CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

76-070

Generic Name: Nifedipine Extended-release Tablets USP, 90 mg

Sponsor: Keller and Heckman LLP

Approval Date: August 16, 2002

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APPLICATION NUMBER: 76-070

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CENTER FOR DRUG
EVALUATION AND RESEARCH

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APPROVAL LETTER

ANDA 76-070

AUG 16 2002

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

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated December 21, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Nifedipine Extended-release Tablets USP, 90 mg.

Reference is also made to your amendments dated September 28, and November 01, 2001; and May 20, and June 24, 2002. We also acknowledge receipt of your correspondence dated June 22, 2001, addressing patent issues associated with this drug product.

The listed drug product (RLD) referenced in your application, Adalat CC Extended-release Tablets of Bayer Corp., is subject to periods of patent protection. As listed in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the "Orange Book", these patents 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 patent certifications under Section 505(j)(2)(A)(vii)(IV) of the Act stating that the '741 and '446 patents will not be infringed by your manufacture, use, or sale of the drug product. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately, unless an action is brought against Biovail Laboratories Inc. (Biovail) for infringement of one or more of the patents that are the subject of the certifications. This action must be brought against Biovail prior to the expiration of forty-five (45) days from the date the notice you provided to the NDA/patent holder under paragraph (2)(B)(i) was received. You have notified the agency that Biovail complied with the

requirements of Section 505(j)(2)(B) of the Act and that no action for patent infringement was brought against Biovail within the statutory forty-five day period.

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, 90 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug Adalat CC® Extended-release Tablets, 90 mg, 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 simulated gastric fluid (without enzyme), pH 1.2 with 0.5% SLS, at 37°C using USP 25 Apparatus II (Paddle) at 100 rpm. The tests should meet the following "interim" specifications:
>
> > Not more than —— (Q) of the Labeled amount is dissolved in 1 hour;
> >
> > —— (Q') of the labeled amount is dissolved in 4 hours; and
> >
> > Not less than —— (Q") is dissolved in 12 Hours.

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.

With respect to 180-day generic drug exclusivity, we note that Biovail was the first applicant to submit a substantially complete ANDA containing Paragraph IV Certifications to the '741 and '446 patents for the 90 mg strength of this drug product. Therefore, with this approval Biovail is eligible for 180-days of market exclusivity for the 90 mg strength as provided for

under the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments) in Section 505(j)(5)(B)(iv) of the Act. Such exclusivity will begin to run on the date Biovail begins commercial marketing of the 90 mg strength.

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 this drug product in a prompt manner. Please submit correspondence to your application stating the date you commenced commercial marketing of this product.

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

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

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

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 FDA 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 FDA 2253 at the time of their initial use.

Sincerely yours,

/S/

Gary Buehler 8/16/02
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-070

Final Printed Labeling

Nifedipine Extended-release Tablets,USP

Rx only

For Oral use

LB-0023-00

Rev. 04/02

AUG 16 2002
APPROVED

DESCRIPTION

Nifedipine extended-release tablets, USP are an extended release tablet dosage form of the calcium channel blocker nifedipine. The product is provided as a general matrix tablet with a polymer coating. Nifedipine is 3,5-pyridinedicarboxylic acid, 1,4-dihydro-2, 6-dimethyl-4-(2-nitrophenyl)-dimethyl ester, $C_{17}H_{18}N_2O_6$, and has the structural formula:

Nifedipine is a yellow crystalline substance, practically insoluble in water but soluble in ethanol. It has a molecular weight of 346.3. Nifedipine extended-release tablets, USP contain 90 mg of nifedipine for once-a-day oral administration.

In addition, each tablet contains the following inactive ingredients: anhydrous lactose, ethylcellulose N-100, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, magnesium stearate, microcrystalline cellulose, opadry II white (titanium dioxide, polydextrose, hydroxypropyl methylcellulose 2910, triacetin, polyethylene glycol 8000), silicon dioxide, sodium lauryl sulphate. Contains FD&C yellow #5 (tartrazine) as a color additive.

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%-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 6-12 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 tablets are administered as multiples of 30 mg tablets over a dose range of 30 mg to 90 mg, the area under the curve (AUC) is dose proportional; however, the peak plasma concentration for the 90 mg dose given as 3 x 30 mg is 29% greater than predicted from the 30 mg and 60 mg doses.

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

Once daily dosing of nifedipine extended-release tablets under fasting conditions results in decreased fluctuations in the plasma concentration of nifedipine when compared to 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

changed 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.

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

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

Because hepatic biotransformation is the predominant route for the disposition of nifedipine, its pharmacokinetics may be altered in patients with chronic liver disease. Nifedipine extended-release 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%-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.

Co-administration of Nifedipine with grapefruit juice results in up to a 2-fold increase in AUC and C_{max}, due to inhibition of CYP3A4 related first pass metabolism.

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 mm Hg systolic), but sometimes larger. With nifedipine extended-release tablets, these decreases in blood pressure are not accompanied by any significant change in heart rate. Hemodynamic studies of the immediate release nifedipine formulation in patients with normal ventricular function have generally found a small increase in cardiac index without major effects on ejection fraction, left ventricular end-diastolic pressure (LVEDP) or volume (LVEDV). In patients with impaired ventricular function, most acute studies have shown some increase in ejection fraction and reduction in left ventricular filling pressure.

Electrophysiologic Effects

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

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).

This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

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 metab-

Other Interactions:

Grapefruit Juice: Co-administration of Nifedipine with grapefruit juice results in up to a 2-fold increase in AUC and C_{max} due to inhibition of CYP3A4 related first pass metabolism.

Co-administration of Nifedipine with grapefruit juice is to be avoided.

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, including stunted fetuses (rats, mice and rabbits), digital anomalies (rats and rabbits), rib deformities (mice), cleft palate (mice), small placentas and underdeveloped chorionic villi (monkeys), embryonic and fetal deaths (rats, mice and rabbits), prolonged pregnancy (rats; not evaluated in other species), and decreased neonatal survival (rats; not evaluated in other species). On a mg/kg or mg/m^2 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, increased cough, rales, pharyngitis
Special Senses: abnormal vision, amblyopia, conjunctivitis, diplopia, tinnitus
Urogenital/Reproductive: kidney calculus, nocturia, breast engorgement

The following adverse events have been reported rarely in patients given nifedipine in other formulations: allergenic hepatitis, alopecia, anemia, arthritis with ANA (+), depression, erythromelalgia, 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.

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 [illegible]

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.

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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 tablets 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 tablets is necessary, sound clinical practice suggests that the dosage should be decreased gradually with close physician supervision.

Care should be taken when dispensing nifedipine extended-release tablets to assure that the extended release dosage form has been prescribed.

Co-administration of Nifedipine with grapefruit juice is to be avoided (See Clinical Pharmacology and Precautions).

HOW SUPPLIED

Nifedipine extended-release tablets, USP are supplied as 90 mg round film coated tablets.

Strength	Color	Markings
90 mg	Yellow	90 mg unscored, round film coated tablets, engraved with "B" on one side and "90" on the other side.

Nifedipine extended-release tablets, USP are supplied in:

	Strength	NDC Code
Bottles of 100	90 mg	0093-1023-01
Bottles of 500	90 mg	0093-1023-05
Bottles of 1000	90 mg	0093-1023-10

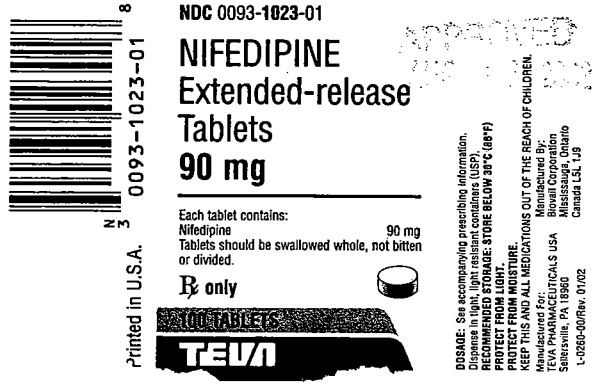
The tablets should be protected from light and moisture and stored below 30°C (86°F). Dispense in tight, light-resistant containers.

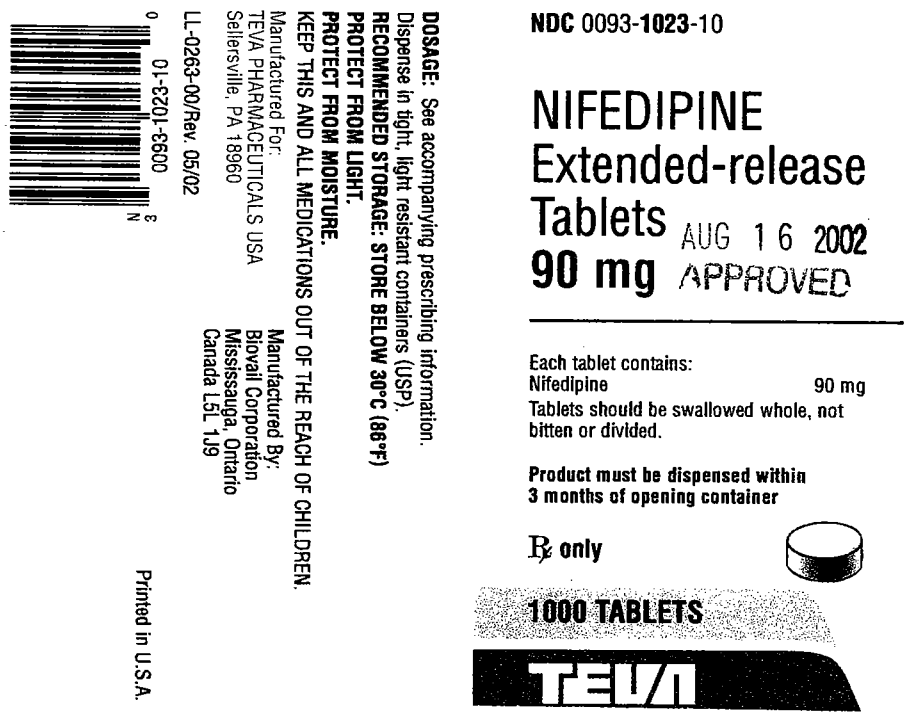
Manufactured by:
Biovail Corporation
Mississauga, ON CANADA
L5L 1J9

Manufactured for:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

LB-0023-00

Rev.04/02

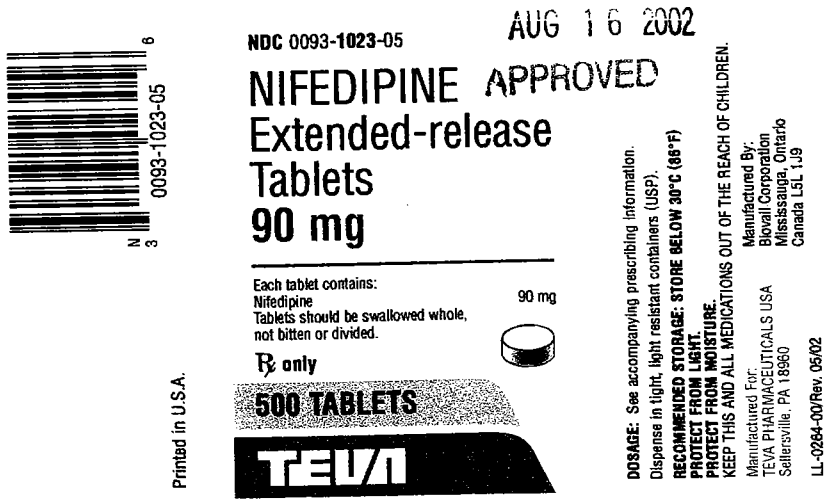




Biovail Laboratories Incorporated
Nifedipine Extended-release Tablets, USP, 90 mg

Minor Amendment – Final Printed Labeling
ANDA #76-070

Nifedipine Extended-release Tablets, USP, 90 mg
Bottles of 300



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-070

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 76-070

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

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

Phone: (202)-434-4125

4. LEGAL BASIS FOR SUBMISSION
Reference Listed drug product: Adalat CC® Tablets by Bayer approved in NDA #20-198. The firm filed a patent certification indicating the Orange Book's listed patents will not be infringed by the manufacture, use, or sale of the Nifedipine product for which this application is submitted. No exclusivities noted (p. 8). The proposed drug product contains the same active ingredient and has the same strength, dosage form, route of administration, indication, and usage as the reference listed drug.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Nifedipine Extended-Release Tablets, 90 mg

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

9. AMENDMENTS AND OTHER DATES:

Firm	Original Submission:	21-DEC-2000
	Amendment, Refuse to File:	07-FEB-2001

FDA Refusal to File 25-JAN-2001
Acceptable for Filing: 21-FEB-2001
Labeling Deficiency: 07-MAR-2001

10. PHARMACOLOGICAL CATEGORY
Antihypertensive

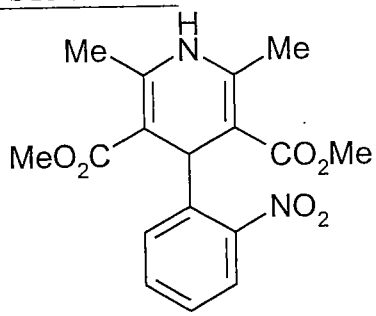
11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
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
Extended-Release Tablets

14. POTENCY
90 mg

15. CHEMICAL NAME AND STRUCTURE



Dimethyl 1,4-dihydro-2,6-dimethyl-4-(*o*-nitrophenyl)-3,5-pyridinedicarboxylate, $C_{17}H_{18}N_2O_6$
Molecular Weight: 346.34

16. RECORDS AND REPORTS
N/A

17. COMMENTS

[ ]

18. CONCLUSIONS AND RECOMMENDATIONS
Not-Approvable (MINOR)

19. REVIEWER: M. Scott Furness

DATE COMPLETED: 4/27/01

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ON ORIGINAL

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Page(s) of trade secret and /or confidential commercial information

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 76-070

3. NAME AND ADDRESS OF APPLICANT

Biovail Laboratories Incorporated
Chelston Park, Building 2
St. Michael, BHI
Barbados, WI

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

Phone: (202)-434-4125

4. LEGAL BASIS FOR SUBMISSION

Reference Listed drug product: Adalat CC® Tablets by Bayer approved in NDA #20-198. The firm filed a patent certification indicating the Orange Book's listed patents will not be infringed by the manufacture, use, or sale of the Nifedipine product for which this application is submitted. No exclusivities noted (p. 8). The proposed drug product contains the same active ingredient and has the same strength, dosage form, route of administration, indication, and usage as the reference listed drug.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Nifedipine Extended-Release Tablets, 90 mg

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

N/A

9. AMENDMENTS AND OTHER DATES:

Firm	Original Submission:	21-DEC-2000
	Amendment, Refuse to File:	07-FEB-2001
	Amendment, Notification/Receipt:	22-JUN-2001
	Labeling/CMC Amendment:	23-JUL-2001

FDA	Refusal to File	25-JAN-2001
	Acceptable for Filing:	21-FEB-2001
	Labeling Deficiency:	07-MAR-2001
	CMC Deficiency:	09-MAY-2001
	Bioequivalency Deficiency:	30-MAY-2001
	Labeling Approval:	30-JUL-2001

10. PHARMACOLOGICAL CATEGORY
Antihypertensive

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

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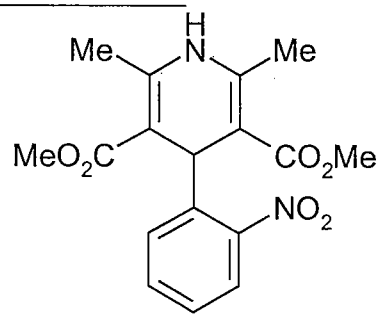
DMF [redacted]

13. DOSAGE FORM
Extended-Release Tablets

14. POTENCY
90 mg

15. CHEMICAL NAME AND STRUCTURE



Dimethyl 1,4-dihydro-2,6-dimethyl-4-(*o*-nitrophenyl)-3,5-pyridinedicarboxylate, $C_{17}H_{18}N_2O_6$
Molecular Weight: 346.34

16. RECORDS AND REPORTS
N/A

17. COMMENTS

[redacted]

drug product are compendial.

18. CONCLUSIONS AND RECOMMENDATIONS
Not-Approvable (MINOR)

19. REVIEWER: M. Scott Furness

DATE COMPLETED: 8/17/01

APPEARS THIS WAY
ON ORIGINAL

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Page(s) of trade secret and /or confidential commercial information

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 76-070

3. NAME AND ADDRESS OF APPLICANT

Biovail Laboratories Incorporated
Chelston Park, Building 2
St. Michael, BHI
Barbados, WI

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

Phone: (202)-434-4125

4. LEGAL BASIS FOR SUBMISSION

Reference Listed drug product: Adalat CC® Tablets by Bayer approved in NDA #20-198. The firm filed a patent certification indicating the Orange Book's listed patents will not be infringed by the manufacture, use, or sale of the Nifedipine product for which this application is submitted. No exclusivities noted (p. 8). The proposed drug product contains the same active ingredient and has the same strength, dosage form, route of administration, indication, and usage as the reference listed drug.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Nifedipine Extended-Release Tablets, 90 mg

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

N/A

9. AMENDMENTS AND OTHER DATES:

Firm	Original Submission:	21-DEC-2000
	Amendment, Refuse to File:	07-FEB-2001
	Amendment, Notification/Receipt:	22-JUN-2001
	Labeling/CMC Amendment:	23-JUL-2001

	Bioequivalency Amendment:	01-NOV-2001
	CMC Amendment:	01-NOV-2001
FDA	Refusal to File	25-JAN-2001
	Acceptable for Filing:	21-FEB-2001
	Labeling Deficiency:	07-MAR-2001
	CMC Deficiency:	09-MAY-2001
	Bioequivalency Deficiency:	30-MAY-2001
	Labeling Approval:	30-JUL-2001
	Bioequivalence Acceptance:	08-DEC-2001

10. PHARMACOLOGICAL CATEGORY
Antihypertensive

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

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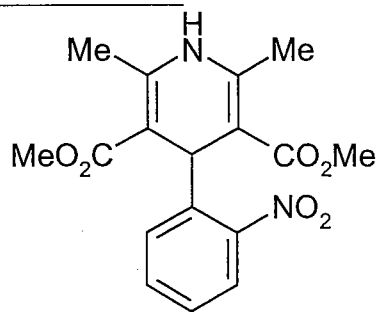
DMF [redacted]

13. DOSAGE FORM
Extended-Release Tablets

14. POTENCY
90 mg

15. CHEMICAL NAME AND STRUCTURE



Dimethyl 1,4-dihydro-2,6-dimethyl-4-(*o*-nitrophenyl)-3,5-pyridinedicarboxylate, $C_{17}H_{18}N_2O_6$
Molecular Weight: 346.34

16. RECORDS AND REPORTS
N/A

17. [redacted]

drug substance and drug product are compendial.

18. CONCLUSIONS AND RECOMMENDATIONS
Not-Approvable (MINOR)

19. REVIEWER: M. Scott Furness

DATE COMPLETED: 12/17/01

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Page(s) of trade secret and /or confidential commercial information

1. CHEMISTRY REVIEW NO. 4

2. ANDA # 76-070

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

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

Phone: (202)-434-4125

4. LEGAL BASIS FOR SUBMISSION
Reference Listed drug product: Adalat CC® Tablets by Bayer approved in NDA #20-198. The firm filed a patent certification indicating the Orange Book's listed patents will not be infringed by the manufacture, use, or sale of the Nifedipine product for which this application is submitted. No exclusivities noted (p. 8). The proposed drug product contains the same active ingredient and has the same strength, dosage form, route of administration, indication, and usage as the reference listed drug.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Nifedipine Extended-Release Tablets, 90 mg

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

9. AMENDMENTS AND OTHER DATES:

Firm	Original Submission:	21-DEC-2000
	Amendment, Refuse to File:	07-FEB-2001
	Amendment, Notification/Receipt:	22-JUN-2001
	Labeling/CMC Amendment:	23-JUL-2001

	Bioequivalency Amendment:	01-NOV-2001
	CMC Amendment:	01-NOV-2001
	CMC Amendment:	08-MAR-2002
FDA	Refusal to File	25-JAN-2001
	Acceptable for Filing:	21-FEB-2001
	Labeling Deficiency:	07-MAR-2001
	CMC Deficiency:	09-MAY-2001
	Bioequivalency Deficiency:	30-MAY-2001
	Labeling Approval:	30-JUL-2001
	Bioequivalence Acceptance:	08-DEC-2001

10. PHARMACOLOGICAL CATEGORY
Antihypertensive

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

DMF [redacted]
DMF [redacted]
DMF [redacted]
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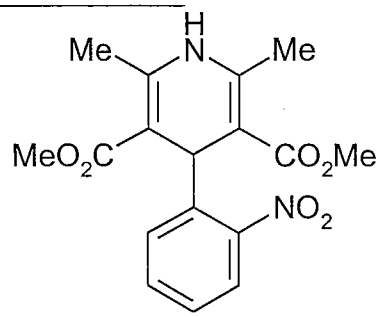
13. DOSAGE FORM
Extended-Release Tablets

14. POTENCY
90 mg

15. CHEMICAL NAME AND STRUCTURE



Dimethyl 1,4-dihydro-2,6-dimethyl-4-(*o*-nitrophenyl)-3,5-pyridinedicarboxylate, $C_{17}H_{18}N_2O_6$
Molecular Weight: 346.34

16. RECORDS AND REPORTS
N/A

17. COMMENTS

[ ]

18. CONCLUSIONS AND RECOMMENDATIONS
Not-Approvable (MINOR)

19. REVIEWER: M. Scott Furness

DATE COMPLETED: 4/29/02

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Page(s) of trade secret and /or confidential commercial information

1. CHEMISTRY REVIEW NO. 5

2. ANDA # 76-070

3. NAME AND ADDRESS OF APPLICANT

Biovail Laboratories Incorporated
Chelston Park, Building 2
St. Michael, BHI
Barbados, WI

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

Phone: (202)-434-4125

4. LEGAL BASIS FOR SUBMISSION

Reference Listed drug product: Adalat CC® Tablets by Bayer approved in NDA #20-198. The firm filed a patent certification indicating the Orange Book's listed patents will not be infringed by the manufacture, use, or sale of the Nifedipine product for which this application is submitted. No exclusivities noted (p. 8). The proposed drug product contains the same active ingredient and has the same strength, dosage form, route of administration, indication, and usage as the reference listed drug.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Nifedipine Extended-Release Tablets, 90 mg

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

N/A

9. AMENDMENTS AND OTHER DATES:

Firm	Original Submission:	21-DEC-2000
	Amendment, Refuse to File:	07-FEB-2001
	Amendment, Notification/Receipt:	22-JUN-2001
	Labeling/CMC Amendment:	23-JUL-2001

	Bioequivalency Amendment:	01-NOV-2001
	CMC Amendment:	01-NOV-2001
	CMC Amendment:	08-MAY-2002
FDA	Refusal to File	25-JAN-2001
	Acceptable for Filing:	21-FEB-2001
	Labeling Deficiency:	07-MAR-2001
	CMC Deficiency:	09-MAY-2001
	Bioequivalency Deficiency:	30-MAY-2001
	Labeling Approval:	30-JUL-2001
	Bioequivalence Acceptance:	08-DEC-2001

10. PHARMACOLOGICAL CATEGORY
Antihypertensive

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

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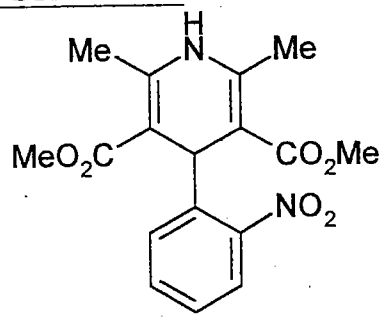
DMF [redacted]

13. DOSAGE FORM
Extended-Release Tablets

14. POTENCY
90 mg

15. CHEMICAL NAME AND STRUCTURE



Dimethyl 1,4-dihydro-2,6-dimethyl-4-(*o*-nitrophenyl)-3,5-pyridinedicarboxylate, $C_{17}H_{18}N_2O_6$
Molecular Weight: 346.34

16. RECORDS AND REPORTS
N/A

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS
Not-Approvable (MINOR)

19. REVIEWER:
M. Scott Furness

DATE COMPLETED:
5/29/02

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ON ORIGINAL

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Page(s) of trade secret and /or confidential commercial information

1. CHEMISTRY REVIEW NO. 6

2. ANDA # 76-070

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

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

Phone: (202)-434-4125

4. LEGAL BASIS FOR SUBMISSION
Reference Listed drug product: Adalat CC® Tablets by Bayer approved in NDA #20-198. The firm filed a patent certification indicating the Orange Book's listed patents will not be infringed by the manufacture, use, or sale of the Nifedipine product for which this application is submitted. No exclusivities noted (p. 8). The proposed drug product contains the same active ingredient and has the same strength, dosage form, route of administration, indication, and usage as the reference listed drug.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Nifedipine Extended-Release Tablets, 90 mg

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

9. AMENDMENTS AND OTHER DATES:

Firm	Original Submission:	21-DEC-2000
	Amendment, Refuse to File:	07-FEB-2001
	Amendment, Notification/Receipt:	22-JUN-2001

	Labeling/CMC Amendment:	23-JUL-2001
	Bioequivalency Amendment:	01-NOV-2001
	CMC Amendment II:	01-NOV-2001
	CMC Amendment III:	08-MAR-2002
	CMC Amendment IV:	08-MAY-2002
	CMC Amendment V:	24-JUN-2002
FDA	Refusal to File	25-JAN-2001
	Acceptable for Filing:	21-FEB-2001
	Labeling Deficiency:	07-MAR-2001
	CMC Deficiency I:	09-MAY-2001
	Bioequivalency Deficiency:	30-MAY-2001
	Labeling Tentative Approval:	30-JUL-2001
	CMC Deficiency II:	11-SEP-2001
	Bioequivalence Approval:	08-DEC-2001
	CMC Deficiency III:	01-FEB-2002
	CMC Deficiency IV:	02-MAY-2002
	CMC Deficiency V:	19-JUN-2002
	Labeling Approval:	24-JUN-2002

10. PHARMACOLOGICAL CATEGORY
Antihypertensive

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

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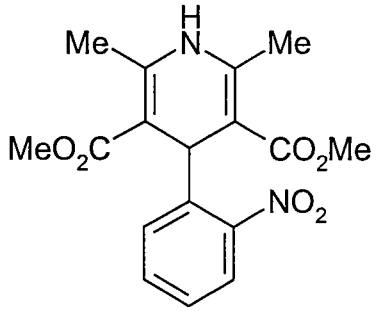
DMF [redacted]

13. DOSAGE FORM
Extended-Release Tablets

14. POTENCY
90 mg

15. CHEMICAL NAME AND STRUCTURE



Dimethyl 1,4-dihydro-2,6-dimethyl-4-(*o*-nitrophenyl)-3,5-pyridinedicarboxylate, $C_{17}H_{18}N_2O_6$
Molecular Weight: 346.34

16. RECORDS AND REPORTS
N/A

17. COMMENTS
This sixth cycle submission successfully addressed all deficiencies with respect to CMC. EER, Labeling and the Bioequivalency Studies have been found satisfactory. Methods validation will not be necessary since both the drug substance and drug product are compendial.

18. CONCLUSIONS AND RECOMMENDATIONS
Approval is recommended.

19. REVIEWER: M. Scott Furness

DATE COMPLETED: 7/15/02

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MINOR AMENDMENT

ANDA 76-070

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

MAY - 2 2002

TO: APPLICANT: Biovail Laboratories, Inc. TEL: 703-995-2280

ATTN: Wayne Kreppner, U.S. Agent FAX: 703-995-2444

FROM: Mark Anderson PROJECT MANAGER: 301-827-5848

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 21, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Nifedipien Extended-release Tablets, 90 mg.

Reference is also made to your amendment(s) dated: March 8, 2002.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__/__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Chemistry comments are provided.

MAY - 2 2002

38. Chemistry Comments to be Provided to the Applicant

ANDA: **76-070** APPLICANT: **Biovail Laboratories, Inc.**

DRUG PRODUCT: **Nifedipine Extended Release Tablets USP, 90 mg**

The deficiencies presented below represent MINOR deficiencies.

1. We again request that you update your list of test methods for drug product release and stability to include the dissolution methodology recommended by the Division of Bioequivalence.

2. We again request that you provide updated long-term stability data using the dissolution methodology recommended by the Division of Bioequivalence.

3. Please add a test for residual ——— to your drug substance release testing protocol.

4. DMF ——— remains inadequate. The DMF holder has been informed of the deficiencies. Please be aware that the application cannot be approved until deficiencies regarding the DMF have been addressed satisfactorily by the holder.

Sincerely yours,

/S/

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

FEB - 1 2002

38. Chemistry Comments to be Provided to the Applicant

ANDA: **76-070** APPLICANT: **Biovail Laboratories, Inc.**

DRUG PRODUCT: **Nifedipine Extended Release Tablets USP, 90 mg**

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Please update your list of test methods for drug product release and stability to include the dissolution methodology recommended by the Division of Bioequivalence.

2. Please provide updated long-term stability data using the dissolution methodology recommended by the Division of Bioequivalence.

3. DMF ——remains inadequate. The DMF holder has been informed of the deficiencies. Please be aware that the application cannot be approved until deficiencies regarding the DMF have been addressed satisfactorily by the holder.

Sincerely yours,

/s/

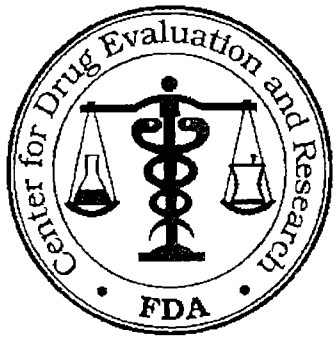
Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

MINOR AMENDMENT

ANDA 76-070

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

JUN 19 2002



TO: APPLICANT: Biovail Laboratories, Inc. TEL: 703-995-2280

ATTN: Wayne Kreppner, U.S. Agent FAX: 703-995-2444

FROM: Mark Anderson PROJECT MANAGER: 301-827-5789

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 21, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Nifedipine Extended-release Tablets, 90 mg.

Reference is also made to your amendment(s) dated: May 8, 2002.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__1__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Chemistry comments are provided.

JUN 19 2002

38. Chemistry Comments to be Provided to the Applicant

ANDA: **76-070** APPLICANT: **Biovail Laboratories, Inc.**

DRUG PRODUCT: **Nifedipine Extended Release Tablets USP, 90 mg**

The deficiencies presented below represent MINOR deficiencies.

1. Please provide appropriate validation data for your GC method used for residual determination of the drug substance.

2 DMF —— remains inadequate. The DMF holder has been informed of the deficiencies. Please be aware that the application cannot be approved until deficiencies regarding the DMF have been addressed satisfactorily by the holder.

Sincerely yours,

/S/

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

MINOR AMENDMENT

ANDA 76-070

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

MAY - 2 2002

TO: APPLICANT: Biovail Laboratories, Inc. TEL: 703-995-2280

ATTN: Wayne Kreppner, U.S. Agent FAX: 703-995-2444

FROM: Mark Anderson PROJECT MANAGER: 301-827-5848

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 21, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Nifedipien Extended-release Tablets, 90 mg.

Reference is also made to your amendment(s) dated: March 8, 2002.

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The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Chemistry comments are provided.

MAY - 2 2002

38. Chemistry Comments to be Provided to the Applicant

ANDA: **76-070** APPLICANT: **Biovail Laboratories, Inc.**

DRUG PRODUCT: **Nifedipine Extended Release Tablets USP, 90 mg**

The deficiencies presented below represent MINOR deficiencies.

1. We again request that you update your list of test methods for drug product release and stability to include the dissolution methodology recommended by the Division of Bioequivalence.

2. We again request that you provide updated long-term stability data using the dissolution methodology recommended by the Division of Bioequivalence.

3. Please add a test for residual ——— to your drug substance release testing protocol.

4. DMF ——/ remains inadequate. The DMF holder has been informed of the deficiencies. Please be aware that the application cannot be approved until deficiencies regarding the DMF have been addressed satisfactorily by the holder.

Sincerely yours,

/S/

for

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

MINOR AMENDMENT

ANDA 76-070

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

JUN 19 2002

TO: APPLICANT: Biovail Laboratories, Inc. TEL: 703-995-2280

ATTN: Wayne Kreppner, U.S. Agent FAX: 703-995-2444

FROM: Mark Anderson PROJECT MANAGER: 301-827-5789

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 21, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Nifedipine Extended-release Tablets, 90 mg.

Reference is also made to your amendment(s) dated: May 8, 2002.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (1 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Chemistry comments are provided.

JUN 19 2002

38. Chemistry Comments to be Provided to the Applicant

ANDA: **76-070** APPLICANT: **Biovail Laboratories, Inc.**

DRUG PRODUCT: **Nifedipine Extended Release Tablets USP, 90 mg**

The deficiencies presented below represent MINOR deficiencies.

1. Please provide appropriate validation data for your GC method used for residual ——— determination of the drug substance.

2. DMF —— remains inadequate. The DMF holder has been informed of the deficiencies. Please be aware that the application cannot be approved until deficiencies regarding the DMF have been addressed satisfactorily by the holder.

Sincerely yours,

/s/

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-070

BIOEQUIVALENCE REVIEW

Nifedipine CC Tablets, 90 mg
ANDA# 76-070
Reviewer: S. P. Shrivastava
v:\firmsam\biovail\ltrs&rev\76070a0302

Biovail Laboratories, Inc.
St. Michael, Barbados, WI
Submission Date:
March 8, 2002

REVIEW OF AN AMENDMENT:
REQUEST FOR CHANGE IN DISSOLUTION SPECIFICATIONS

The firm had submitted three *in vivo* bioequivalence studies (a single-dose fasting, a single-dose non-fasting, and a multiple dose non-fasting) and *in vitro* dissolution data comparing its drug, to Bayer's Adalat® CC, 90 mg, tablet (see reviews, SShrivastava, 5/22/01, 1/8/02). The studies were accepted and tentative dissolution specifications were recommended. In this amendment the firm is requesting a change in the dissolution specifications.

BACKGROUND

The Division recommended the following:

Tentatively, the dissolution testing should be conducted in 900 mL of simulated gastric fluid (without enzyme), pH 1.2 with 0.5% SLS, at 37 °C using USP 24 Apparatus II (Paddle) at 100 rpm. The test should meet the following specifications:

Not more than — (Q) of the labeled amount is dissolved in -	1 Hour
— (Q') of the labeled amount is dissolved in -	4 Hours
Not less than — (Q") is dissolved in -	8 Hours.

The firm has conducted dissolution testing according to the recommended method. However, it is experiencing difficulty meeting the specifications. Therefore, the firm is requesting a change in the specifications as follows:

Not more than — (Q) of the labeled amount is dissolved in -	1 Hour
— (Q') of the labeled amount is dissolved in -	4 Hours
Not less than — (Q") is dissolved in -	12 Hours.

COMMENTS

1. The firm has tested three stability (up to 18 months) lots. At one hour, all three lots passed the dissolution specifications. The mean dissolution ranged from 10 to 12% and the dissolution of individual units varied from —. The product still met the specifications (Table 1). Therefore, the specification of "not more than — at the one hour time point" is valid.

2. At the 4-hour sampling time point, the same three lots passed the dissolution specifications. The mean dissolution ranged from 40 to 43%, and the dissolution of individual units varied

from [redacted] The product still met the specifications (Table 1). Therefore, the specification of "[redacted], at the 4-hour time point" is valid.

3. At the eight-hour time point, a number of samples showed dissolution below the [redacted] level (range [redacted]. The mean dissolution ranged from 77 to 82%. The bioequivalence lot also showed a dissolution range of [redacted] at 8 hours (Table 1). Since the final time point should show dissolution of at least [redacted], and the drug is administered once a day, the final test time point of 12 hours is appropriate. The other USP dissolution tests for nifedipine ER tablets also have final test time points of 12 and 24 hours. At the 12-hour time point, the bioequivalence lot showed mean dissolution, dissolution range, and %CV, respectively, of 94.5, [redacted] and 4.9%. Based on these values, a dissolution specification of "not less than [redacted] at 12-hour time point" is appropriate.

RECOMMENDATION

1. Based on the dissolution data provided for the three stability lots, and bioequivalence lot, the dissolution specifications are modified. The dissolution testing should be conducted in 900 mL of simulated gastric fluid (without enzyme), pH 1.2 with 0.5% SLS, at 37 °C using USP 25 Apparatus II (Paddle) at 100 rpm. The test should meet the following specifications:

Not more than [redacted] (Q) of the labeled amount is dissolved in -	1 Hour
[redacted] (Q') of the labeled amount is dissolved in -	4 Hours
Not less than [redacted] (Q") is dissolved in -	12 Hours.

The firm should be informed of the comments #1-3 and the recommendation.

/S/

S. P. Shrivastava, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR /S/ Date 4/30/2002

Concur /S/ Date 5/2/02
Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
CDER, FDA

SPS/04-4-02/76070a0302
cc: ANDA #76-070 (Original, Duplicate) HFD-655 (SNerurkar, SShrivastava), Drug File, Division File.

Table 1. Summary of Dissolution

Method: Apparatus: Type 2 (Paddles) at 100 rpm.
Media: SGF with 0.5% SLS, pH 1.2
Volume: 900 mL
Tolerance (Q): 1 h – NMT ——; 4 h – ' —— ; 8 h – NLT '—

Lot #	Storage Period	Dosage Units	Sampling Time	Mean	Range	% CV	Out of Spec. Values
00G034	18 months	6	1 h	10.3		22.2	None
			4 h	40.1		9.8	None
			8 h	76.6		7.7	74, 68, 74
		12	1 h	10.7		21.1	None
			4 h	40.8		9.5	None
			8 h	77.4		6.5	74, 68, 74, 74, 78, 73
		24	1 h	10.8		18.7	None
			4 h	41.6		8.3	None
			8 h	78.9		5.6	74, 68, 74, 74, 78, 73, 77, 75, 78, 76, 79
00G035	18 months	6	1 h	10.4		8.9	None
			4 h	41.8		5.9	None
			8 h	79.9		5.2	72
		12	1 h	10.2		10.2	None
			4 h	41.4		4.7	None
			8 h	79.7		4.2	72, 79, 75, 78
00G036	18 months	6	1 h	11.6		12.2	None
			4 h	43.2		3.0	None
			8 h	81.5		1.2	None

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-070 APPLICANT: Biovail Laboratories, Inc.

DRUG PRODUCT: Nifedipine CC tablets, 90 mg

The Division of Bioequivalence has completed its review of your dissolution testing results on three lots and has the following recommendations:

1. You have tested three stability (up to 18 months) lots. At one hour, all three lots passed the dissolution specifications. The mean dissolution ranged from 10 to 12% and the dissolution of individual units varied from [redacted] The product still met the specifications. Therefore, the specification of "not more than [redacted] at the one hour time point" is valid.

2. At the 4-hour sampling time point, the same three lots passed the dissolution specifications. The mean dissolution ranged from 40 to 43%, and the dissolution of individual units varied from [redacted] The product still met the specifications. Therefore, the specification of [redacted] at the 4-hour time point" is valid.

3. At the eight-hour time point, a number of samples showed dissolution below the [redacted] level (range, [redacted]). The mean dissolution ranged from 77 to 82%. The bioequivalence lot also showed a dissolution range of [redacted] at 8 hours. Since the final time point should show dissolution of at least [redacted], and the drug is administered once a day, the final test time point of 12 hours is appropriate. The other USP dissolution tests for nifedipine ER tablets also have final test time points of 12 and 24 hours. At the 12-hour time point, the bioequivalence lot showed mean dissolution, dissolution range, and %CV, respectively, of 94.5, [redacted] and 4.9%. Based on these values, a dissolution specification of "not less than [redacted] at 12-hour time point" is appropriate.

4. 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 simulated gastric fluid (without enzyme), pH 1.2 with 0.5% SLS, at 37 °C using USP 25 Apparatus II (Paddle) at 100 rpm. The test should meet the following specifications:

   Not more than [redacted] (Q) of the labeled amount is dissolved in - 1 Hour
   [redacted] % (Q') of the labeled amount is dissolved in - 4 Hours
   Not less than [redacted] (Q") is dissolved in - 12 Hours.

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

Sincerely yours,

/S/

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

CC: ANDA 76-070
DIVISION FILE
HFD-651 / Bio Drug File
HFD-655 / S. P. Shrivastava

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Printed in final on 4/4/02

Endorsements: (Final with Da/S/ 4/25/02
HFD-655 / S.P.Shrivastav /S/ 4/25/02
HFD-655 / S. Nerurkar
HFD-650 / D. Conne /S/ 5/2/02

DISSOLUTION SPECIFICATION MODIFIED.....

1. AMENDMENT (DIS) .....Submission Date 3/8/02
.....Strength: 90 mg
.....OUTCOME: AC

OUTCOME DECISION: ACCEPTABLE

WinBio Comments: Dissolution specifications are modified.

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-070	SPONSOR : Biovail Laboratories, Inc.
DRUG AND DOSAGE FORM:	Nifedipine CC Tablets
STRENGTH(S) :	90 mg
TYPES OF STUDIES:	N/A
CLINICAL STUDY SITE(S):	N/A
ANALYTICAL SITE(S):	N/A

STUDY SUMMARY : BE studies are acceptable.

DISSOLUTION : Dissolution specifications are modified

DSI INSPECTION STATUS

Inspection needed: No	Inspection status:	Inspection results:
First Generic __No__ New facility __No_ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : S. P. Shrivastava, Ph.D. BRANCH : II

INITIAL : /S/ DATE : 4/25/02

TEAM LEADER : S. Nerurkar, Ph.D. BRANCH :

INITIAL : /S/ DATE : 4/25/2002

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

INITIAL : DATE : 5/2/02

Nifedipine CC Tablets, 90 mg
ANDA# 76-070
Reviewer: S. P. Shrivastava
v:\firmsam\biovail\ltrs&rev\76070o.N01

Biovail Laboratories, Inc.
St. Michael, Barbados, WI
Submission Date:
November 1, 2001 — AR

REVIEW OF BIOEQUIVALENCE STUDY AMENDMENT: DEFICIENCY RESPONSE

The firm had submitted three *in vivo* bioequivalence studies (a single-dose fasting, a single-dose non-fasting, and a multiple dose non-fasting) and *in vitro* dissolution data comparing its drug, to Bayer's Adalat® CC, 90 mg, tablet. The reviewer had cited few deficiencies (see review SShrivastava, 5/22/01). In this amendment the firm has responded to the deficiencies.

DEFICIENCIES/REVIEWER'S COMMENTS AND SPONSOR'S RESPONSE

DEFICIENCY 1. *In the fasting study, subjects were recruited in two groups (Group1 - Subject #1-54 dosed on 9/16/00 and 9/23/00, and Group 2 – Subject #55-74 dosed on 9/23/00 and 9/30/00). You should evaluate if there was any Group effect by adding Group term in the ANOVA analysis. Thus,*

*Model y = GRP SEQ GRP*SEQ SUB(GRP*SEQ) PER(GRP) TRT GRP*TRT*

Response

The firm has reanalyzed the data. There is no significant group effect.

Conclusion: The response is acceptable.

DEFICIENCY #2. *Once it is determined that there is no GRP*TRT effect (p>0.1), the term should be dropped from the analysis.*

Response

The firm has reanalyzed the data, and no group effect was found. The reviewer also checked the statistical analysis, and results obtained with and without Group*Treatment (GRP*TRT) term in the ANOVA model were as follows:

Parameter	With GRP*TRT Term			Without GRP*TRT Term		
		LS means*			LS Means*	
	90% CI	Test	Ref	90% CI	Test	Ref.
LAUC	84.53-95.81	1085.61	1206.34	86.40-96.31	1093.02	1198.17
LAUCI	81.78-94.14	1157.87	1319.56	84.86-95.44	1174.08	1304.64
LCmax	80.14-99.89	79.04	88.34	83.16-100.64	79.93	87.36

* Log-transformed data were converted to anti-log values.

Conclusion: The response is acceptable.

DEFICIENCY 3. *The firm has conducted dissolution in 6 media, SGF at pH 1.2 with 0.5% SLS.*

[redacted]

Response

The firm has confirmed that:

[redacted]

Table 1).

d. The volume of buffer media in each case was 900 mL.

Conclusion: The response is acceptable.

Table 1. Dissolution in [redacted]
Volume 900 mL; Apparatus 2 (Paddle) at 100 rpm

Time Hrs.	%Dissol	% Dissol.	%Dissol	Dissol.
	[redacted]		[redacted]	
	Test Product, Lot # 00D025			
	pH [redacted]	**pH** [redacted]	**pH** [redacted]	**pH** [redacted]
1	[redacted]			
2				
4				
8				
12				
16				
20				

[redacted]

Conclusion: The response is acceptable.

Table 2. Dissolution in SGF pH 1.2 with 0.5% SLS (A), [redacted] with 0.1% SLS (B), [redacted] (C), [redacted] with [redacted] SLS (D)
Volume 900 mL; Apparatus 2 (Paddle) at 100 rpm

Time Hrs.	%Dissol	% Dissol.	%Dissol	% Dissol.
	Test Product, Lot # 00D025			
	A	**B**	**C**	**D**
1	[redacted]	[redacted]	N/A	[redacted]
2	[redacted]	[redacted]	N/A	[redacted]
4	[redacted]	[redacted]	N/A	[redacted]
8	[redacted]	[redacted]	N/A	[redacted]
12	[redacted]	[redacted]	N/A	[redacted]
16	[redacted]	[redacted]	N/A	[redacted]
20	[redacted]	[redacted]	12	[redacted]

DEFICIENCY 5. [redacted]

Response

[redacted]

Conclusion: The response is acceptable.

Table 3. Dissolution in SGF pH 1.2 with 0.5% SLS (A), [illegible] with [illegible] SLS (B) Volume 900 mL; Apparatus 2 (Paddle) at [illegible]

Time Hrs.	% Dissol	% Dissol.
	Acetate Buffer	
	Test Product, Lot # 00D025	
	A	B
1	[illegible]	[illegible]
2	[illegible]	[illegible]
4	[illegible]	[illegible]
8	[illegible]	[illegible]
12	[illegible]	[illegible]
16	[illegible]	[illegible]
20	[illegible]	[illegible]

DEFICIENCY 6. *Based on available data, the firm should suggest a workable method for dissolution testing.*

Response: The firm suggests SGF at pH 1.2 (without enzyme) with 0.5% SLS, using Paddle at 100 rpm. It provides a dissolution of [illegible] in 8 hours.

Conclusion: Dissolution method is acceptable.

DEFICIENCY 7. *Firm should also refer to the following:*

a. *USP dissolution Test 1 and Test 2 for nifedipine extended release products (USP 24, Supplement 1, pages 2644-45, 2001).*
b. *Guidance for Industry: Extended Release Oral Dosage Forms - Development, Evaluation, and Application of in vitro/in vivo correlations.*

Response: The firm did refer to the publications during the development of the dissolution method. However, they have not provided data using USP Test 1 or Test 2.

Conclusion: The response is acceptable.

RECOMMENDATIONS

1. The *in vivo* bioequivalence study conducted under fasting conditions by Biovail Laboratories, Inc. on its nifedipine CC tablets, 90 mg, Lot # 00D025, comparing it to the reference product, Adalat® CC tablets, 90 mg, Lot # 8LB1, by Bayer, has been found to be acceptable by the Division of Bioequivalence.

2. The firm has previously conducted an acceptable bioequivalence study under nonfasting conditions on its nifedipine CC tablets, 90 mg, Lot # 00D025, comparing it to the reference product, Adalat® CC tablets, 90 mg, Lot # 8LB1.

3. The *in vitro* dissolution testing submitted by the firm on its nifedipine CC tablets, 90 mg, Lot # 00D025, comparing it to the reference product, Adalat® CC tablets, 90 mg, Lot # 8LB1, by Bayer, has been found to be acceptable.

4. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program.

   Tentatively, the dissolution testing should be conducted in 900 mL of simulated gastric fluid (without enzyme), pH 1.2 with 0.5% SLS, at 37 °C using USP 24 Apparatus II (Paddle) at 100 rpm. The test should meet the following specifications:

   Not ~~less~~ more than ___ (Q) of the labeled amount is dissolved in - 1 Hour
   ___ (Q') of the labeled amount is dissolved in - 4 Hours
   Not less than ___ (Q") is dissolved in - 8 Hours.

5. From the bioequivalence point of view, the firm has met the requirements of *in vivo* bioequivalence and *in vitro* dissolution testing, and the application is complete.

The firm should be informed of the recommendations.

/S/

S. P. Shrivastava, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR

/S/ Date 11/21/2001

Concur: /S/ Date 1/8/02
Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
CDER, FDA

SPS/11-16-01/76070o.N01
cc: ANDA #76-070 (Original, Duplicate) HFD-655 (SNerurkar, SShrivastava), Drug File, Division File.

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-070 APPLICANT: Biovail Laboratories, Inc.

DRUG PRODUCT: Nifedipine CC tablets, 90 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:

Tentatively, the dissolution testing should be conducted in 900 mL of simulated gastric fluid (without enzyme), pH 1.2 with 0.5% SLS, at 37 °C using USP 24 Apparatus II (Paddle) at 100 rpm. The test should meet the following specification:

Not less than (Q) of the labeled amount is dissolved in -	1 Hour
(Q') of the labeled amount is dissolved in -	4 Hours
Not less than (Q") is dissolved in -	8 Hours.

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

Sincerely yours,

/S/

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

CC: ANDA 76-070
DIVISION FILE
HFD-651 / Bio Drug File
HFD-655 / S. P. Shrivastava

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Printed in final on / /

Endorsements: (Final with Dates)
HFD-655 / S.P.Shrivastav /S/ 11/21/01
HFD-655 / S. Nerurkar
HFD-650 / D. Conner /S/ 1/8/02

/S/ 11/21/01

BIOEQUIVALENCY - INCOMPLETE .....

1. AMENDMENT (STF) .....Submission Date:11/1/01
CLINICAL: Biovail Contract Research .....Strength: 90 MG
ANALYTICAL: Biovail Contract Research OUTCOME: ..... AC

AMENDMENT (DIS) .....Submission Date 11/1/2001
.....Strength: 90 mg
.....OUTCOME: AC

OUTCOME DECISION: ACCEPTABLE

WinBio Comments: *In vivo* and *in vitro* studies are acceptable, and the application is complete.

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-070 BE Studies SPONSOR : Biovail Laboratories, Inc.

DRUG AND DOSAGE FORM : Nifedipine CC Tablets

STRENGTH(S) : 90 mg

TYPES OF STUDIES: Single-dose fasting, Single-dose nonfasting, and dissolution studies

CLINICAL STUDY SITE(S): Biovail Contract Research, Toranto, Canada

ANALYTICAL SITE(S) : Biovail Contract Research, Toranto, Canada

STUDY SUMMARY : BE studies are acceptable.

DISSOLUTION : Dissolution study is acceptable

DSI INSPECTION STATUS

Inspection needed: No	Inspection status:	Inspection results:
First Generic __No__ New facility __No_ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : S. P. Shrivastava, Ph.D. BRANCH : II

INITIAL :_ /S/ DATE : 11/21/01

TEAM LEADER : S. Nerurkar, Ph.D BRANCH :

INITIAL : /S/ DATE : 11/21/2001

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

INITIAL : /S/ DATE : 1/8/02

Nifedipine CC Tablets, 90 mg
ANDA# 76-070
Reviewer: S. P. Shrivastava
File Name: WD 76070SD.201

Biovail Laboratories, Inc.
St. Michael, Barbados, WI
Submission Date:
~~**December 21, 2000**~~ rea
February 7, 2001

REVIEW OF THREE BIOEQUIVALENCE STUDIES, AND DISSOLUTION DATA

The firm has submitted three *in vivo* bioequivalence studies (a single-dose fasting, a single-dose non-fasting, and a multiple dose non-fasting) and *in vitro* dissolution data comparing its drug, to Bayer's Adalat® CC, 90 mg, tablet. Since dissolution data in the original application were incomplete, the firm submitted an amendment to the application (Letter date, 02/07/01).

I. INTRODUCTION

Nifedipine is a dihydropyridine-derivative calcium-channel blocker, which exerts its pharmacologic effects by inhibiting calcium influx across the membranes of the myocardial and vascular smooth muscle cells. By inhibiting calcium influx across the slow calcium channels, nifedipine inhibits the contractile processes of cardiac and vascular smooth muscles, thereby dilating the main coronary and systemic arteries. Extended-release tablets (30 mg, 60 mg and 90 mg) have been reported to deliver the drug in the gastrointestinal tract at a constant rate of about 1.7, 3.4 and 5.1 mg/hour, respectively. Serum peak levels are attained in 2 hours and 6 hours with the immediate-release (IR) capsules and extended-release tablets, respectively. After steady-state, the bioavailability of the ER tablets has been reported to increase to about ⟶ Nifedipine is highly (92-98%) protein bound. It is completely metabolized in the liver to inactive metabolites. The elimination half-life is 2 to 5 hours.

The reference listed drug is Adalat^{R} CC Tablets, 90 mg (Bayer).

II. FINANCIAL DISCLOSURE

The sponsor has certified that the investigator(s), has/have not entered into any financial arrangement with the sponsor, has/have no proprietary interest in the product(s), or was/were recipient(s) of significant payments of other sorts.

III. SINGLE-DOSE FASTING STUDY (# 2400)

A. Study Information

Protocol #:	2400
IRB Approval:	Yes
Consent Form Signed:	Yes
Clinical Site:	Biovail Contract Research, Toranto, Canada
Analytical Site:	Biovail Contract Research, Toranto, Canada
Principal Investigator:	Paul Y. Tam, M.D., F.R.C.P., F.A.C.P.
Study Dates:	Group I, Period I: 9/16/00
	Group I, Period II: 9/23/00

	Group II, Period I: 9/23/00 Group II, Period II: 9/30/00
Analysis Dates:	10/3/00 – 10/25/00
Storage Period	39 Days
Study Design:	Randomized, Two-way, single dose, crossover design with 7-day washout period.
Randomization Scheme:	**Group 1. AB:** 1, 3, 4, 5, 7, 8, 11, 15, 18, 19, 20, 23, 24, 25, 26, 27, 28, 31, 33, 37, 42, 43, 44, 51, 52, 53, 54 **Group 1. BA:** 2, 6, 9, 10, 12, 13, 14, 16, 17, 21, 22, 29, 30, 32, 34, 35, 36, 38, 39, 40, 41, 45, 46, 47, 48, 49, 50 **Group 2, AB:** 57, 61, 62, 66, 67, 68, 69, 70, 71, 72 **Group 2, BA:** 55, 56, 58, 59, 60, 63, 64, 65, 73, 74
Treatments:	**A:** Nifedipine CC, 1 x 90 mg tablets; Biovail, Lot #00D025; Manuf. Date: 4/6/00; Lot size: ——— Assay: 98.3%; Content Uniformity: 97.9%, RSD 1.6% **B:** Adalat^{R} CC, 1 x 90 mg Tablets; Bayer; Lot #8LB1; Expiry Date: 12/00; Assay: 99.6%; Content Uniformity: 99.7%, RSD 0.9%
Formulation of Test Drug:	See Table 8.
Subjects and Dropouts:	74 Healthy, non-smoking male subjects were enrolled, 54 in Group I and 20 in Group II. Sixty-seven subjects completed the study. Subject # 27 and 35 were dismissed due to adverse reactions, Subjects 29, 44 and 67 withdrew on personal reasons, and Subjects 57 and 60 did not show up for Period II.
Housing:	Subjects were confined from evening before dosing until 48 hours after dosing.
Food/Water:	Fasted for 10 hours pre-dose and 4.5 hrs post-dose. At 4.5, 9.5, 24, 28.5 and 33.5 hrs. post-dose, caffeine-free and grapefruit-free standardized meals were provided. Water was given *ad libitum* until one hour pre-dose and one hour post-dose, except 240 mL during the drug administration.
Dosing:	Each treatment given with 240 mL water following a 10-hour fast.
Sampling Times:	Blood samples (7 mL) were collected at 0 hr (pre-dose), and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20, 24, 30, 36 and 48 hours post-dosing time points.

Health Monitoring: Health status, vital signs (heart rate, blood pressure) and ECG monitoring were carried out periodically according to schedule.

B. Study Results

1. Clinical

Drop-outs: Out of 74 subjects, 67 subjects completed the study. Subject # 27 and 35 were dismissed due to adverse reactions, Subjects 29, 44 and 67 withdrew on personal reasons, and Subjects 57 and 60 did not show up for Period II.

Adverse Events: All of the adverse events were considered mild or moderate in severity.

Adverse Event	Test	Reference
Headache	31	34
Shoulder Pain	1	0
Sinus Bradycardia	5	3
Dizziness	2	5
Rash on Arm	1	0
BP Outside Unsafe Limits	1	0
Shaking Body	1	0
Nausea	3	3
Twitching	0	1
Diaphoresis	0	2
Lightheadedness	1	2
Vomiting (8 hrs post-dose)	1	0
Borderline 1^0 AV Block	0	1
Stomach Upset/Pain	1	1
Weakness	0	1
Pallor (Pale lips)	0	2

Protocol Deviations: Most of them were blood sampling deviations. None appear to affect the study.

2. Analytical

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information

Nifedipine:

Mean Plasma Concentrations:Table 1, Figure 1
Pharmacokinetic Parameters: Tables 2 and 3.

1. The elimination constants were calculated for all subjects appropriately.

2. There were no subjects with 0-hour drug level, first scheduled post-dose time point as T_{max}, or subjects with first measurable drug concentration as C_{max}.

3. The 90% confidence intervals for log transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} are within acceptable limits of 80-125%. ANOVA analysis showed statistically significant effects as follows:

   There were treatment and period effects on AUC_{0-t}, AUC_{0-inf}, $LAUC_{0-t}$, and $LAUC_{0-inf}$.

4. Test/Ref ratios for PK parameters were:

   AUCT = 0.47-1.81 (mean=0.95), AUCI = 0.47-1.90 (mean=0.93), and Cmax = 0.22-3.67 (mean = 1.02).

5. The AUC_{0-t}/AUC_{0-inf} ratios:

   Ranged from 0.84 to 0.99 (Ave. 0.96) for test and from 0.77-1.00 (Ave. 0.97) for reference product.

6. ANOVA coefficient of variation for AUC_{0-t}, AUC_{0-inf}, and C_{max}, respectively, were:

   19.98, 20.59 and 38.85%.

7. Root Mean Square Error for log transformed parameters were:

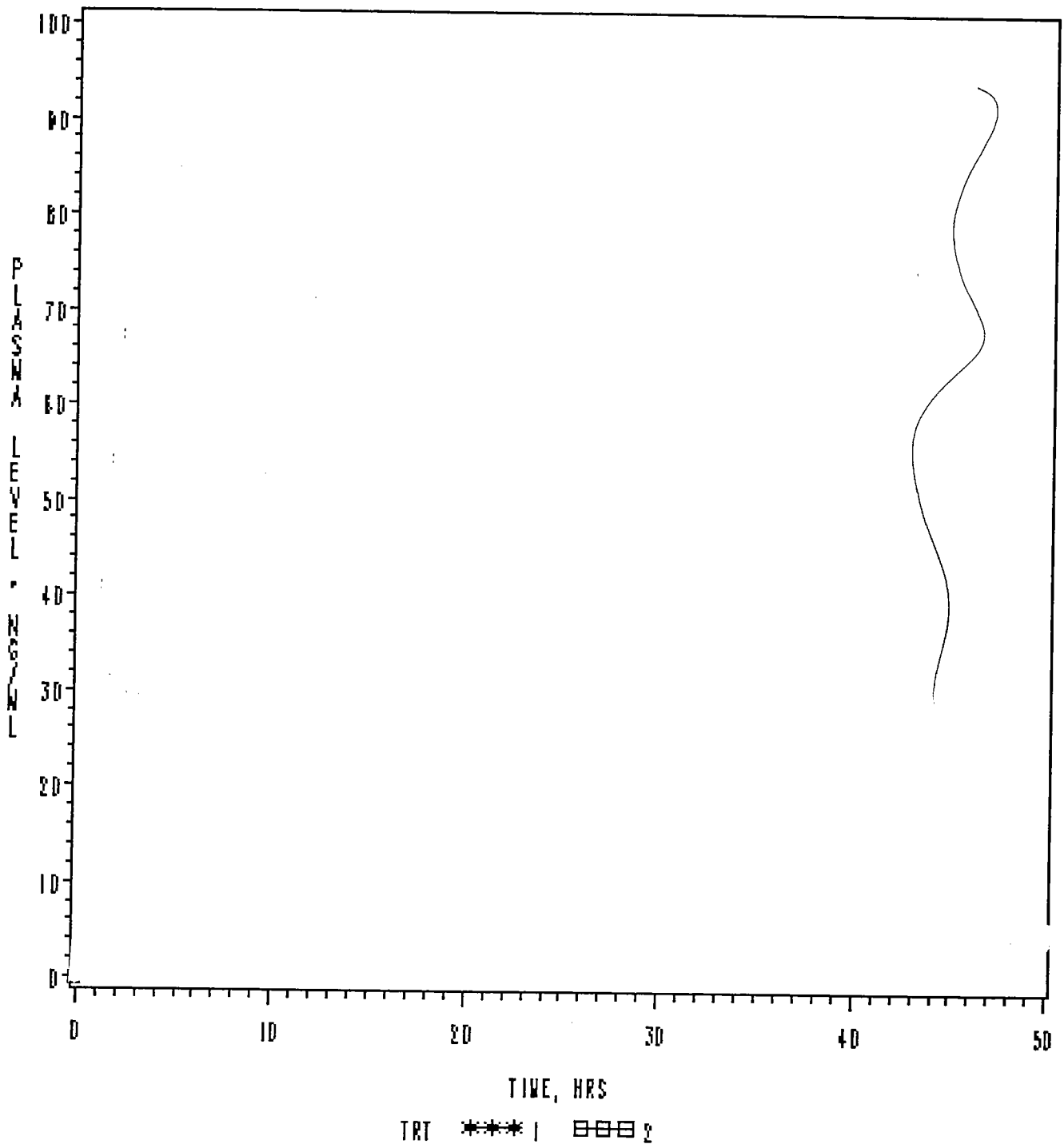
   AUC_{0-t} - 0.19049, AUC_{0-inf} - 0.19017, and C_{max} – 0.32862

8. Subjects were dosed in two groups. The firm is requested to check the group effect on the PK parameters (see Deficiencies/Comments Section).

Conclusion: The fasting study is incomplete.

FIG P—1. PLASMA NIFEDIPNE LEVELS (N=67)

NIFEDIPNE TABLETS, 1X80 MG, ANDA #78-070
UNDER FASTING CONDITIONS
DOSE=1 X 80 MG



1=TEST (BIOVAIL) 2=REF (BAYER)

2.

TABLE 1. MEAN PLASMA NIFEDIPNE LEVELS FOR TEST AND REFERENCE PRODUCTS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.5	5.13	6.19	3.56	3.23	1.44
1	23.85	14.95	19.31	12.41	1.24
1.5	41.02	18.23	33.18	19.41	1.24
2	54.23	26.59	44.89	24.14	1.21
2.5	67.39	36.51	57.78	26.84	1.17
3	68.68	37.01	65.87	35.93	1.04
4	68.39	38.04	74.48	44.64	0.92
5	74.08	49.10	91.18	65.73	0.81
6	62.19	38.86	77.59	63.56	0.80
8	45.84	27.96	56.92	46.71	0.81
10	35.30	21.82	42.74	31.23	0.83
12	32.38	19.94	41.33	31.24	0.78
14	34.57	20.97	43.20	29.36	0.80
16	33.57	21.41	37.01	20.03	0.91
20	24.18	15.71	28.66	24.55	0.84
24	22.87	15.40	22.94	15.50	1.00
30	16.88	12.50	17.69	15.09	0.95
36	11.20	9.69	10.97	8.46	1.02
48	4.47	5.95	3.69	3.83	1.21

MEAN1=TEST, MEAN2=REF UNIT: PLASMA LEVEL=NG/ML TIME=HRS

TABLE 2. ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	1282.56	629.19	1447.23	737.17	0.89
AUCT	1218.43	579.18	1348.57	707.94	0.90
CMAX	92.37	48.63	105.25	66.95	0.88
KE	0.10	0.03	0.10	0.04	0.91
LAUCI	1152.22	0.46	1299.95	0.46	0.89
LAUCT	1101.38	0.45	1207.37	0.46	0.91
LCMAX	81.91	0.48	89.45	0.56	0.92
THALF	8.23	3.22	7.67	3.17	1.07
TMAX	4.13	2.71	5.00	2.71	0.83

TABLE 3. LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	1291.21	1440.20	0.90	83.69	95.62
AUCT	1219.82	1351.70	0.90	84.77	95.71
CMAX	92.39	105.45	0.88	77.12	98.12
LAUCI	1164.26	1297.48	0.90	84.67	95.10
LAUCT	1102.31	1209.99	0.91	86.23	96.24
LCMAX	81.95	89.64	0.91	83.16	100.51

IV. SINGLE-DOSE BIOEQUIVALENCE STUDY UNDER NON-FASTING CONDITIONS (STUDY #2325)

A. Study Information:

Protocol #:	2325
IRB Approval:	Yes
Consent Form Signed:	Yes
Clinical Site:	Biovail Contract Research, Toranto, Canada
Analytical Site:	Biovail Contract Research, Toranto, Canada
Principal Investigator:	Paul Y. Tam, M.D., F.R.C.P., F.A.C.P.
Study Dates:	Period I 4/15/00 Period II 4/22/00 Period III 4/29/00
Analysis Dates:	May 15-June 20, 2000
Storage Period:	66 Days
Study Design:	Randomized, three-way, single dose, crossover design with 7-day washout period.
Randomization Scheme:	ABC: 2, 16, 19, 22, 30 ACB: 3, 4, 9, 18, 26 BAC: 6, 7, 21, 24, 28 BCA: 8, 14, 15, 23, 27 CAB: 1, 10, 11, 20, 25 CBA: 5, 12, 13, 17, 29
Treatments:	A: Nifedipine CC, 1 x 90 mg tablets; Biovail, Lot #: 00D025; (Test non-fasting). B: Adalat^{R} CC, 1x90 mg Tablets; Bayer; Lot #8LB1; (Reference non-fasting). C: Nifedipine CC, 1 x 90 mg tablets; Biovail, Lot #: 00D025; (Test fasted).
Formulation of Test Drug:	Table 1
Subjects:	24 (15 females and 9 males) plus 6 alternates were enrolled per protocol, but analyses were conducted on 24 evaluable subjects only.
Housing:	Confined from evening before dosing until 48 hours post-dosing.
Dosing:	Treatments A and B: 5 minutes after a standard (OGD-recommended) high-fat breakfast with 240 ml water Treatment A: Administered with 240 ml water following a 10 hour fast.

Sampling Times: Blood samples (7 mL each) collected at pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20, 24, 30, 36 and 48 hours post-dose.

B. Study Results:

1. Clinical:

Drop-outs: None

Adverse Events: All of the adverse events were considered mild or moderate in severity. They were not considered to influence the outcome of the study.

Adverse Event	Test (Fed)	Reference (Fed)	Test (Fast)
Headache	14	13	13
Constipation	1	0	0
Dizziness	0	3	1
Lightheadedness	0	0	1
Borderline 1^0 AV Block	1	2	0
Weakness	1	0	0
Nausea	2	0	0
Hot Flashes	1	0	0
Swollen Feet	1	0	0
Sinus Bradycardia	0	0	1
Sinus Tachycardia	2	1	0
Flushed sensation	0	2	0
Heartburn	1	1	0
Upset Stomach	0	0	1

Protocol Deviations: None significant. Since calculations were carried out using actual sampling time points, deviations did not impact on the PK parameter calculations.

2. Analytical

[ ] [ ] %

Conclusion: The analytical assay is acceptable.

3. Pharmacokinetics / Statistics:

Mean Plasma Concentrations: Table 4; Figure P-2
Pharmacokinetic Parameters: Tables 5-7

Commments:

1. The reviewer recalculated the PK parameters and ratios of means. The reported values are in good agreement with those obtained by the reviewer.

2. No subjects are with zero-hour drug level, and no subjects with first scheduled post-dose time point as C_{max}.

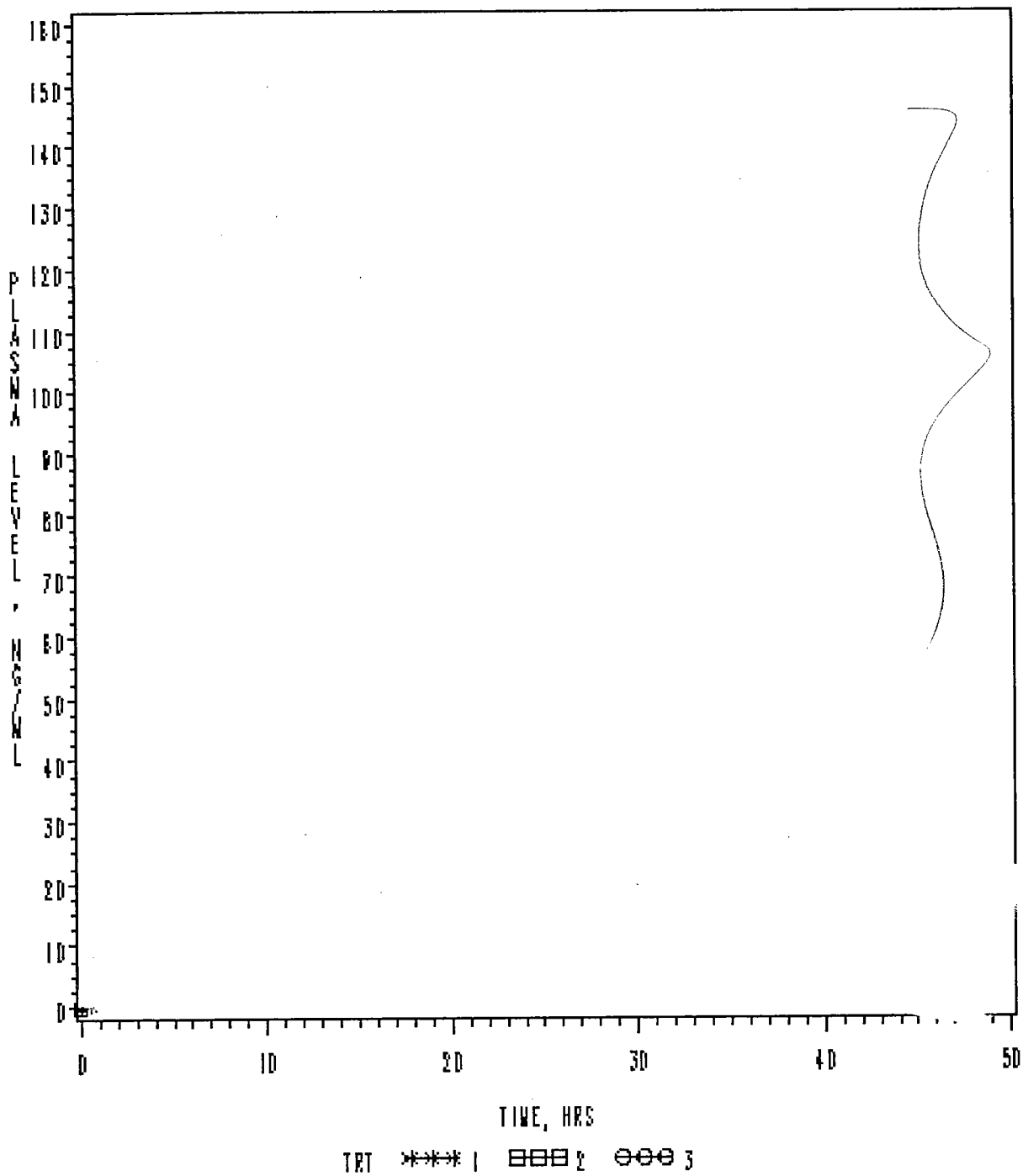
3. Ratios of means for AUC_{o-t}, AUC_{o-inf}, and C_{max} between test (non-fasting) and reference (non-fasting) are within acceptable limits of 80-125.

5. The non-fasting study is acceptable.

APPEARS THIS WAY
ON ORIGINAL

FIG P–2. PLASMA NIFEDIPINE LEVELS (N=24)

NIFEDIPINE CC TABLETS, 90 MG, ANDA #74-070
UNDER FASTING/NONFASTING CONDITIONS
DOSE=1 X 90 MG



1=TEST (BIOVAIL-FOOD) 2=REF (BAYER-FOOD) 3=TEST (BIOVAIL-FAST)

TABLE 4. MEAN PLASMA NIFEDIPINE LEVELS FOR TEST AND REFERENCE PRODUCTS

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
TIME HR							
0	0.00	0.00	0.00	0.00	0.00	0.00	.
0.5	0.52	1.28	2.07	5.46	5.65	9.19	0.25
1	4.83	9.59	8.14	14.12	19.32	12.46	0.59
1.5	20.35	37.93	21.35	34.69	32.53	15.04	0.95
2	42.54	57.30	38.34	51.70	45.27	19.40	1.11
2.5	71.77	69.47	53.05	54.78	55.64	23.38	1.35
3	88.72	72.49	73.78	62.63	68.19	34.45	1.20
4	117.51	76.63	106.79	87.56	63.42	32.05	1.10
5	158.83	73.13	157.43	125.92	68.65	39.41	1.01
6	130.32	63.20	128.57	115.11	59.29	30.00	1.01
8	93.63	58.26	77.76	44.81	42.11	23.06	1.20
10	66.56	48.13	58.57	43.33	32.57	14.15	1.14
12	49.15	32.82	53.84	50.01	29.39	12.91	0.91
14	34.19	20.20	39.72	29.96	28.29	11.15	0.86
16	26.54	14.85	30.78	15.09	29.56	13.33	0.86
20	17.09	11.37	25.23	22.45	22.04	10.50	0.68
24	11.36	6.96	18.61	20.21	21.32	13.62	0.61
30	6.22	4.17	8.86	6.65	18.03	10.37	0.70
36	3.58	2.65	5.05	4.20	12.33	8.48	0.71
48	1.00	0.97	1.55	1.65	4.65	4.34	0.65

TRT: MEAN1=TEST FED, MEAN2=REF FED, MEAN3=TEST FAST, UNIT: PLASMA LEVEL=NG/ML TIME=HRS

TABLE 3 (CONT'D). MEAN PLASMA NIFEDIPINE LEVELS FOR TEST AND REFERENCE PRODUCTS

	RMEAN13	RMEAN23
TIME HR		
0	.	.
0.5	0.09	0.37
1	0.25	0.42
1.5	0.63	0.66
2	0.94	0.85
2.5	1.29	0.95
3	1.30	1.08
4	1.85	1.68
5	2.31	2.29
6	2.20	2.17
8	2.22	1.85
10	2.04	1.80
12	1.67	1.83
14	1.21	1.40
16	0.90	1.04
20	0.78	1.14
24	0.53	0.87
30	0.35	0.49
36	0.29	0.41
48	0.22	0.33

TRT: MEAN1=TEST FED, MEAN2=REF FED, MEAN3=TEST FAST, UNIT: PLASMA LEVEL=NG/ML TIME=HRS

TABLE 5. ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
PARAMETER							
AUCI	1388.34	594.13	1454.24	661.36	1251.13	505.40	0.95
AUCT	1374.39	588.25	1426.11	670.87	1154.90	434.65	0.96
CMAX	186.61	61.39	187.57	116.84	86.21	35.39	0.99
KE	0.11	0.02	0.11	0.04	0.08	0.03	0.95
LAUCI	1284.81	0.39	1338.79	0.41	1164.98	0.38	0.96
LAUCT	1271.39	0.40	1301.81	0.43	1085.26	0.36	0.98
LCMAX	177.67	0.32	159.25	0.58	78.66	0.45	1.12
THALF	6.67	1.24	7.32	4.90	10.26	6.80	0.91
TMAX	5.71	2.14	6.90	4.80	4.19	2.04	0.83

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

TABLE 6. LSMEANS AND RATIOS

	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
PARAMETER						
AUCI	1388.34	1454.24	1251.13	0.95	1.11	1.16
AUCT	1374.39	1426.11	1154.90	0.96	1.19	1.23
CMAX	186.61	187.57	86.21	0.99	2.16	2.18
LAUCI	1284.81	1338.79	1164.98	0.96	1.10	1.15
LAUCT	1271.39	1301.81	1085.26	0.98	1.17	1.20
LCMAX	177.67	159.25	78.66	1.12	2.26	2.02

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

TABLE 7. LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	LSM3	LOWCI12	UPPCI12	LOWCI13	UPPCI13
PARAMETER							
AUCI	1388.34	1454.24	1251.13	87.60	103.33	101.83	120.11
AUCT	1374.39	1426.11	1154.90	88.67	104.07	109.50	128.51
CMAX	186.61	187.57	86.21	83.35	115.63	181.35	251.57
LAUCI	1284.81	1338.79	1164.98	89.78	102.59	103.17	117.89
LAUCT	1271.39	1301.81	1085.26	91.70	104.01	110.00	124.76
LCMAX	177.67	159.25	78.66	93.76	132.75	189.83	268.76

TABLE 7 CONT'D. LSMEANS AND 90% CONFIDENCE INTERVALS

	LOWCI23	UPPCI23
PARAMETER		
AUCI	107.09	125.38
AUCT	113.98	132.99
CMAX	182.46	252.68
LAUCI	107.51	122.84
LAUCT	112.64	127.75
LCMAX	170.15	240.90

V. SUMMARY OF TWO-WAY, STEADY-STATE, MULTIPLE-DOSE BIOEQUIVALENCE STUDY (STUDY # 2326)

Multiple-dose study is not required. However, a comparative biostudy on nifedipine CC 90 mg extended release tablet formulations from Biovail and Bayer [Adalat® CC 90 mg] was conducted prior to the release of the new BE Guidance (October, 2000). The study was carried out in 48 subjects, in the same laboratory, using the same products, lot numbers, conditions and methodology. Subjects were dosed for 7 consecutive days with test and reference products in a crossover design and with a 7-day washout period. Blood samples were collected pre-dose on Day 1, 4, 5, 6 and 7. On Day 7, blood samples were collected at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 16, 20, and 24 hours post-dose. The 90% CI for LAUC and LCmax were found to be within 80-125 % range. Results were as follows:

MEAN PLASMA NIFEDIPNE LEVELS FOR TEST AND REFERENCE PRODUCTS (NG/ML)

Sampling Day	Sampling Time, Hr.	MEAN1	SD1	MEAN2	SD2
Day 1	0.0	0.00	0.00	0.00	0.00
Day 4	0.0	42.90	34.10	42.70	31.43
Day 5	0.0	42.80	31.29	41.75	29.24
Day 6	0.0	38.09	28.88	41.05	34.91
Day 7	0.0	42.43	27.73	42.94	36.42
Day 7	0.5	47.74	28.44	47.10	32.22
Day 7	1.0	70.27	38.70	66.17	35.57
Day 7	1.5	90.55	47.15	79.76	36.90
Day 7	2.0	110.74	51.40	96.26	44.15
Day 7	2.5	121.47	47.18	106.74	43.71
Day 7	3.0	129.54	47.35	114.62	41.06
Day 7	3.5	127.55	47.39	120.66	49.73
Day 7	4	123.20	47.18	120.81	51.56
Day 7	5	112.95	50.25	114.11	60.11
Day 7	6	106.98	48.68	116.33	57.95
Day 7	7	93.22	40.75	98.45	45.53
Day 7	8	86.70	41.32	89.16	40.99
Day 7	10	71.38	31.94	72.73	33.27
Day 7	12	72.67	31.69	80.42	35.60
Day 7	16	57.23	29.61	64.92	30.26
Day 7	20	43.48	28.85	47.59	33.93
Day 7	24	44.73	27.13	50.74	34.01

MEAN1=TEST, MEAN2=REF; UNIT: PLASMA LEVEL=NG/ML TIME=HRS; AUC=NG.HR/ML

Cmax	Test: 149.93 ±45.66	Ref.: 144.80±55.57
AUC0-24	Test: 1748.07±742.14	Ref.: 1821.08±783.20
Cmin	Test: 44.73±27.13	Ref.: 50.74±34.01
Cav	Test: 72.84±30.92	Ref.: 75.88±32.63

90% Confidence Intervals:	$LAUC_{0-24}$	91-102%
	LC_{max}	99-115%
Test/Reference Ratio:	AUC_{0-24}	0.96
(Geometric means)	C_{max}	1.07
	C_{min}	0.88
	C_{ave}	0.96
	DFluctuation	1.21

Conclusion: The multiple study is acknowledged.

VI. FORMULATION

All inactive ingredients are within the IIG limits.

VII. *IN VITRO* DISSOLUTION TESTING

Using the same biostudy lots, the firm has conducted *in vitro* dissolution testing on 90 mg tablets of the test and reference products in six media: (1) SGF pH 1.2 and 0.5% SLS, (2) Phosphate buffer at [redacted] (3) phosphate buffer at [redacted] (4) phosphate buffer at [redacted], (5) phosphate buffer at [redacted] and (6) [redacted] Results are summarized in Table 9. The firm needs to conduct further dissolution tests, and provide some clarification to the current data.

Conclusion: Dissolution testing is incomplete (see Deficiencies/Comments Section).

VIII. DEFICIENCIES/COMMENTS

1. In the fasting study, subjects were recruited in two groups (Group1 - Subject #1-54 dosed on 9/16/00 and 9/23/00, and Group 2 – Subject #55-74 dosed on 9/23/00 and 9/30/00). The firm should evaluate if there was any Group effect by adding Group term in the ANOVA analysis. Thus,

   Model y = GRP SEQ GRP*SEQ SUB(GRP*SEQ) PER(GRP) TRT GRP*TRT

2. Once it is determined that there is no GRP*TRT effect ($p>0.1$), the term should be dropped from the analysis.

[redacted]

4. Since dissolution of nifedipine in all media except SGF with SLS, is only [redacted] in 20 hours, the firm is advised to try buffers at [redacted] with SLS, preferably with lower levels of SLS.

5. The firm should also evaluate dissolution in media at paddle speed of [redacted]

6. Based on available data, the firm should suggest a workable method for dissolution testing.

7. Firm should also refer to the following:

a. USP dissolution Test 1 and Test 2 for nifedipine extended release products (USP 24, Supplement 1, pages 2644-45, 2001).
b. Guidance for Industry: Extended Release Oral Dosage Forms - Development, Evaluation, and Application of in *vitro/in vivo* correlations.

IX. RECOMMENDATIONS

1. The *in vivo* bioequivalence study conducted under fasting conditions by Biovail Laboratories, Inc. on its nifedipine CC tablets, 90 mg, Lot # 00D025, comparing it to the reference product, Adalat® CC tablets, 90 mg, Lot # 8LB1, by Bayer, has been found to be incomplete by the Division of Bioequivalence.

2. The *in vivo* bioequivalence study conducted under non-fasting conditions by Biovail Laboratories, Inc. on its nifedipine CC tablets, 90 mg, Lot # 00D025, comparing it to the reference product, Adalat® CC tablets, 90 mg, Lot # 8LB1, by Bayer, has been found to be acceptable by the Division of Bioequivalence.

3. The *in vivo* bioequivalence multiple–dose study conducted by Biovail Laboratories, Inc. on its nifedipine CC tablets, 90 mg, Lot # 00D025, comparing it to the reference product, Adalat® CC tablets, 90 mg, Lot # 8LB1, by Bayer, acknowledged by the Division of Bioequivalence.

4. The *in vitro* dissolution testing submitted by the firm on its nifedipine CC tablets, 90 mg is incomplete due to Deficiencies/Comments 1-7 cited above.

5. From bioequivalence point of view, the firm has not met the requirements of *in vitro* dissolution testing, and the application is incomplete.

The firm should be informed of the Deficiencies/Comments #1-7.

/S/

S. P. Shrivastava, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR /S/ Date 5/14/2001

Concur: /S/ Date 5/22/2001
for Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
CDER, FDA

SPS/04-20-01/76070sd.201
cc: ANDA #76-070 (Original, Duplicate) HFD-655 (SNerurkar, SShrivastava), Drug File, Division File.

Table 8. Quantitative Composition of Nifedipine ER 90 mg Tablet

INGREDIENT	(mg/TABLET)
Nifedipine, USP	90.00
Hydroxypropyl Methylcellulose	
Hydroxyethyl Methylcellulose	
Anhydrous Lactose, NF	
Silicon Dioxide, NF	
Microcrystalline Cellulose	
Sodium Lauryl Sulfate	
Ethylcellulose N-100, NF	
Magnesium Stearate, NF	
Opadry II White	
FD&C Yellow #5	
Total Wt.	**319.0764**

How Supplied: The test product is a round, yellow, film-coated, unscored tablet debossed with "B" on one side and "90" on the other side. The reference listed drug, Adalat^{R} CC is round, dark red, film coated, unscored tablet debossed "90" on one side and "ADALAT CC" on the other side.

APPEARS THIS WAY
ON ORIGINAL

In Vitro DISSOLUTION TESTING

Table 9. Summary of Comparative Dissolution

Drug: Nifedipine CC tablets **Dose Strength(s): 90 mg** **ANDA #: 76-070**						
Conditions for Dissolution/Release Testing:			**FIRM'S METHOD**			
USP XXIII **Apparatus: Type 2 (Paddles)** **RPM: 100** **No. Units Tested: 12** **Reference Drug: Adalat® CC (Bayer)**			**Media: See below**		**Volume: 900 mL**	
A. Results of *In vitro* Dissolution/Release Testing: SGF with 0.5% SLS, pH 1.2						
Sampling Times (hours)	**Test Product: Nifedipine CC Tablet Lot No.: 00D025**			**Reference Product: Adalat® CC Lot No.: 8LB1** $F_2 =$		
	Mean %	Range	CV%	Mean %	Range	CV%
1	8.0		34.5	4.7		19.8
2	17.1		27.7	19.0		124.0
3	26.6		23.1	20.6		19.0
4	36.4		20.2	30.0		24.1
5	45.9		18.1	40.2		30.1
6	55.6		16.4	49.1		30.7
7	64.9		15.0	56.7		28.9
8	73.8		13.4	65.3		25.8
9	81.9		10.7	77.4		17.3
10	87.4		7.9	86.6		10.3
12	94.5		4.9	94.6		4.6
16	97.8		4.3	98.0		3.0
20	99.2		4.4	99.2		2.9
B. Results of *In vitro* Dissolution/Release Testing:						
Sampling Times (hours)	**Test Product: Nifedipine ER Tablet Lot No.: 00D025**			**Reference Product: Adalat® CC Lot No.: 8LB1** $F_2 =$		
	Mean %	**Range**	**CV%**	**Mean %**	**Range**	**CV%**
1	3.0		9.8	3.2		23.2
2	5.5		6.8	6.4		16.4
3	7.3		4.1	8.6		10.6
4	8.4		2.4	9.8		7.1
5	9.1		2.5	10.4		7.2
6	9.7		3.3	11.1		6.2
7	10.2		4.6	11.5		4.4
8	10.8		7.1	11.8		3.2
9	10.9		6.0	12.1		3.6
10	11.2		7.1	12.1		4.3
12	11.7		7.9	12.1		5.7
16	12.3		9.0	12.0		7.6
20	12.7		11.9	12.6		9.7

Table 9 Cont'd.

C. Results of *In vitro* Dissolution/Release Testing:						
Sampling Times (hours)	**Test Product: Nifedipine CC Tablet Lot No.: 00D025**			**Reference Product: Adalat® CC Lot No.: 8LB1** $F_2 =$		
	Mean %	Range	CV%	Mean %	Range	CV%
1	1.9		16.1	1.5		34.0
2	2.9		13.4	2.8		35.8
3	4.6		26.8	4.3		33.8
4	6.6		24.2	5.6		28.4
5	7.8		12.2	6.5		23.7
6	8.5		8.5	7.2		19.8
7	8.7		6.3	7.8		18.0
8	8.9		6.1	8.2		15.2
9	8.8		6.4	8.5		13.3
10	8.8		6.7	8.8		11.7
12	8.6		6.8	9.2		8.8
16	8.1		10.8	9.4		7.0
20	8.4		21.5	9.3		15.5

D. Results of *In vitro* Dissolution/Release Testing:						
Sampling Times (hours)	**Test Product: Nifedipine ER Tablet Lot No.: 00D025**			**Reference Product: Adalat® CC Lot No.: 8LB1** $F_2 =$		
	Mean %	**Range**	**CV%**	**Mean %**	**Range**	**CV%**
1	3.4		7.9	3.2		20.3
2	5.9		5.6	6.3		14.6
3	7.6		6.6	8.1		9.1
4	8.5		6.8	9.5		3.5
5	9.2		7.8	10.2		3.7
6	9.7		8.3	10.6		4.9
7	10.1		9.0	11.3		3.7
8	10.4		10.1	11.8		2.4
9	10.7		9.9	11.9		2.1
10	10.9		10.7	11.8		2.1
12	11.1		9.9	12.3		6.3
16	11.5		10.0	12.0		14.0
20	12.5		14.6	12.1		18.8

Table 9 Cont'd.

E. Results of *In vitro* Dissolution/Release Testing:						
Sampling Times (hours)	**Test Product: Nifedipine ER Tablet Lot No.: 00D025**			**Reference Product: Adalat® CC Lot No.: 8LB1** $F_2 =$		
	Mean %	**Range**	**CV%**	**Mean %**	**Range**	**CV%**
1	3.1		10.1	2.5		16.1
2	5.1		8.6	5.5		12.5
3	6.5		7.0	7.8		9.9
4	7.4		5.7	9.1		7.4
5	8.0		5.5	9.6		4.3
6	8.5		5.2	10.5		6.2
7	8.8		6.0	10.9		7.2
8	9.0		5.5	11.4		7.3
9	9.3		5.4	11.8		7.2
10	9.5		5.7	12.1		6.0
12	9.9		5.7	12.7		5.9
16	10.4		6.6	13.2		5.0
20	10.9		7.8	13.6		3.5

F. Results of *In vitro* Dissolution/Release Testing:						
Sampling Times (hours)	**Test Product: Nifedipine ER Tablet Lot No.: 00D025**			**Reference Product: Adalat® CC Lot No.: 8LB1** $F_2 =$		
	Mean %	**Range**	**CV%**	**Mean %**	**Range**	**CV%**
1	4.5		15.7	3.3		24.6
2	7.7		9.4	6.5		17.9
3	9.1		8.2	8.5		10.7
4	10.0		7.1	9.7		6.7
5	10.5		7.2	10.5		6.4
6	10.9		7.4	11.2		5.9
7	11.1		7.8	11.7		4.5
8	11.1		9.1	12.0		4.3
9	11.2		10.6	12.3		3.9
10	11.1		10.8	12.5		4.2
12	11.2		10.1	12.7		4.5
16	10.2		24.2	12.9		10.1
20	11.0		11.8	12.9		10.9

2.1

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 76-070 APPLICANT: Biovail Laboratories, Inc.

DRUG PRODUCT: Nifedipine CC tablets, 90 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies and comments are provided for your cosideration:

1. In the fasting study, subjects were recruited in two groups (Group1 - Subject #1-54 dosed on 9/16/00 and 9/23/00, and Group 2 – Subject #55-74 dosed on 9/23/00 and 9/30/00). You should evaluate if there was any Group effect by adding Group term in the ANOVA analysis. Thus,

   Model y = GRP SEQ GRP*SEQ SUB(GRP*SEQ) PER(GRP) TRT GRP*TRT

2. Once it is determined that there is no GRP*TRT effect ($p>0.1$), the term should be dropped from the analysis.

3. You have conducted dissolution in 6 media, SGF at pH 1.2 with 0.5% SLS, water and in [redacted]. However, it is not clear:

   [redacted]

4. Since dissolution of nifedipine in all media except SGF with SLS, is only [redacted] in 20 hours you are advised to try [redacted] with SLS, preferably with lower levels of SLS.

5. You should also evaluate dissolution in media at paddle speed of [redacted]

6. Based on available data, you should suggest a workable method for dissolution testing.

7. You should also refer to the following:

   a. USP dissolution Test 1 and Test 2 for nifedipine extended release products (USP 24, Supplement 1, pages 2644-45, 2001).
   b. Guidance for Industry: Extended Release Oral Dosage Forms - Development, Evaluation, and Application of in *vitro/in vivo* correlations.

Please note that the bioequivalence 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

bioequivalence 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

CC: ANDA 76-070
DIVISION FILE
HFD-651 / Bio Drug File
HFD-655 / S. P. Shrivastava

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Printed in final on / /

Endorsements: (Final with Dates)
HFD-655 / S.P.Shrivastava 5/11/01
HFD-655 / S. Nerurkar /S/ 5/14/01
HFD-650 / D. Conner fw 5/22/2001

BIOEQUIVALENCY - INCOMPLETE 02/07/01

1. FASTING STUDY (STF) ..... Submission Date: ~~12/21/00~~
CLINICAL: Biovail Contract Research ..... Strength: 90 MG
ANALYTICAL: Biovail Contract Research ✓ OUTCOME: ..... IC 02/07/01

2. FOOD STUDY (STP) ..... Submission Date: ~~12/21/00~~
CLINICAL: Biovail Contract Research ..... Strength: 90 MG
ANALYTICAL: Biovail Contract Research ✓ OUTCOME: ..... AC 02/07/01

3. MULTIPLE DOSE STUDY (STM) ..... Submission Date: ~~12/21/00~~
CLINICAL: Biovail Contract Research ..... Strength: 90 MG
ANALYTICAL: Biovail Contract Research ✓ OUTCOME: ..... ACKNOWLEDGED

4.. AMENDMENT (DIS) ..... Submission Date 2/7/2001
..... Strength: 90 mg
..... ✓ OUTCOME: IC

OUTCOME DECISION: INCOMPLETE

WinBio Comments:

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-070

ADMINISTRATIVE DOCUMENTS

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

ANDA Number: **76-070** Date of Submission: **February 7, 2001**

Applicant's Name: **Biovail Laboratories Incorporated**

Established Name: **Nifedipine Extended-release Tablets USP, 90 mg**

Labeling Deficiencies:

1. GENERAL COMMENT

   We encourage you to use "USP" with the established name where indicated below.

2. CONTAINER 100s, 500s, 1000s

   a. See GENERAL COMMENT above.

   b. PROTECT FROM MOISTURE. (delete '

   c. Add the statement "PROTECT FROM LIGHT."

3. INSERT

   a. GENERAL COMMENT

      We encourage you to use "USP" with the established name in the TITLE, DESCRIPTION, and HOW SUPPLIED sections of the package insert labeling.

   b. DESCRIPTION

      i. Place the molecular formula all on the same line of printed text.

      ii. Increase the prominence of the ring "N" in the structural formula.

      iii. Inactive ingredients

         A). We encourage you to place the listing of inactive ingredients in alphabetical order.

         B). It is not necessary to list "USP" or "NF" with the listing of inactive ingredients.

         C). List the ingredients of "opadry II white".

      iv. We encourage you to describe the nature of your drug product's extended-release system as does the innovator.

v. State the USP Drug Release Test number to which this product conforms and if not assigned yet place the statement "USP Drug Release test number pending." as the last sentence in this section.

c. CLINICAL PHARMACOLOGY

i. Pharmacokinetics and Metabolism, fifth paragraph, last sentence – Delete the word " [redacted]

ii. Clinical Studies, first sentence – "90 mg" (place a space between "90" and "mg")

d. INDICATIONS AND USAGE

Revise the section title as seen above.

e. PRECAUTIONS

Include the warning statement "This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity." in this section as required by 21 CFR 201.20 (b).

f. ADVERSE REACTIONS

i. Revise the section title as seen above.

ii. Delete the last sentence ([redacted] in this section as that text has not yet been approved for the referenced listed drug.

g. HOW SUPPLIED

Delete the statement ' [redacted]

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

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

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

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

/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: 76-070

DRUG PRODUCT: Nifedipine Extended Release Tablets USP

FIRM: Biovail Laboratories Incorporated

DOSAGE FORM: Extended Release Tablets

STRENGTH(s): 90 mg

CGMP STATEMENT/EER UPDATE STATUS: Signed cGMP certification was provided on p. 14586 of the original submission. EER found acceptable on 1/23/02.

BIO STUDY: Bioequivalency studies were found acceptable on 1/8/02. The Division of Bioequivalence approved revised dissolution tolerances on 5/2/02.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S): The drug substance and drug product are both USP. The firm is using the USP testing methods with the following exception: The firm has developed their own GC methods for

Appropriate validation data were provided for those in-house methods.

STABILITY - (ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?): Accelerated and room temperature stability data support the proposed 24 month expiration date for the drug product. Containers used in the stability studies were identical to those described in the container section.

LABELING: Labeling was tentatively approved on 30-JUL-2001. Final approval was granted on 24-JUN-2002.

STERILIZATION VALIDATION (IF APPLICABLE): N/A

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?): The firm provided executed batch records (pp. 14703-14722) for the Nifedipine , Lot 00C169). This material was used to manufacture the uncoated Nifedipine Tablets 90 mg, lot 00D006 (pp. 14724-14732). Finally, executed batch records were provided for the coating process, lot 00D025 (pp. 14734-14744). The 90 mg tablets were packaged into bottles of 100's 500's, and 1000's designated as lot 00G034, lot 00G035, and lot 00G036,

respectively. Master batch records were also provided (same batch size as in the exhibit batch). The manufacturing process described in the executed batch records is essentially the same as that provided in the master batch records.

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?): See Above.

CHEMIST: SCOTT FURNESS **DATE:** 7/15/02 /S/ 7/30/02

SUPERVISOR: RICHARD ADAMS **DATE:** 7/23/02 /S/ 7/30/02

APPEARS THIS WAY
ON ORIGINAL

Spec sheet

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trade secret and/or

confidential

commercial

information

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-070

CORRESPONDENCE

BIOVAIL
TECHNOLOGIES LTD.

BY OVERNIGHT COURIER

MINOR AMENDMENT

June 24, 2002

ORIG AMENDMENT
N/AM

Gary Buehler
Director (HFD-600)
Office of Generic Drugs, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Nifedipine Extended-release Tablets, USP, 90 mg, ANDA #76-070
Minor Amendment

Dear Mr. Buehler:

Biovail Laboratories Inc. wishes to amend its application, ANDA 76-070, to include responses to the Agency correspondence of June 24, 2002. Biovail has responded to all questions posed by the Agency in this amendment.

We look forward to receiving Agency comment on our responses, if any, in due course.

Should you require any further information, or have any questions or comments, please do not hesitate to contact the undersigned directly at (703) 995-2280, or by fax at (703) 995-2444.

Yours sincerely,
On Behalf of Biovail Laboratories Incorporated

Wayne Kreppner, M.Sc.
Manager, Regulatory Affairs
Biovail Technologies Limited

Encl.

RECEIVED
JUN 2 5 2002
OGD / CDER

BIOVAIL TECHNOLOGIES LTD.
3701 Concorde Parkway, Chantilly, Virginia 20151
Tel: **(703) 995-2400** Fax: (703) 995-2490

BIOVAIL
TECHNOLOGIES LTD.

MINOR AMENDMENT – FINAL PRINTED LABELING
VIA OVERNIGHT COURIER

ORIG AMENDMENT
N/AF-FPL

May 20, 2002

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, USP, 90 mg, ANDA #76-070
Minor Amendment – Final Printed Labeling

Dear Mr. Buehler;

Biovail Laboratories Inc. is submitting a Minor Amendment to ANDA #76-070, Nifedipine Extended-release Tablets, USP, 90 mg, in anticipation of full approval of this file. This amendment contains 12 mounted copies of the final printed bottle labels and package insert.

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

Encl.

BIOVAIL TECHNOLOGIES LTD.
3701 Concorde Parkway, Chantilly, Virginia 20151
Tel: **(703) 995-2400** Fax: (703) 995-2490

BIOVAIL
TECHNOLOGIES LTD.

BY OVERNIGHT COURIER

BIOEQUIVALENCY AMENDMENT

May 9, 2002

Gary Buehler
Director, Office of Generic Drugs
CDER
FDA (HFD-600)
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
AB

Re: Nifedipine Extended-release Tablets, USP, 90 mg, ANDA #76-070
Bioequivalency Deficiency

Dear Mr. Buehler:

Biovail Laboratories Inc. wishes to amend its application, ANDA 76-070, to include responses to the Agency correspondence of May 3, 2002.

Biovail has responded to all questions posed by the Agency.

We look forward to receiving Agency comment on our responses, if any, in due course.

Should you require any further information, or have any questions or comments, please do not hesitate to contact the undersigned directly at (703) 995-2280, or by fax at (703) 995-2444.

Yours sincerely,
On Behalf of Biovail Laboratories Inc.

Wayne Kreppner, M.Sc.
Manager, Regulatory Affairs
Biovail Technologies Limited

RECEIVED
MAY 1 3 2002
OGD / CDER

Encl.

BIOVAIL TECHNOLOGIES LTD.
3701 Concorde Parkway, Chantilly, Virginia 20151
Tel: **(703) 995-2400** Fax: (703) 995-2490

BIOVAIL
TECHNOLOGIES LTD.

BY OVERNIGHT COURIER

MINOR AMENDMENT

March 8, 2002

ORIG AMENDMENT
N/AM
BIOAVAILABILITY

Gary Buehler
Director (HFD-600)
Office of Generic Drugs, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Noted.
To Scott F.

Re: Nifedipine Extended-release Tablets, USP, 90 mg, ANDA #76-070
Minor Amendment

Dear Mr. Buehler:

Biovail Laboratories Inc. wishes to amend its application, ANDA 76-070, to include responses to the Agency correspondence of February 1, 2002.

Biovail has responded to all questions posed by the Agency.

We look forward to receiving Agency comment on our responses, if any, in due course.

Should you require any further information, or have any questions or comments, please do not hesitate to contact the undersigned directly at (703) 995-2280, or by fax at (703) 995-2444.

Yours sincerely,
On Behalf of Biovail Laboratories

Wayne Kreppner, M.Sc.
Manager, Regulatory Affairs
Biovail Technologies Limited

Encl.

RECEIVED
MAR 1 1 2002
OGD / CDER

3/11/02

BIOVAIL TECHNOLOGIES LTD.
3701 Concorde Parkway, Chantilly, Virginia 20151
Tel: **(703) 995-2400** Fax: (703) 995-2490

BIOVAIL
TECHNOLOGIES LTD.

BY OVERNIGHT COURIER

MINOR AMENDMENT

November 1, 2001

Gary Buehler
Director (HFD-600)
Office of Generic Drugs, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Nifedipine Extended-release Tablets, USP, 90 mg, ANDA #76-070
Minor Amendment

Dear Mr. Buehler:

Biovail Laboratories Inc. wishes to amend its application, ANDA 76-070, to include responses to the Agency correspondence of September 11, 2001.

Biovail has responded to all questions posed by the Agency.

Please note that the applicant has removed Biovail Laboratories Incorporated, Carolina, Puerto Rico as an alternate/contract testing facility, for finished product and stability testing, including chemical testing.

We look forward to receiving Agency comment on our responses, if any, in due course.

Should you require any further information, or have any questions or comments, please do not hesitate to contact the undersigned directly at (703) 995-2280, or by fax at (703) 995-2444.

Yours sincerely,
On Behalf of Biovail Laboratories

CENTER FOR DRUG EVALUATION AND RESEARCH
NOV 07 2001

Wayne Kreppner, M.Sc.
Manager, Corporate Regulatory Affairs
Biovail Technologies Limited

Encl.

BIOVAIL TECHNOLOGIES LTD.
3701 Concorde Parkway, Chantilly, Virginia 20151
Tel: **(703) 995-2400** Fax: (703) 995-2490

BIOVAIL
TECHNOLOGIES LTD.

BY OVERNIGHT COURIER

BIOEQUIVALENCY AMENDMENT

November 1, 2001

Gary Buehler
Director, Office of Generic Drugs
CDER
FDA (HFD-600)
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
AB

Re: Nifedipine Extended-release Tablets, USP, 90 mg, ANDA #76-070
Bioequivalency Deficiency

Dear Mr. Buehler:

Biovail Laboratories Inc. wishes to amend its application, ANDA 76-070, to include responses to the Agency correspondence of May 30, 2001.

Biovail has responded to all questions posed by the Agency.

We look forward to receiving Agency comment on our responses, if any, in due course.

Should you require any further information, or have any questions or comments, please do not hesitate to contact the undersigned directly at (703) 995-2280, or by fax at (703) 995-2444.

Yours sincerely,
On Behalf of Biovail Laboratories Inc.

CENTER FOR DRUG
NOV 0 7 2001
OGD
EVALUATION AND RESEARCH

Wayne Kreppner, M.Sc.
Manager, Corporate Regulatory Affairs
Biovail Technologies Limited

Encl.

BIOVAIL TECHNOLOGIES LTD.
3701 Concorde Parkway, Chantilly, Virginia 20151
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BIOVAIL
TECHNOLOGIES LTD.

NEW CORRESP

BY OVERNIGHT COURIER

MINOR AMENDMENT

September 28, 2001

N/NC

I updated ECS to WD the site

/S/
10/1/01

Gary Buehler
Director (HFD-600)
Office of Generic Drugs, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Nifedipine Extended-release Tablets, USP, 90 mg, ANDA #76-070
Minor Amendment; General Correspondence

Dear Mr. Buehler:

Biovail Laboratories Inc. wishes to amend its application, ANDA 76-070, to remove Biovail Laboratories Incorporated, Carolina, Puerto Rico as an alternate/contract testing facility, for finished product and stability testing, including chemical testing.

Should you require any further information, or have any questions or comments, please do not hesitate to contact the undersigned directly at (703) 995-2280, or by fax at (703) 995-2444.

Yours sincerely,
On Behalf of Biovail Laboratories Incorporated

Wayne Kreppner, M.Sc.
Manager, Corporate Regulatory Affairs
Biovail Technologies Limited

CENTER FOR DRUG EVALUATION AND RESEARCH
OCT 0 1 2001
OGD

Encl.

BIOVAIL TECHNOLOGIES LTD.
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cm2 10/1/01

BIOVAIL
TECHNOLOGIES LTD.

labeling review drafted 7/27/01
/S/

BY OVERNIGHT COURIER

MINOR AMENDMENT

July 23, 2001

ORIG AMENDMENT
NDAm

Gary Buehler
Acting Director (HFD-600)
Office of Generic Drugs, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Nifedipine Extended-release Tablets, USP, 90 mg, ANDA #76-070
Minor Amendment

Dear Mr. Buehler:

Biovail Laboratories Inc. wishes to amend its application, ANDA 76-070, to include responses to the Agency correspondence of May 9, 2001.

Biovail has responded to all questions posed by the Agency. Our amendment includes revised draft labeling.

We look forward to receiving Agency comment on our responses, if any, in due course.

Should you require any further information, or have any questions or comments, please do not hesitate to contact the undersigned directly at (703) 995-2280, or by fax at (703) 995-2444.

Yours sincerely,

Wayne Kreppner, M.Sc.
Manager, Corporate Regulatory Affairs

CENTER FOR DRUG
JUL 2 5 2001
OGD
EVALUATION AND RESEARCH

Encl.

7-27-01

BIOVAIL TECHNOLOGIES LTD.
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Tel: **(703) 995-2400** Fax: (703) 995-2490

BIOVAIL
TECHNOLOGIES LTD.

OVERNIGHT COURIER

June 22, 2001

PATENT AMENDMENT

NEW CORRESP
NC

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Metro Park North II
Attention: Document Control Room, Mail Code: HFD-110
7500 Standish Place, Room 150
Rockville, MD 20855

/S/
NDA
6/27/01

ATTN: Peter Rickman
Acting Director, Division of Labeling and Program Support

Re: Nifedipine Extended-release Tablets, 90 mg Notification Issuance/Receipt of Notice; Litigation

Enclosed, please find enclosed in triplicate:

- A signed and dated FDA 356h
- A copy of the Patent Certificate Notice that was sent to Bayer Corporation in Connecticut and Bayer Aktiengesellschaft in Germany
- Proof of delivery by Registered Mail from US Post Service indicating the notice had been received by Bayer USA on March 5, 2001 and Bayer Germany on March 5, 2001.
- Bayer has not filed suit against Biovail with respect to these patents for this product.

If you have any questions or comments, please contact me directly at telephone number (703) 995-2400 or at fax number (703) 995-2444

Kindest regards,
ON BEHALF OF BIOVAIL LABORATORIES INCORPORATED

Wayne Kreppner
Manager, Regulatory Affairs
Biovail Corporation International

CENTER FOR DRUG EVALUATION AND RESEARCH
JUN 25 2001
OGD

BIOVAIL TECHNOLOGIES LTD.
3701 Concorde Parkway, Chantilly, Virginia 20151
Tel: **(703) 995-2400** Fax: (703) 995-2490

ANDA 76-070

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

FEB 21 2001

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to our "Refuse to Receive" letter dated January 25, 2001 and your amendment dated February 7, 2001.

NAME OF DRUG: Nifedipine Extended-release Tablets USP, 90 mg

DATE OF APPLICATION: December 21, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: February 9, 2001

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 copy of a court order or judgement or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Gregory Davis, 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:

Bonnie McNeal
Project Manager
(301) 827-5849

Sincerely yours,

/S/ for

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

BIOVAIL
TECHNOLOGIES LTD.

OVERNIGHT COURIER

505(b)(2)(A) OK
/S/ 21-FEB-2001

ORIG AMENDMENT
N/AC

February 7, 2001

Gary Buehler
Acting 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, 90 mg
Amendment to ANDA 76-070

Dear Mr. Buehler,

Biovail Laboratories Inc. wishes to amend its application, ANDA # 76-070, to include responses to the Agency correspondence of January 25, 2001.

Biovail has addressed all questions and comments posed by the Agency.

We look forward to receiving Agency comment on this amendment, if any, in due course. Should you have any questions or comments about this submission, please contact our US Agent or the undersigned directly at telephone number (703) 995-2400 or at fax number (703) 995-2444.

Yours respectfully,
ON BEHALF OF BIOVAIL LABORATORIES INC.

Wayne Kreppner, MSc, RAC
Manager, Regulatory Affairs
Biovail Technologies Limited

Encl.

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
FEB - 9 2001
OGD

BIOVAIL TECHNOLOGIES LTD.
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Tel: **(703) 995-2400** Fax: (703) 995-2490

BIOVAIL
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OVERNIGHT COURIER

January 15, 2001

NC

1/22/01

MAZ

Gary Buehler
Acting 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, 90 mg
ANDA 76-070

Dear Mr. Buehler,

Please find enclosed the following amendment for ANDA 76-070 (Nifedipine Extended-release Tablets, 90 mg) received by the Office of Generic Drugs on December 26, 2000. During a routine review of the application it was observed that some documentation intended for submission was omitted in error.

Specifically in Section 6.3 dissolution profiles for the test lot (Lot # 00D025) and reference lot (Lot # 8LB1) at [redacted] included but the dissolution profiles at [redacted] were not included. To ensure that all necessary information is submitted the dissolution profiles for the test and the reference lots at [redacted] have been included in Appendix 1 of this submission.

We apologize for any inconvenience this may have caused. Should you have any questions or comments about this submission, please contact me directly at telephone number (703) 995-2400 or at fax number (703) 995-2444.

Yours respectfully,
ON BEHALF OF BIOVAIL LABORATORIES INC.

Wayne Kreppner, MSc, RAC
Manager, Regulatory Affairs
Biovail Technologies Limited

Encl.

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3701 Concorde Parkway, Chantilly, Virginia 20151
Tel: **(703) 995-2400** Fax: (703) 995-2490

ANDA 76-070

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:

Please refer to your abbreviated new drug application (ANDA) dated December 21, 2000, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Nifedipine Extended-release Tablets USP, 90 mg.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to receive this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

You have failed to submit complete comparative *in vitro* dissolution data. A complete dissolution report should contain the individual data for twelve tablets, including means, range and relative standard deviation (RSD) at each time point, a description of the methodology being used, and the lot numbers being tested.

Please provide a financial certification/disclosure statement with an original signature. This information must be provided using FDA form 3454 and/or 3455.

Please provide a signed, dated letter of authorization from the applicant, Biovail Laboratories Incorporated, that authorizes Keller and Heckman to act as their U.S. agent for this abbreviated new drug application.

Please provide a side by side comparison of your container labels with all differences annotated and explained.

Please provide original signatures for FDA form 356h, patent certification, exclusivity statement, field copy certification, cGMP certification, debarment certification, list of convictions statement and environmental impact analysis statement.

Please revise your statement of sample availability to include the active drug substance and the finished drug product.

Thus, it will not be received as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Upon receipt of this communication, you may either amend your application to correct the deficiencies or withdraw your application under 21 CFR 314.99. If you have any questions please call:

Paras Patel
Project Manager
(301) 827-5862

Sincerely yours,

/S/ for

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

BIOVAIL
TECHNOLOGIES LTD.

OVERNIGHT COURIER

Refuse to receive.
4-JAN-2001
/S/
/S/

December 21, 2000

Gary Buehler
Acting Director, Office of Generic Drugs (HFD-110)
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Abbreviated New Drug Application
Nifedipine Extended-release Tablets, 90 mg

Dear Mr. Buehler,

Please find enclosed an Abbreviated New Drug Application for Nifedipine Extended-release Tablets, 90 mg. This Abbreviated New Drug Application has been prepared as outlined in section 314.94 of 21 CFR and is submitted based on the provisions of 505(j) of the Federal Food, Drug and Cosmetic Act by the sponsor and ANDA holder Biovail Laboratories Incorporated.

Biovail Laboratories Incorporated is a wholly owned-subsidiary of Biovail Corporation (BCI) (see attached summary). Further to written communications by Mr. Kreppner, our Manager of Corporate Regulatory Affairs, John Dubeck, Keller and Heckman, is the US Agent for this application.

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
DEC 26 2000
OGD

BIOVAIL TECHNOLOGIES LTD.
3701 Concorde Parkway, Chantilly, Virginia 20151
Tel: **(703) 995-2400** Fax: (703) 995-2490

BIOVAIL
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The submission is comprised of 61 booklets. In accordance with the requirements of the Agency a number of copies have been included in support of this application. These copies have been separated as follows:

- Archival – Blue jackets (all sections, Volumes 1-61)
- Review – Red jackets (CMC, Volumes 1, 58-61) and Orange jackets (Bioequivalence, Volumes 1-57 studies).
- Filed – Burgundy jackets (CMC, Volumes 1, 58-61)

Also, the bioequivalence data has been included on diskettes. These can be found in the first volume of the respective studies in both the Archival and Review copies.

If you have any questions or comments, please contact me directly at telephone number (703) 995-2400 or at fax number (703) 995-2444.

Yours respectfully,
ON BEHALF OF BIOVAIL LABORATORIES INC.

Wayne Kreppner, MSc, RAC
Manager, Regulatory Affairs
Biovail Technologies Limited

Encl.

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