), and is indicated for the treatment of hypertension.

Biovail Laboratories Incorporated (BLI) in Barbados has sponsored the development of this product and is the ANDA holder. Biovail Laboratories Incorporated (BLI) in Puerto Rico is the US Agent for this application. Biovail Corporation International (BCI), Manufacturing Division, will manufacture the commercial product. Upon approval, BLI will market the product in the USA under the BLI labeling which is submitted in this ANDA. This ANDA submission has been prepared by BCI (Corporate) on behalf of BLI.

Biovail Laboratories Incorporated is the subsidiary of Biovail Corporation International. Biovail Laboratories Incorporated has its head office at Chelston Park, Building 2, Collymore Rock, St. Michael, BH1, Barbados, W.I., and its manufacturing site at Ave. Iturregui Street B Lot # 34, Sabana Abajo Industrial Park, Carolina, Puerto Rico, 00984, USA.

Biovail Corporation International (Corporate) is located at 2488 Dunwin Drive, Mississauga, Ontario, Canada L5L 1J9. Its manufacturing site is at 100 LifeSciences Parkway, Box 21390, Steinbach, Manitoba, Canada R0A 2T3.

BIOVAIL CORPORATION INTERNATIONAL
I:\projects\Nif-B32 (CC)\us\submission\ANDA\Original\30mg\cove
2488 DUNWIN DRIVE, MISSISSAUGA, ONTARIO, CANADA L5L 1J9 • TEL (416) 285-6000 FAX (416) 285-6499

We trust that this ANDA is complete and satisfactory for filing and review by the Office of Generic Drugs. The Archival Copy, the Review Copy, and the Field Copy of this ANDA are included in this package that has been sent via Federal Express.

A total of 73 books are included in this submission. The contents are as follows:

1. Archival Copy :
   - Blue Jackets - 32 books
2. Review Copy :
   - Red Jackets (CMC) - 4 books
   - Orange Jackets (Bioequivalence) - 29 Books
3. Field Copy :
   - Burgundy Jackets (CMC) - 4 books
4. Copies of Non-Compendial Methods :
   - Red Jackets (CMC) - 2 separately bound copies
5. Copies of Sections 6.3 – 7.0
   - Blue Jacket - 1 separately bound copy
   - Orange Jacket - 1 separately bound copy
6. Diskettes - one diskette for each biostudy ; total of six diskettes (3 x Archive ; 3 x Review).
   Diskettes found in books: 2 of 32
   11 of 32
   16 of 32

If you have any questions or comments, please contact the undersigned at Biovail Corporation International, telephone number 1-416-285-6000 extension 418; fax number (905) 608-1616.

Sincerely yours,
BIOVAIL CORPORATION INTERNATIONAL

for:

Mimi Brennan, B.Sc., ART, CIM, P.Mgr.
Director Regulatory Affairs and Quality Assurance
(on behalf of Biovail Laboratories Incorporated)

Encl.

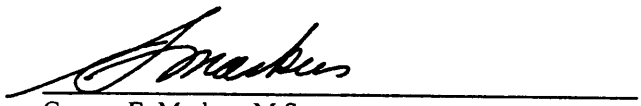
BIOVAIL CORPORATION INTERNATIONAL
2488 Dunwin Drive, Mississauga, Ontario L5L 1J9 • Tel: (416) 285-6000 · Fax (416) 285-6499

VIRUS-FREE CERTIFICATION

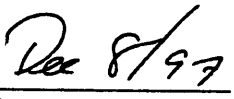
Biovail Corporation International certifies that any electronic files associated with this submission, namely:

- Study Number 1866-1 (B97-310PK-NIFB32)
- Study Number 1867-1 (B97-311PK-NIFB32)
- Study Number 1868-1 (B97-312PK-NIFB32)

are virus-free. The virus detection software used to in this certification is Norton AntiVirus version 2.0.1 for Windows 95. Any diskette found to contain a virus will be returned to the sponsor.



George E. Markus, M.Sc.
Manager, Regulatory Affairs
BIOVAIL CORPORATION INTERNATIONAL



Date

BIOVAIL
TECHNOLOGIES LTD.

FAX AMENDMENT

November 27, 2000

Gary Buehler
Director, Office of Generic Drugs (HFD-600)
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Nifedipine Extended-release Tablets, 30 mg, ANDA #75-269
November 27, 2000 Fax Amendment Letter

Dear Mr. Buehler,

Biovail Laboratories Inc. wishes to amend its application, ANDA #75-269, to include a response to the Division of Bioequivalence comment noted in the November 27, 2000 Agency communication.

Please find attached copies of the Quality Standard Specification Forms and Interim Stability report forms included in the April 22, 1999 Amendment to ANDA #75-269. These forms reflect the dissolution specifications recommended by the Division of Bioequivalence in correspondence received from the Agency on April 15, 1999 and November 27, 2000.

We trust that this amendment is acceptable for review and look forward to the full approval of this product on November 29, 2000.

If you have any questions or comments, please contact me at telephone number (703) 995-2400, or, at fax number (703) 995-2446.

Yours respectfully,
BIOVAIL TECHNOLOGIES LTD.

Kenneth S. Albert, Ph.D.
Vice President, Scientific Affairs
(on behalf of Biovail Laboratories Incorporated)

Encl.

labeling review
drafted 11/27/00

BIOVAIL
TECHNOLOGIES LTD.

MINOR AMENDMENT
VIA OVERNIGHT COURIER

November 22, 2000

ORIG AMENDMENT
N/FA

Gary Buehler
Director, Office of Generic Drugs (HFD-600)
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Nifedipine Extended-release Tablets, 30 mg, ANDA #75-269
Minor Amendment to Tentative Approval, dated June 29, 1999

Dear Mr. Buehler;

With reference to the tentative approval letter dated June 29, 1999, Biovail Laboratories Inc. is enclosing a Minor Amendment to ANDA #75-269, in anticipation of full approval of both the 30 mg and 60 mg strengths on November 29, 2000 (expiry of 30-month period provided for in section 505(j)(5)(B)(iii) of the Act). Although ANDA #75-269 includes the 30 mg and the 60 mg strengths, this minor amendment only contains labeling for the 30 mg strength as final printed labeling for the 60 mg strength was previously submitted under separate cover on July 31, 2000.

Biovail Laboratories has not made any changes to the Chemistry, Manufacturing and Controls terms of the application since the time of the tentative approval and has included 12 copies of final printed bottle labels and package insert for the 30 mg strength.

We trust that this amendment is complete and satisfactory for review by the Office of Generic Drugs. We look forward to your acceptance of this minor amendment and full approval of our application.

Should you have any questions or comments, please contact the undersigned at (703) 995-2280, or by fax at (703) 995-2444.

Respectfully,
On Behalf of Biovail Laboratories Incorporated

Wayne Kreppner, M.Sc.
Manager, Regulatory Affairs
BIOVAIL TECHNOLOGIES LIMITED

CENTER FOR DRUG
REC'D
NOV 24 2000
OGD
EVALUATION AND RESEARCH

Encl.

BIOVAIL TECHNOLOGIES LTD.
3701 Concorde Parkway, Chantilly, Virginia 20151
Tel: **(703) 995-2400** Fax: (703) 995-2490

BIOVAIL
TECHNOLOGIES LTD.

FAX AMENDMENT

November 9, 2000

Gary Buehler
Director, Office of Generic Drugs (HFD-600)
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/FA

Re: Nifedipine Extended-release Tablets, 60 mg, ANDA #75-269
November 6, 2000 Fax Amendment Letter

Dear Mr. Buehler,

Biovail Laboratories Inc. wishes to amend its application, ANDA # 75-269, to include a response to the Chemistry deficiency raised in the November 6, 2000 Agency communication.

Biovail has revised the Quality Standard Specification Forms and Interim Stability report forms to include the dissolution specifications as recommended by the Division of Bioequivalence. Copies of these revised forms are attached.

We trust that this amendment is acceptable for review and look forward to the full approval of this product on November 29, 2000.

If you have any questions or comments, please contact me at telephone number (703) 995-2400, or, at fax number (703) 995-2446.

Yours respectfully,
BIOVAIL TECHNOLOGIES LTD.

Wayne Kreppner, M.Sc.,
Manager, Regulatory Affairs
(on behalf of Biovail Laboratories Incorporated)

Encl.

BIOVAIL TECHNOLOGIES LTD.
3701 Concorde Parkway, Chantilly, Virginia 20151
Tel: (703) 995-2400 Fax: (703) 995-2490

BIOVAIL
TECHNOLOGIES LTD.

OVERNIGHT COURIER

TELEPHONE AMENDMENT

October 4, 2000

ORIG AMENDMENT
N/AM

Gary Buehler
Director, Office of Generic Drugs (HFD-600)
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Nifedipine Extended-release Tablets, 60 mg, ANDA #75-269
Telephone Amendment

Dear Mr. Buehler,

Further to the request received from Mr. Tim Ames on September 6, 2000, Biovail Laboratories Inc. is enclosing revised copies of the Quality Standard Specification Forms and Interim Stability Reports for Nifedipine Extended-release Coated Tablets, 60 mg. The dissolution specifications have been revised as indicated in the minor amendment filed by Biovail on June 30, 2000.

If you have any questions or comments, please contact me directly at telephone number (703) 995-2280 or at fax number (703) 995-2444.

Yours respectfully,
BIOVAIL TECHNOLOGIES LTD.

Wayne Kreppner, M.Sc.,
Manager, Regulatory Affairs
(on behalf of Biovail Laboratories Incorporated)

Encl.

CENTER FOR DRUG
REC'D
OCT - 5 2000
OGD
EVALUATION AND RESEARCH

BIOVAIL TECHNOLOGIES LTD.
3701 Concorde Parkway, Chantilly, Virginia 20151
Tel: **(703) 995-2400** Fax: (703) 995-2490

BIOVAIL

BIOVAIL

BIOVAIL

BIOVAIL

BIOVAIL

OVERNIGHT COURIER
FACSIMILE AMENDMENT

FA Noted,
To CMC Reviewer for review. /S/ 4/27/99

FA
NDA ORIG AMENDMENT

April 22, 1999

Douglas Sporn
Director, Office of Generic Drugs (HFD-600)
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Nifedipine Extended-release Tablets, 30 and 60 mg
Response to a Facsimile Amendment of April 15, 1999.
ANDA #75-269

Dear Mr. Sporn,

Biovail Laboratories Inc. wishes to amend its application, ANDA 75-269, to include responses to the Agency correspondence of April 15, 1999.

Biovail has responded to all questions posed by the Agency and has included updated Finished Product labeling.

The applicant is also affecting a minor change in the specifications for the Nifedipine raw material. In particular we are amending the specifications for particle size and specific surface area in order to fulfill our legal commitments. These non-compendial testing requirements have been included for in-house release purposes only. A justification and supporting documentation in the form of an updated Quality Standard Form and Certificate of Analysis from the Nifedipine raw material manufacturer are attached in Appendix 2.

If you have any questions or comments, please contact me at telephone number (416) 285-6000, extension 219 or, at fax number (905) 608-1616.

Yours respectfully,
BIOVAIL CORPORATION INTERNATIONAL

CENTER FOR DRUG
REC'D
APR 23 1999
OGD
EVALUATION AND RESEARCH

Wayne Kreppner, M.Sc.,
Manager, Corporate Regulatory Affairs
(on behalf of Biovail Laboratories Incorporated)

Encl.

7/19/2000 AM noted To TL earlier assignment ISI

BIOVAIL
TECHNOLOGIES LTD.

OVERNIGHT COURIER

MINOR AMENDMENT

June 30, 2000

BIOAVAILABILITY

Gary Buehler
Director, Office of Generic Drugs (HFD-600)
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AM

Re: Nifedipine Extended-release Tablets, 60 mg, ANDA #75-269
Minor Amendment to Tentative Approval, dated June 29, 1999

Dear Mr. Buehler,

With reference to the tentative approval letter dated June 29, 1999, Biovail Laboratories Inc. is enclosing a Minor Amendment to ANDA #75-269, in anticipation of full approval of this application. Although ANDA #75-269 includes the 30 mg and the 60 mg strengths, this minor amendment refers only to the pending full approval of the 60 mg strength as the 30 mg strength is subject to unexpired "first-to-file" market exclusivity.

Since the time of the tentative approval, the applicant has manufactured three validation batches at commercial scale. Based on the results from these validation lots, Biovail is requesting a revision to the tentatively approved dissolution specifications. Specifically, the applicant wishes to revise the dissolution specifications at the 1-hour time-point from [redacted] to NMT [redacted] and at the 4-hour time-point from [redacted].

In support of these new dissolution specifications the applicant has included the dissolution data from the three commercial scale validation batches. Other than the proposed revision to the dissolution specifications, the applicant has not made any changes to the Chemistry, Manufacturing and Controls terms of the application since the time of the tentative approval.

Should the Agency feel that this amendment does not qualify as a Minor Amendment and wish to re-classify it, the applicant will respectfully withdraw the amendment.

We look forward to the Agency's comments, if any, in due course. If you have any questions, please contact me directly at telephone number (703) 995-2280 or at fax number (703) 995-2280.

Yours respectfully,
BIOVAIL TECHNOLOGIES LTD.

Beth Fugerson for -

Wayne Kreppner, M.Sc.,
Manager, Regulatory Affairs
(on behalf of Biovail Laboratories Incorporated)

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUL 14 2000
OGD

Encl.

BIOVAIL
BIOVAIL
BIOVAIL
BIOVAIL
BIOVAIL

OVERNIGHT COURIER

September 24, 1998

MAJOR AMENDMENT

labeling pieces drafted 11/17/98
/S/

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Metro Park North II
Document Control Room
7500 Standish Place, Room 150
Rockville, MD 20855

DR. Labeling
THIS IS A MAJOR AMENDMENT
/S/

ATTN: Frank O. Holcombe, Jr., Ph.D.
Director, Division of Chemistry II

Re: ANDA # 75-269: Nifedipine Extended-release Tablets, 30 mg (code: B32): Reply to Non-Approvable Letter, dated June 30, 1998

Dear Dr. Holcombe,

Further to your letter of June 30, 1998, pursuant to 21 CFR 314.120, we enclose our responses to your questions in the order as they were presented.

Thank you for the opportunity to respond to your questions.

Kindest regards,
ON BEHALF OF BIOVAIL LABORATORIES INCORPORATED

Martin Levy

Martin Levy, M.Sc., FBIRA
Manager, Corporate Regulatory Affairs
Biovail Corporation International

Encl.

RECEIVED
SEP 28 1998
GENERIC DRUGS

BIOVAIL CORPORATION INTERNATIONAL
2488 DUNWIN DRIVE, MISSISSAUGA, ONTARIO, CANADA L5L 1J9 • TEL (416) 285-6000 FAX (416) 285-6499

BIOVAIL
BIOVAIL
BIOVAIL
BIOVAIL
BIOVAIL

OVERNIGHT COURIER

July 28, 1998

BIOEQUIVALENCY AMENDMENT

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

AMENDMENT
N/AB

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

Re: ANDA # 75-269: Nifedipine Extended-release Tablets 30 mg : Response to Bioequivalence Deficiency of June 9, 1998.

Dear Mr. Conner,

Further to your letter of June 9, 1998, we enclose our responses to your queries in the order as they were asked.

If you have any questions or comments, please contact me directly at telephone number (416) 285-6000, extension 213 or at fax number (905) 608-1616.

Kindest regards,
ON BEHALF OF BIOVAIL LABORATORIES INCORPORATED

Martin Levy.

Martin Levy, FBIRA
Manager, Worldwide Regulatory Affairs
Biovail Corporation International

Encl.

RECEIVED
JUL 29 1998
GENERIC DRUGS

I:\projects\Nif-B32 (CC)\us\submission\Amendment\30 mg-deficiency-resp-98\biostudy-june-98\Cov-letter-1.doc

BIOVAIL
BIOVAIL
BIOVAIL
BIOVAIL
BIOVAIL

NAI
Proof of notification and Corl action
ISI 4/10/98

6 April, 1998

PATENT AMENDMENT

NEW CORRESP
NC

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855
USA

Attention: Dr. Jerry Phillips
Director,
Division of Labeling and Program Support

Re: ANDA # 75-269
Nifedipine Extended-release Tablets, 30 mg – ANDA # 75-269
(Code Name B32-30mg)
Notification Issuance / Receipt of Notice ; Litigation

Dear Dr. Phillips,

This amendment is to notify FDA that

1. In accordance with 21 CFR 314.95(b), the Notice has been provided to each person identified under 314.95 (a) and the notice met the content requirements under 314.95 (c). As such, the applicant certifies that the Notice required pursuant to the provisions of 505(j)(2)(B)(ii) was sent to each of Bayer Corporation (USA), holder of the approved application of NDA No. 20-198, and to Bayer Aktiengesellschaft (Federal Republic of Germany), assignee of U.S. Patent No's. 4,892,741 and 5,264,446 for the reference listed Adalat CC brand of once-daily nifedipine on February 3, 1998, for delivery on February 5, 1997.

2. In Accordance with 21 CFR 314.95(e), Biovail is providing documentation of receipt of Notice by providing a copy of the return receipt by each person provided the notice:
   - Bayer Corporation (USA).
   - Bayer Aktiengesellschaft (Federal Republic of Germany). **Note:** As this site was overseas, permission was granted by Dr. Jerry Phillips on February 2, 1998 to provide a FedEx proof of delivery of the Notice for this product.

RECEIVED
APR 0 8 1998
GENERIC DRUGS

BIOVAIL CORPORATION INTERNATIONAL
I:\projects\Nif-B32 (CC)\us\submission\ANDA\patent-
2488 DUNWIN DRIVE, MISSISSAUGA, ONTARIO, CANADA L5L 1J9 • TEL (416) 285-6000 FAX (416) 285-6499

3. An action for patent infringement against Biovail concerning the controlled-release, once-daily nifedipine tablets has been filed by Bayer within the 45-day period as provided for in section 505 (j) (4) (B) (iii) of the Act.

Please find attached , in triplicate:

- A signed and dated FDA 356 h Form.
- A copy of the return receipt by each person provided the notice (i.e. from both Bayer Corporation, USA and Bayer Aktiengesellschaft, Federal Republic of Germany).
- A copy of the original Patent Certificate Notice that was sent to each of the above stated companies.

If you have any questions or comments, please contact the undersigned at Biovail Corporation International, telephone number 416-285-6000 ext. 212 ; fax number (905) 608-1616.

Sincerely,
BIOVAIL CORPORATION INTERNATIONAL
(on behalf of Biovail Laboratories, Inc.)

George E. Markus, M.Sc.
Manager, Regulatory Affairs

BIOVAIL CORPORATION INTERNATIONAL
2488 Dunwin Drive, Mississauga, Ontario L5L 1J9 • Tel: (416) 285-6000 · Fax (416) 285-6499