CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

75-289

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

Sponsor: Keller and Heckman.

Approval Dates: September 27, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
75-289

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-289

APPROVAL LETTER

ANDA 75-289

SEP 27 2000

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

Dear Sir:

This is in reference to your abbreviated new drug application dated December 24, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Nifedipine Extended-release Tablets USP, 30 mg and 60 mg.

Reference is also made to your amendments dated December 29, 1998; February 23, July 2, July 23, 1999; April 3, August 7, and September 12, 2000. and September 26, 2000. 9/24/00

We have completed the review of this abbreviated application and have concluded that, based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. Please note that because of the unique regulatory issues associated with this drug product, the agency is unable to approve both strengths at this time. **Accordingly, with respect to the 60 mg strength only, the application is approved.** The Division of Bioequivalence has determined that your Nifedipine Extended-release Tablets USP, 60 mg, to be bioequivalent and therefore therapeutically equivalent to the listed drug (Procardia XL® Tablets, 60 mg, of Pfizer Laboratories).

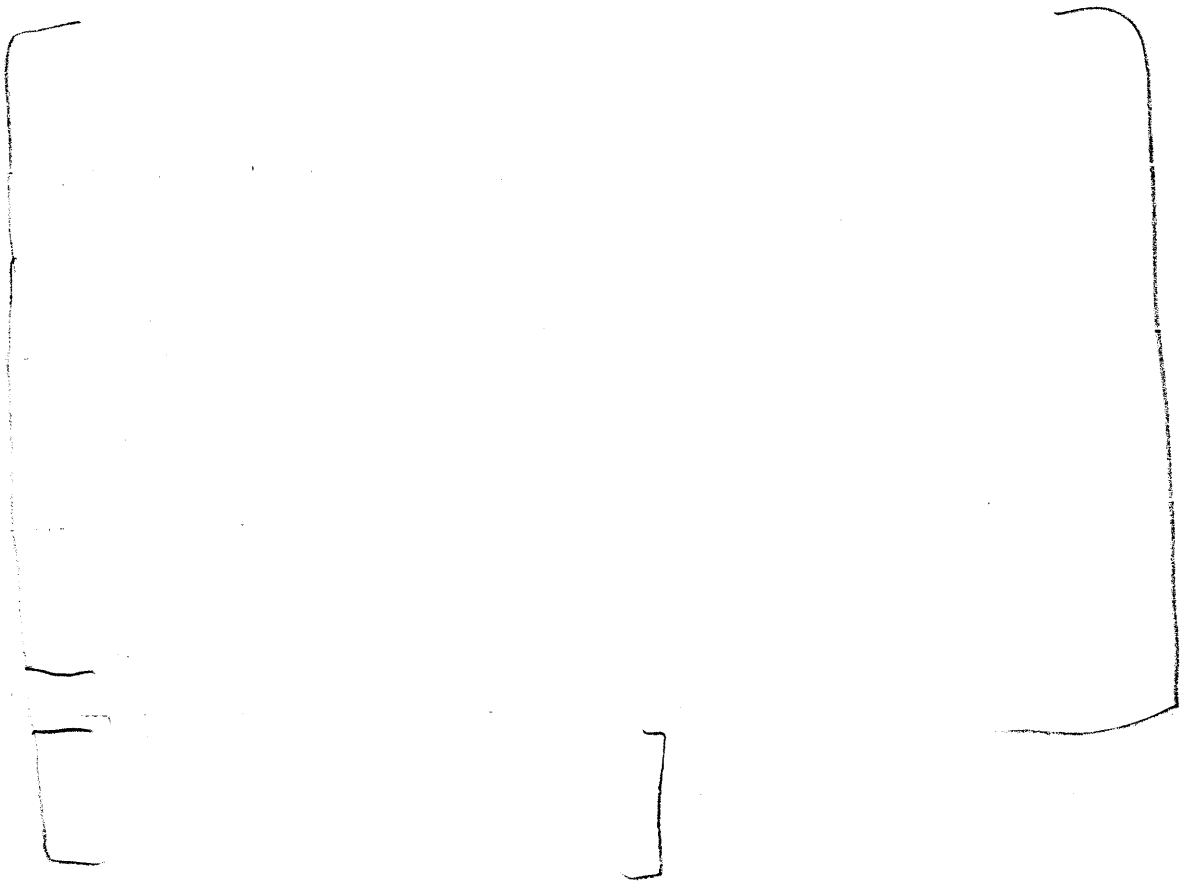
However, due to regulatory issues associated with 180-day generic drug exclusivity which are discussed at the conclusion of this letter, **the 30 mg strength shall remain tentatively approved** and will not receive final approval until all exclusivity issues are satisfactorily resolved.

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:

60 mg Tablet

Dissolution Apparatus/Method

Apparatus	USP rotating paddle method (Apparatus 2)
Rotation speed	100 rpm



For each dosage unit, add the corresponding amount released in phosphate buffer of pH 7.5 to the amount released at each time point in pH 1.2 with SLS.

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 Supplemental-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.

The listed drug product (RLD) noted above and referenced in your application is subject to a period of patent protection which will expire on November 25, 2000, (Patent No. 4327725), September 16, 2003, (Patent No. 4612008, 4765989, 4783337) and November 23, 2010, (Patent No. 5264446). However, litigation is underway in the United States District Court for the District of Puerto Rico involving a challenge to the '446 patent (Bayer AG, Bayer Corp., Pfizer, Inc. v. Biovail Laboratories, Inc., Biovail Corporation International, Civil Action No. 98-1340). Today's approval is based upon the Agency's recognition that the 30-month period identified in Section 505(j)(5)(B)(iii) of the Act, during which time FDA was precluded from approving your 60 mg strength, has expired.

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

We note that with respect to the 60 mg strength only of this drug product, Biovail Laboratories Incorporated (Biovail) was the first applicant to submit a substantially complete ANDA with a Paragraph IV Certification. Therefore, Biovail is eligible for 180-days of market exclusivity for this strength. Such exclusivity will begin to run either from the date Biovail begins commercial marketing of the 60 mg strength, or from the date of a decision of a court finding the patent invalid or not infringed, whichever event occurs earlier [Section 505(j)(5)(B)(iv)]. With respect to the "first commercial marketing" trigger for the commencement of exclusivity, please refer to 21 C.F.R. 314.107(c)(4). The Agency expects that you will begin commercial marketing of the 60 mg strength of this drug product in a prompt manner.

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

Post-marketing reporting requirements for this abbreviated application for the 60 mg strength are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of the 60 mg strength of Nifedipine Extended-release Tablets USP.

We request that you submit, in duplicate, any proposed advertising or promotional copy that 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-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

With respect to the tentative approval of the 30 mg strength of this drug product, our decision to continue the tentative approval status is based upon information available to the Agency at this time (i.e., information in your application and the status of current good manufacturing practices (CGMPs) of the facilities used in the manufacture and testing of the drug product), and is subject to change on the basis of new information that may come to our attention.

We are unable to grant final approval to the 30 mg strength at this time because an abbreviated application for Nifedipine Extended-release Tablets USP, 30 mg, containing a Paragraph IV Certification was accepted for filing by OGD prior to the filing of your application. Accordingly, your application for the 30 mg strength will be eligible for final approval beginning on the date that is one hundred and eighty days after the date the Agency receives notice of the first commercial marketing of the 30 mg strength under the previous application, or the date of a court decision described under section 505(j)(5)(B)(iv), whichever event occurs earlier (Section 505(j)(5)(B)(iv). We refer you to the Agency's recently issued guidance document "180-Day Generic Drug Exclusivity Under the Hatch-Waxman Amendments" (June 1998), for additional information.

Because the Agency is continuing the tentative approval status under this application for the 30 mg strength, you must submit a supplemental application to provide for its full approval. The Agency will provide written notice of the information needed to determine the earliest possible final approval date of your supplemental application for the 30 mg strength under section 505(j)(5)(B)(iv) as soon as such information becomes available.

The supplemental application, which must be submitted for prior approval at least 60, but not more than 90 days prior to the date you believe the 30 mg strength will be eligible for final approval should include updated information such as final-printed labeling, and chemistry, manufacturing and controls data as appropriate. Alternatively, a prior approval supplement should be submitted to request final approval of the 30 mg strength and stating that no changes have been made to the application since the date of this letter.

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

In addition to, or instead of the supplemental application referred to above, the Agency may at any time prior to final approval, request that you submit an informational document containing the information stated above. Regarding the validation of the regulatory methods of this drug product, the Office may wish to repeat this validation and we acknowledge your commitment to satisfactorily resolve any deficiencies, which may be identified.

Failure to submit the supplemental application or informational document may result in rescission of this tentative approval determination, or delay in issuance of the final approval letter for the 30 mg strength.

The 30 mg strength of Nifedipine Extended-release Tablets USP, may not be marketed without final Agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of the 30 mg strength before the final approval date is prohibited under section 501 of the Act. Also, until the Agency issues the final approval letter, the 30 mg strength of the drug product will not be listed in the Agency's "Approved Drug Products with Therapeutic Equivalence Evaluations" list (the "Orange Book").

The supplemental application should be clearly designated as a prior approval supplement in your cover letter. Because of the unique circumstances associated with this drug product, you may request that the supplemental application be granted "expedited review" status. Before you submit the supplement, please

contact Timothy Ames, Project Manager, at (301) 827-5798, for further instructions.

Sincerely yours,

/S/ 9/27/00

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

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-289

TENTATIVE APPROVAL LETTER

ANDA 75-289

JUL 24 2000

JUL 24 2000

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

Dear Sir:

This is in reference to your abbreviated new drug application dated December 24, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Nifedipine Extended-release Tablets USP, 30 mg and 60 mg.

Reference is also made to your amendments dated February 9, and December 29, 1998; February 23, April 7, July 2, July 23, and December 3, 1999; and April 3, April 10, April 12, May 10 and June 12, 2000.

We have completed the review of this abbreviated application and have concluded that, based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. Therefore, the application is **tentatively approved**. This determination is based upon information available to the Agency at this time (i.e., information in your application and the status of current good manufacturing practices of the facilities used in the manufacturing and testing of the drug product) and is therefore subject to change on the basis of new information that may come to our attention. This letter does not address notice issues related to the 180-day exclusivity provisions under section 505(j)(5)(B)(iv) of the Act.

The listed drug product referenced in your application, Procardia XL Tablets of Pfizer Laboratories, is subject to periods of patent protection which expire on November 25, 2000, (Patent No. 4327725), September 16, 2003, (Patent No. 4612008, 4765989, 4783337) and November 23, 2010, (Patent No. 5264446). However, litigation is underway in the United States District Court for the District of Puerto Rico involving a challenge to the '446 patent (Bayer AG, Bayer

Corp., Pfizer, Inc. v. Biovail Laboratories, Inc., Biovail Corporation International, Civil Action No. 98-1494). Therefore, final approval cannot be granted until:

1. a. the expiration of the 30-month period provided for in section 505(j)(5)(B)(iii) since the date of receipt of the 45-day notice required under section 505(j)(2)(B)(i), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or,

   b. the date of court decision [505(j)(5)(B)(iii) (I), (II), or (III)], or,

   c. the patent has expired, and

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

Because the Agency is granting a tentative approval for this application, when you believe that your application may be considered for final approval, you must amend your application to notify the Agency whether circumstances have or have not arisen that may affect the effective date of final approval. Your amendment must provide:

1. a copy of an order or judgement, a settlement agreement between the parties, or a licensing agreement between you and the patent holder, or any other relevant information, and

2. a. updated information related to labeling or chemistry, manufacturing and controls data, or any other change in the conditions outlined in this abbreviated application, or

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

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

In addition to, or instead of, the amendments referred to above, the Agency may, at any time prior to the final date of approval, request that you submit amendments containing the information requested above.

Failure to submit either or both amendments may result in rescission of this tentative approval determination, or delay in issuance of the final approval letter.

The drug product that is the subject of this abbreviated application may not be marketed without final Agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug before the effective final approval date is prohibited under section 501 of the Act. Also, until the Agency issues the final approval letter, this drug product will not be listed in the Agency's "Approved Drug Products with Therapeutic Equivalence Evaluations" list.

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

Sincerely yours,

/S/ 7/24/00

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-289

Final Printed Labeling

Nifedipine Extended-release Tablets, 60 mg in Bottles of 300

N 3 0093-0822-55 1

NDC 0093-0822-55

NIFEDIPINE
Extended-release
Tablets
60 mg

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

℞ only

TEVA

Printed in U.S.A.

APPROVED SEP 27 2000

USUAL DOSAGE: See accompanying prescribing information.
Dispense in tight containers (USP).
Store below 30°C (86°F)
PROTECT FROM MOISTURE AND HUMIDITY.
Contains desiccant.
KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Manufactured By:
Biovail Corporation International
Mississauga, Ontario
Canada L5L 1J9

LL-0194-00/Iss. 2/2000

N 3 0093-0822-55 1

NDC 0093-0822-55

NIFEDIPINE
Extended-release
Tablets
60 mg

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

℞ only

TEVA

Printed in U.S.A.

SEP 27 2000

USUAL DOSAGE: See accompanying prescribing information.
Dispense in tight containers (USP).
Store below 30°C (86°F)
PROTECT FROM MOISTURE AND HUMIDITY.
Contains desiccant.
KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Manufactured By:
Biovail Corporation International
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Canada L5L 1J9

LL-0194-00/Iss. 2/2000

N 3 0093-0822-55 1

NDC 0093-0822-55

NIFEDIPINE
Extended-release
Tablets
60 mg

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

℞ only

TEVA

Printed in U.S.A.

APPROVED SEP 27 2000

USUAL DOSAGE: See accompanying prescribing information.
Dispense in tight containers (USP).
Store below 30°C (86°F)
PROTECT FROM MOISTURE AND HUMIDITY.
Contains desiccant.
KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Manufactured By:
Biovail Corporation International
Mississauga, Ontario
Canada L5L 1J9

LL-0194-00/Iss. 2/2000

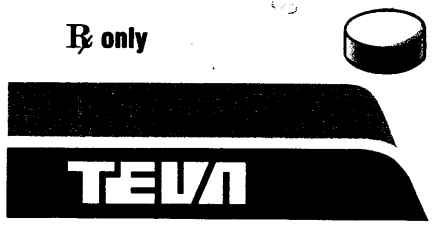
Nifedipine Extended-release Tablets, 60 mg in Bottles of 1000

NDC 0093-0822-10

NIFEDIPINE Extended-release Tablets 60 mg

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

Rx only



USUAL DOSAGE: See accompanying prescribing information.
Dispense in tight containers (USP).
Store below 30°C (86°F)
PROTECT FROM MOISTURE AND HUMIDITY.
Contains desiccant.
KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

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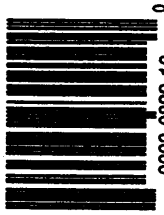
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Manufactured By:
Biovail Corporation International
Mississauga, Ontario
Canada L5L 1J9

LL-0195-00/Iss. 2/2000



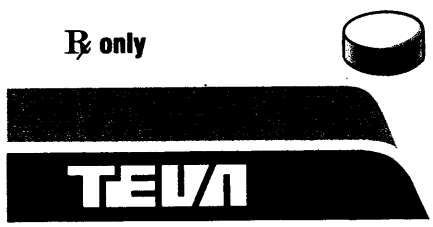
Printed in U.S.A.

NDC 0093-0822-10

NIFEDIPINE Extended-release Tablets 60 mg

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

Rx only



USUAL DOSAGE: See accompanying prescribing information.
Dispense in tight containers (USP).
Store below 30°C (86°F)
PROTECT FROM MOISTURE AND HUMIDITY.
Contains desiccant.
KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

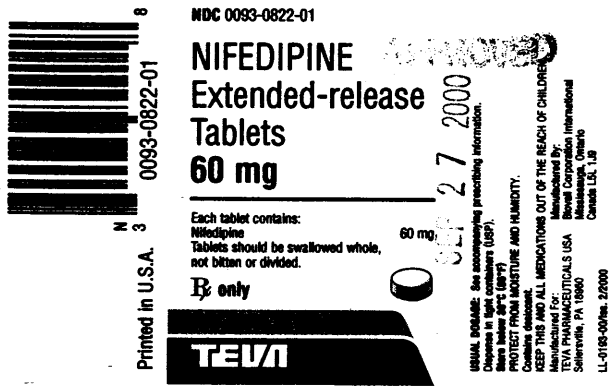
Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

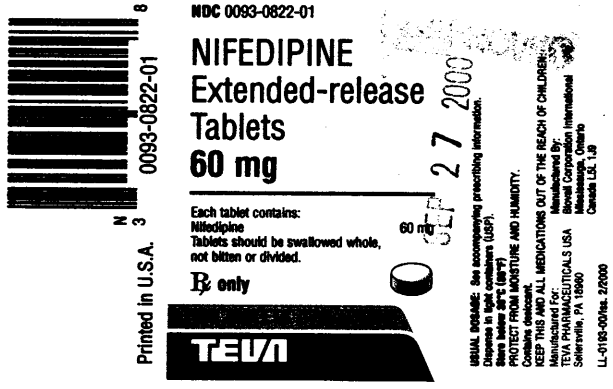
Manufactured By:
Biovail Corporation International
Mississauga, Ontario
Canada L5L 1J9

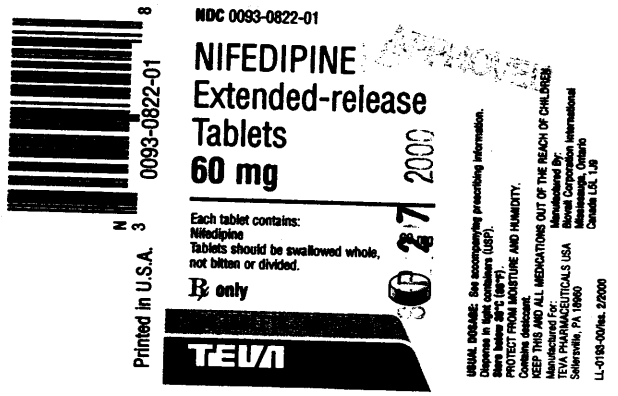
LL-0195-00/Iss. 2/2000

Printed in U.S.A.

Nifedipine Extended-release Tablets, 60 mg in Bottles of 100



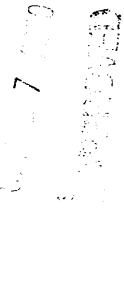




Nifedipine Extended-release Tablets
60 mg

Rx only

For Oral use



DESCRIPTION

Nifedipine is a drug belonging to a class of pharmacological agents known as the calcium channel blockers. Nifedipine is Dimethyl 1,4-dihydro-2, 6-dimethyl-4-(o-nitrophenyl)-3,5-pyridinedicarboxylate, $C_{17}H_{18}N_2O_6$, 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 346.34. Each extended-release tablet, formulated as a once-a-day controlled release tablet for oral administration, delivers 60 mg of nifedipine. In addition, each extended-release tablet contains the following inactive ingredients: anhydrous lactose, colloidal silicon dioxide, ethylcellulose N-100, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, magnesium stearate, methacrylic acid copolymer type A, methacrylic acid copolymer type B, microcrystalline cellulose, polyethylene glycol 600, red ferric oxide, sodium lauryl sulfate, talc, titanium dioxide.

CLINICAL PHARMACOLOGY

Nifedipine is a calcium ion influx inhibitor (slow-channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac muscle and smooth muscle. The contractile processes of cardiac muscle and vascular smooth 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 cardiac muscle and vascular smooth muscle without altering serum calcium concentrations.

Mechanism of Action

A) Angina

The precise mechanisms by which inhibition of calcium influx relieves angina has not been fully determined, but includes at least the following two mechanisms:

1) Relaxation and Prevention of Coronary Artery Spasm

Nifedipine dilates the main coronary arteries and coronary arterioles, both in normal and ischemic regions, and is a potent inhibitor of coronary artery spasm, whether spontaneous or ergonovine-induced. This property increases myocardial oxygen delivery in patients with coronary artery spasm, and is responsible for the effectiveness of nifedipine in vasospastic (Prinzmetal's or variant) angina. Whether this effect plays any role in classical angina is not clear, but studies of exercise tolerance have not shown an increase in the maximum exercise rate-pressure product, a widely accepted measure of oxygen utilization. This suggests that, in general, relief of spasm or dilation of coronary arteries is not an important factor in classical angina.

2) Reduction of Oxygen Utilization

Nifedipine regularly reduces arterial pressure at rest and at a given level of exercise by dilating peripheral arterioles and reducing the total peripheral vascular resistance (afterload) against which the heart works. This unloading of the heart reduces myocardial energy consumption and oxygen requirements, and probably accounts for the effectiveness of nifedipine in chronic stable angina.

B) Hypertension

The mechanism by which nifedipine reduces arterial blood pressure involves peripheral arterial vasodilatation and the resulting 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. Plasma drug concentrations rise at a gradual, controlled rate after a nifedipine extended-release tablet dose and reach a plateau at approximately six hours after the first dose. For subsequent doses, relatively constant plasma concentrations at this plateau are maintained with minimal fluctuations over the 24-hour dosing interval. About a four-fold higher fluctuation index (ratio of peak to trough plasma concentration) was observed with the conventional immediate-release nifedipine capsule at t.i.d. dosing than with once daily nifedipine extended-release tablet. At steady-state the bioavailability of the nifedipine extended-release tablet is 86% relative to nifedipine capsules. Administration of the nifedipine extended-release tablet in the presence of food slightly alters the

Pharmacokinetics and Metabolism
Nifedipine is completely absorbed after oral administration. Plasma drug concentrations rise at a gradual, controlled rate after a nifedipine extended-release tablet dose and reach a plateau at approximately six hours after the first dose. For subsequent doses, relatively constant plasma concentrations at this plateau are maintained with minimal fluctuations over the 24-hour dosing interval. About a four-fold higher fluctuation index (ratio of peak to trough plasma concentration) was observed with the conventional immediate-release nifedipine capsule at t.i.d. dosing than with once daily nifedipine extended-release tablet. At steady-state the bioavailability of the nifedipine extended-release tablet is 86% relative to nifedipine capsules. Administration of the nifedipine extended-release tablet in the presence of food slightly alters the early rate of drug absorption, but does not influence the extent of drug bioavailability. Markedly reduced GI retention time over prolonged periods (i.e., short bowel syndrome), however, may influence the pharmacokinetic profile of the drug which could potentially result in lower plasma concentrations. Pharmacokinetics of nifedipine extended-release tablets are linear over the dose range of 30 to 180 mg in that plasma drug concentrations are proportional to dose administered. There was no evidence of dose dumping either in the presence or absence of food for over 150 subjects in pharmacokinetic studies.

Nifedipine is extensively metabolized to highly water-soluble, inactive metabolites accounting for 60 to 80% of the dose excreted in the urine. The elimination half-life of nifedipine is approximately two hours. Only traces (less than 0.1% of the dose) of 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. Thus, the pharmacokinetics of nifedipine are not significantly influenced by the degree of renal impairment. Patients in hemodialysis or chronic ambulatory peritoneal dialysis have not reported significantly altered pharmacokinetics of nifedipine. Since hepatic biostransformation is the predominant route for the disposition of nifedipine, the pharmacokinetics may be altered in patients with chronic liver disease. Patients with hepatic impairment (liver cirrhosis) have a longer disposition half-life and higher bioavailability of nifedipine than healthy volunteers. The degree of serum protein binding of nifedipine is high (92-98%). Protein binding may be greatly reduced in patients with renal or hepatic impairment.

Hemodynamics
Like other slow-channel blockers, nifedipine exerts a negative inotropic effect on isolated myocardial tissue. This is rarely, if ever, seen in intact animals or man, probably because of reflex responses to its vasodilating effects. In man, nifedipine decreases peripheral vascular resistance which leads to a fall in systolic and diastolic pressures, usually minimal in normotensive volunteers (less than 5-10 mm Hg systolic), but sometimes larger. With nifedipine extended-release tablets, these decreases in blood pressure are not accompanied by any significant change in heart rate. Hemodynamic studies 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 has had no tendency to prolong atrioventricular conduction or sinus node recovery time, or to slow sinus rate.

INDICATIONS AND USAGE

I. Vasospastic Angina
Nifedipine extended-release tablets are indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation. 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. Nifedipine extended-release tablets may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina
(Classical Effort-Associated Angina)
Nifedipine extended-release tablets are indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) nifedipine has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients is incomplete.

Controlled studies in small numbers of patients suggest concomitant use of nifedipine and beta-blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatments, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See WARNINGS.)

III. Hypertension
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 reaction to nifedipine.

WARNINGS

Excessive Hypotension
Although in most angina 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 on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving nifedipine together with a beta-blocking agent 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.

beta-blocking agent who [illegible] anesthesia. The interaction with surgery using high dose fentanyl anesthesia appears to be due to the combination of high dose fentanyl and nifedipine with 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.

The following information should be taken into account in those patients who are being treated for hypertension as well as angina:

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 on starting nifedipine or at the time of dosage increase. The mechanism of this effect is not established.

Beta Blocker Withdrawal
It is important to taper beta blockers if possible, rather than stopping them 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 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 those 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 is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See WARNINGS.)

Peripheral Edema: Mild to moderate peripheral edema occurs in a dose dependent manner with an incidence ranging from approximately 10% to about 30% at the highest dose studied (180 mg). It 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 angina or hypertension is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Other: As with any other non-deformable material, caution should be used when administering nifedipine extended-release tablets in patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of nifedipine extended-release product.

Information for Patients: Nifedipine extended-release tablets should be swallowed whole. 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 (5.4%) increase in mean alkaline phosphatase was noted in patients treated with nifedipine extended-release tablets. This was an isolated finding not associated with clinical symptoms and it rarely resulted in values which fell outside the normal range. Rare instances of allergic hepatitis have been reported. In controlled studies, nifedipine extended-release tablets did not adversely affect serum uric acid, glucose, or cholesterol. Serum potassium was unchanged in patients receiving nifedipine extended-release tablets in the absence of concomitant diuretic therapy, and slightly decreased in patients receiving concomitant diuretics.

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 an 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/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 preexisting chronic renal insufficiency. The relationship to nifedipine therapy is uncertain in most cases but probable in some.

Drug Interactions: Beta-adrenergic blocking agents: (See INDICATIONS AND USAGE and WARNINGS.) Experience in over 1400 patients with nifedipine capsules in a noncomparative clinical trial has shown that concomitant administration of nifedipine and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension, or exacerbation of angina.

Long-acting Nitrates: Nifedipine may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of nifedipine with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing nifedipine 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.

Cimetidine: A study in six healthy volunteers has shown a signif-

icant increase in peak nifedipine plasma levels (80%) and area-under-the-curve (74%), after a one week course of cimetidine at 1000 mg per day and nifedipine at 40 mg per day. Ranitidine produced smaller, non-significant increases. The effect may be mediated by the known inhibition of cimetidine on hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of nifedipine. If nifedipine therapy is initiated in a patient currently receiving cimetidine, cautious titration is advised.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Nifedipine was administered orally to rats for two years and was not shown to be carcinogenic. When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose. There is a literature report of reversible reduction in the ability of human sperm obtained from a limited number of infertile men taking recommended doses of nifedipine to bind to and fertilize an ovum *in vitro*. *In vitro* mutagenicity studies were negative.

Pregnancy: Pregnancy Category C: Nifedipine has been shown to produce teratogenic findings in rats and rabbits, including digital anomalies similar to those reported to phenytoin. Digital anomalies have been reported to occur with other members of the dihydropyridine class and are possibly a result of compromised uterine blood flow. Nifedipine administration was associated with a variety of embryotoxic, placentotoxic, and fetotoxic effects, including stunted fetuses (rats, mice, rabbits), rib deformities (mice), cleft palate (mice), small placentas and underdeveloped chorionic villi (monkeys), embryonic and fetal deaths (rats, mice, rabbits), and prolonged pregnancy/decreased neonatal survival (rats: not evaluated in other species). On a mg/kg basis, all of the doses associated with the teratogenic embryotoxic or fetotoxic effects in animals were higher (3.5 to 42 times) than the maximum recommended human dose of 120 mg/day. On a mg/m² basis, some doses were higher and some were lower than the maximum recommended human dose but all are within an order of magnitude of it. The doses associated with placentotoxic effects in monkeys were equivalent to or lower than the maximum recommended human dose on a mg/m² basis.

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.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Over 1000 patients from both controlled and open trials with nifedipine extended-release tablets in hypertension and angina were included in the evaluation of adverse experiences. All side effects reported during nifedipine extended-release tablet therapy were tabulated independent of the causal relation to medication. The most common side effect reported with nifedipine extended-release tablet was edema which was dose related and ranged in frequency from approximately 10% to about 30% at the highest dose studied (180 mg). Other common adverse experiences reported in placebo-controlled trials include:

Adverse Event	NIFEDIPINE EXTENDED-RELEASE TABLETS (%) (n=707)	PLACEBO (%) (n=266)
Headache	15.8	9.8
Fatigue	5.9	4.1
Dizziness	4.1	4.5
Constipation	3.3	2.3
Nausea	3.3	1.9

Of these, only edema and headache were more common in patients given nifedipine extended-release tablets than placebo patients.

The following adverse reactions occurred with an incidence of less than 3.0%. With the exception of leg cramps, the incidence of these side effects was similar to that of placebo alone.

Body as a Whole/Systemic: asthenia, flushing, pain
Cardiovascular: palpitations
Central Nervous System: insomnia, nervousness, paresthesia, somnolence
Dermatologic: pruritus, rash
Gastrointestinal: abdominal pain, diarrhea, dry mouth, dyspepsia, flatulence
Musculoskeletal: arthralgia, leg cramps
Respiratory: chest pain (nonspecific), dyspnea
Urogenital: impotence, polyuria

Other adverse reactions were reported sporadically with an incidence of 1.0% or less. These include:

Body as a Whole/Systemic: face edema, fever, hot flashes, malaise, periorbital edema, rigors
Cardiovascular: arrhythmia, hypotension, increased angina, tachycardia, syncope
Central Nervous System: anxiety, ataxia, decreased libido, depression, hypertonia, hypoesthesia, migraine, paroniria, tremor, vertigo
Dermatologic: alopecia, increased sweating, urticaria, purpura
Gastrointestinal: eructation, gastroesophageal reflux, gum hyperplasia, melena, vomiting, weight increase
Musculoskeletal: back pain, gout, myalgias
Respiratory: coughing, epistaxis, upper respiratory tract infection, respiratory disorder, sinusitis
Special Senses: abnormal lacrimation, abnormal vision, taste perversion, tinnitus
Urogenital/Reproductive: breast pain, dysuria, hematuria, nocturia

Adverse experiences which occurred in less than 1 in 1000 patients cannot be distinguished from concurrent disease states or medications.

The following adverse experiences, reported in less than 1% of patients, occurred under conditions (e.g., open trials, marketing experiences) where a causal relationship is uncertain: gastrointestinal irritation, gastrointestinal bleeding, gynecomastia.

In multiple-dose U.S. and foreign controlled studies with nifedipine capsules in which adverse reactions were reported spontaneously, adverse effects were frequent but generally not serious and rarely required discontinuation of therapy or dosage adjustment. Most were expected consequences of the vasodilator effects of nifedipine.

Adverse Event	NIFEDIPINE Capsule (%) (n=226)	PLACEBO (%) (n=235)
Dizziness/lightheadedness giddiness	27	15
Flushing/heat sensation	25	8
Headache	23	20
Weakness	12	10
Nausea, heartburn	11	8
Muscle cramps, tremor	8	3
Peripheral Edema	7	1

Dizziness/lightheadedness		
giddiness	27	15
Flushing/heat sensation	25	8
Headache	23	20
Weakness	12	10
Nausea, heartburn	11	8
Muscle cramps, tremor	8	3
Peripheral Edema	7	1
Nervousness, mood changes	7	4
Palpitations	7	5
Dyspnea, cough, wheezing	6	3
Nasal congestion/sore throat	6	8

There is also a large uncontrolled experience in over 2100 patients in the United States. Most of the patients had vasospastic or resistant angina pectoris, and about half had concomitant treatment with beta-adrenergic blocking agents. The relatively common adverse events were similar in nature to those seen with nifedipine extended-release tablets.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

In a subgroup of over 1000 patients receiving nifedipine with concomitant beta blocker therapy, the pattern and incidence of adverse experiences was not different from that of the entire group of nifedipine treated patients. (See PRECAUTIONS.)

In a subgroup of approximately 250 patients with a diagnosis of congestive heart failure as well as angina, dizziness or lightheadedness, peripheral edema, headache or flushing each occurred in one in eight patients. Hypotension occurred in about one in 20 patients. Syncope occurred in approximately one patient in 250. Myocardial infarction or symptoms of congestive heart failure each occurred in about one patient in 15. Atrial or ventricular dysrhythmias each occurred in about one patient in 150.

In post-marketing experience, there have been rare reports of exfoliative dermatitis caused by nifedipine. There have been rare reports of exfoliative or bullous skin adverse events (such as erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis) and photosensitivity reactions.

OVERDOSAGE

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

There has been one reported case of massive overdosage with nifedipine extended-release tablets. The main effects of ingestion of approximately 4800 mg of nifedipine extended-release tablets 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. Electrolyte 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 also 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 must be adjusted according to each patient's needs. Therapy for either hypertension or angina should be initiated with 30 or 60 mg once daily. Nifedipine extended-release tablets should be swallowed whole and should not be bitten or divided. In general, titration should proceed over a 7-14 day period so that the physician can fully assess the response to each dose level and monitor blood pressure before proceeding to higher doses. Since steady-state plasma levels are achieved on the second day of dosing, if symptoms so warrant, titration may proceed more rapidly provided the patient is assessed frequently. Titration to doses above 120 mg are not recommended.

Angina patients controlled on nifedipine capsules alone or in combination with other antianginal medications may be safely switched to nifedipine extended-release tablets at the nearest equivalent total daily dose (e.g., 30 mg t.i.d. of nifedipine capsules may be changed to 90 mg once daily of nifedipine extended-release tablets). Subsequent titration to higher or lower doses may be necessary and should be initiated as clinically warranted. Experience with doses greater than 90 mg in patients with angina is limited. Therefore, doses greater than 90 mg should be used with caution and only when clinically warranted.

No "rebound effect" has been observed upon discontinuation of nifedipine extended-release tablets. However, if discontinuation of nifedipine 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 with Other Antianginal Drugs

Sublingual nitroglycerin may be taken as required for the control of acute manifestations of angina, particularly during nifedipine titration. See PRECAUTIONS, Drug Interactions, for information on co-administration of nifedipine with beta blockers or long-acting nitrates.

HOW SUPPLIED

Nifedipine Extended-release tablets are supplied as 60 mg reddish brown, unscored, film-coated, round tablets, debossed with

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HOW SUPPLIED

Nifedipine Extended-release tablets are supplied as 60 mg reddish brown, unscored, film-coated, round tablets, debossed with "B" on one side and "60" on the other.

Nifedipine Extended-release tablets are supplied in:

	Strength	NDC Code
Bottles of 100	60 mg	0093-0822-01
Bottles of 300	60 mg	0093-0822-55
Bottles of 1000	60 mg	0093-0822-10

Store below 30°C (86°F).
Protect from moisture and humidity.
Packed with desiccant.

Manufactured for:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
USA

Manufactured by:
Biovail Corporation
Mississauga, Ontario
Canada L5L 1J9

LB-0009-00 Iss. 2/00

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-289

CHEMISTRY REVIEW(S)

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

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 75-289

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

4. LEGAL BASIS FOR SUBMISSION
Procardia XL® Tablets, 30 mg and 60 mg
Pfizer Inc.
235 East 42nd Street
New York, NY 10017-5755

The firm filed Paragraph IV Certification, February 18, 1998, with respect to Patents 5264446, 4783337, 4765989, 4612008, and 4327725 for the innovator product, and submitted evidence of notification April 22, 1998. In response to notification of Biovail's Paragraph IV patent certification, Pfizer Inc./Bayer Corp. brought action against Biovail on April 2, 1998 for patent infringement.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Nifedipine USP

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

9. AMENDMENTS AND OTHER DATES:
Firm:
12/24/97 Original submission.
2/5/98 Amendment - Response to Agency's letter of 2/3/98.
2/11/98 Original submission [redacted]
4/22/98 Amendment - Paragraph IV Notification.
4/22/98 Amendment - Paragraph IV Notification [redacted]
6/17/98 Correspondence - US Agent notification.
6/17/98 Correspondence - US Agent notification [redacted]

FDA:
2/3/98 Issuance of Refusal to File Letter
2/11/98 Receipt Acknowledged - Paragraph IV Notice Request

3/10/98 Receipt Acknowledged - Paragraph IV Notice Request

10/7/98 Notification of Merging ANDA 75-289 and ANDA [redacted] issued.

10. PHARMACOLOGICAL CATEGORY
Calcium Channel Blocker

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
NDA #19-684 - Pfizer
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
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DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]

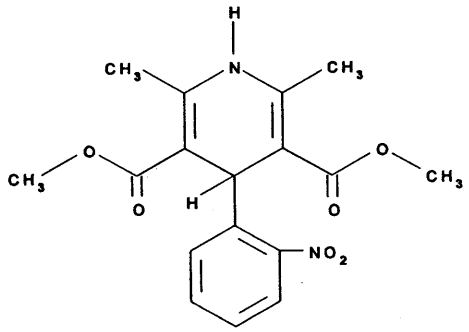
13. DOSAGE FORM
Coated tablet for oral administration

14. POTENCIES
30 mg and 60 mg

15. CHEMICAL NAME AND STRUCTURE

Nifedipine USP

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



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

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

16. RECORDS AND REPORTS
6/29/98 - Bioequivalence review, A. Jackson.
7/6/98 - Bioequivalence review, H. Nyugen
7/31/98 - Labeling review, C. Park.
8/7/98 - Labeling review, C. Park

17. COMMENTS

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

19. REVIEWER:
Glen Jon Smith

DATE COMPLETED:
August 13, 1998
November 13, 1998 (revised)

Redacted 32

pages of trade secret and/or confidential commercial information

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

1. **CHEMISTRY REVIEW NO:** 2

2. **ANDA # 75-289**

3. **NAME AND ADDRESS OF APPLICANT:**
Biovail Laboratories Incorporated
#34 Iturregui Avenue
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N/A

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

7. **NONPROPRIETARY NAME:**
Nifedipine USP

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

9. **AMENDMENTS AND OTHER DATES:**
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4/22/98	Amendment - Paragraph IV Notification [redacted]
6/17/98	Correspondence - US Agent notification.
6/17/98	Correspondence - US Agent notification [redacted]
4/5/99	Major Amendment (CMC, Bio, & Labeling)
4/7/99	Fax Amendment
7/2/99	Bio amendment

FDA:

2/3/98	Issuance of Refusal to File Letter
2/11/98	Receipt Acknowledged - Paragraph IV Notice Request
3/10/98	Receipt Acknowledged - Paragraph IV Notice Request [redacted]
10/7/98	Notification of Merging ANDA 75-289 and ANDA [redacted] issued.
11/30/98	Not approvable Major deficiency letter
4/27/99	Labeling approved

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

11. **Rx or OTC:**
Rx

12. **RELATED IND/NDA/DMF(s):**
NDA #19-684 - Pfizer
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
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13. **DOSAGE FORM:**
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14. POTENCIES:
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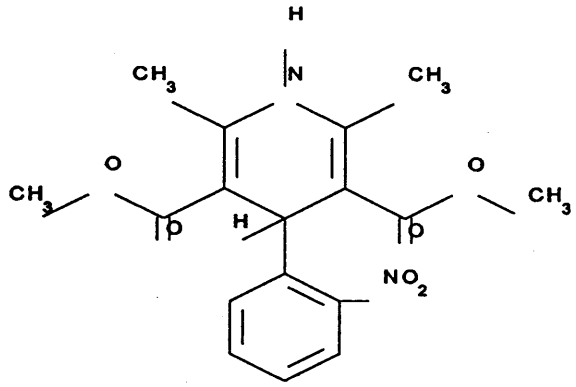

Dimethyl 1,4-dihydro-2,6-dimethyl-4-(*o*-nitrophenyl)-3,5-pyridinedicarboxylate. CAS [21829-25-4]

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

16. RECORDS AND REPORTS:

4/5/99	Submission of Major Amendment by the Firm(CMC, Bio, & Labeling)
4/7/99	Fax Amendment
7/2/99	Bio amendment
11/30/98	Not approvable Major deficiency letter from FDA
4/27/99	Labeling approved

17. **COMMENTS:**

All deficiencies from the first review have been answered with appropriate data. CMC deficiencies include controls for DS, laboratory controls.
Overall EER is issued by the Office of Compliance for all Facilities, as Acceptable, and the printed copy is attached.
Recent Bio Amendment is being reviewed.
Labeling has been approved.
Methods Validation for the drug product has been evaluated by NE Regional Lab and found deficient.
The DMF for the drug substance is adequate. Reviewed by Mouna Selvam, 10/05/1999.

18. **CONCLUSIONS AND RECOMMENDATIONS:**
This Application is presently not Approvable.

19. **REVIEWER:** Mouna P. Selvam

DATE COMPLETED: 9/27/1999-10/15/1999, 10-27-1999

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pages of trade secret and/or confidential commercial information

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs

Chemistry Division II - Branch VIII
Abbreviated New Drug Application Review

1. **CHEMISTRY REVIEW NO:** 3

2. **ANDA # 75-289**

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

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

4. **LEGAL BASIS FOR SUBMISSION:**
Procardia XL Tablets, 30 mg and 60 mg
Pfizer Inc.
235 East 42nd Street
New York, NY 10017-5755

The firm filed Paragraph IV Certification, February 18, 1998, with respect to Patents 5264446, 4783337, 4765989, 4612008, and 4327725 for the innovator product, and submitted evidence of notification April 22, 1998. In response to notification of Biovail's Paragraph IV patent certification, Pfizer Inc./Bayer Corp. brought action against Biovail on April 2, 1998 for patent infringement.

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

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

7. **NONPROPRIETARY NAME:**
Nifedipine USP

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

9. AMENDMENTS AND OTHER DATES:
Firm:

12/24/97	Original submission
2/5/98	Amendment - Response to Agency's letter of 2/3/98
2/11/98	Original submission [redacted]
4/22/98	Amendment - Paragraph IV Notification
4/22/98	Amendment - Paragraph IV Notification
6/17/98	Correspondence - US Agent notification
6/17/98	Correspondence - US Agent notification
4/5/99	Major Amendment (CMC, Bio, & Labeling)
4/7/99	Fax Amendment
7/2/99	Bio amendment
12/3/99	Minor Amendment
04/03/00	Facsimile Amendment **Subject of this review**
04/10/00	Telephone Amendment **Subject of this review**
04/12/00	Telephone Amendment **Subject of this review**
05/10/00	Telephone Amendment **Subject of this review**
06/12/00	Telephone Amendment **Subject of this review**

FDA:

2/3/98	Issuance of Refusal to File Letter
2/11/98	Receipt Acknowledged - Paragraph IV Notice Request
3/10/98	Receipt Acknowledged - Paragraph IV Notice Request [redacted]
10/7/98	Notification of Merging ANDA 75-289 and ANDA [redacted] issued.
11/30/98	Not approvable Major deficiency letter
4/27/99	Labeling approved
11/8/99	Not Approvable Minor Deficiency letter
04/03/00	Bioequivalence letter
04/10/00	Telecon
06/20/00	Bioequivalence Final approval letter

10. PHARMACOLOGICAL CATEGORY:
Calcium Channel Blocker

11. Rx or OTC:
Rx

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

NDA #19-684 - Pfizer

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

13. DOSAGE FORM:

Coated tablet for oral administration

14. POTENCIES:

30 mg and 60 mg

15. CHEMICAL NAME AND STRUCTURE:

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

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

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

16. RECORDS AND REPORTS:

4/5/99	Submission of Major Amendment by the Firm(CMC, Bio, & Labeling)
4/7/99	Fax Amendment
7/2/99	Bio amendment

11/30/98	Not approvable Major deficiency letter from FDA
4/27/99	Labeling approved
8/23/99	Bioequivalence Approved
04/03/00	Bioequivalence New Specification
04/10/00	Telecon
06/20/00	Bioequivalence Final approval letter

17. COMMENTS:

CMC is acceptable. Biovail reconfirms the recent finished product release and stability specifications including impurity limits, residual solvent limits and interim dissolution specifications, for the Nifedipine Extended-release Tablets 30 and 60 mg. Recent Bio Amendment has been reviewed and approved on 06/20/2000.
EER is Acceptable, and the printed copy is attached.
Labeling has been approved. The DMF for the drug substance is adequate. Reviewed by Mouna Selvam, 04/03/2000.
Methods Validation Package submitted.

18. CONCLUSIONS AND RECOMMENDATIONS:
This Application is Approved

19. **REVIEWER:** Mouna P. Selvam, Ph.D., **DATE COMPLETED:** 06/29/2000

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

1. **CHEMISTRY REVIEW NO:** 4

2. **ANDA # 75-289**

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

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

4. **LEGAL BASIS FOR SUBMISSION:**
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Pfizer Inc.
235 East 42nd Street
New York, NY 10017-5755

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

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

7. **NONPROPRIETARY NAME:**

Nifedipine Extended-release Tablets, USP

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

9. **AMENDMENTS AND OTHER DATES:**

Firm:

12/24/97	Original submission
2/5/98	Amendment - Response to Agency's letter of 2/3/98
2/11/98	Original submission [redacted]
4/22/98	Amendment - Paragraph IV Notification
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04/10/00	Telephone Amendment
04/12/00	Telephone Amendment
05/10/00	Telephone Amendment
06/12/00	Telephone Amendment
08/07/00	Minor Amendment, Labeling
08/16/00	Facsimile Amendment, Labeling
08/18/00	Facsimile Amendment, Labeling
09/06/00	Facsimile Amendment, Chemistry
09/14/00	Facsimile Amendment, Chemistry

FDA:

2/3/98	Issuance of Refusal to File Letter
2/11/98	Receipt Acknowledged - Paragraph IV Notice Request
3/10/98	Receipt Acknowledged - Paragraph IV Notice Request [redacted].
10/7/98	Notification of Merging ANDA 75-289 and ANDA [redacted] issued.
11/30/98	Not approvable Major deficiency letter
4/27/99	Labeling approved
11/8/99	Not Approvable Minor Deficiency letter
04/03/00	Bioequivalence letter
04/10/00	Telecon
06/20/00	Bioequivalence Final approval letter

08/17/00 Labeling Approval of 60 mg ER Tablet
09/06/00 Telecon
09/13/00 Telecon (faxed MV deficiencies)

10. PHARMACOLOGICAL CATEGORY:
Calcium Channel Blocker

11. Rx or OTC:
Rx

12. RELATED IND/NDA/DMF(s):
NDA #19-684 - Pfizer
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
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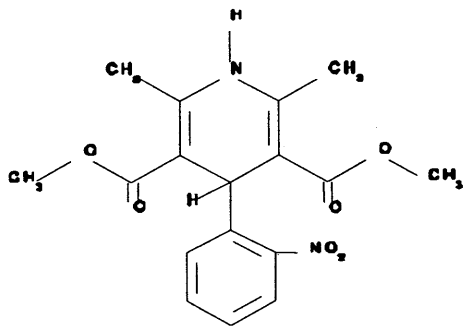
13. DOSAGE FORM:
Coated tablet for oral administration

14. POTENCIES:
30 mg and 60 mg

15. CHEMICAL NAME AND STRUCTURE:

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



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

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

16. RECORDS AND REPORTS:

4/5/99	Submission of Major Amendment by the Firm(CMC, Bio, & Labeling)
4/7/99	Fax Amendment
7/2/99	Bio amendment
11/30/98	Not approvable Major deficiency letter from FDA
4/27/99	Labeling approved
8/23/99	Bioequivalence Approved
04/03/00	Bioequivalence New Specification
04/10/00	Telecon
06/20/00	Bioequivalence Final approval letter
08/17/00	Labeling approval for 60 mg ER Tablet

17. COMMENTS:

[ ]

[redacted]

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

19. **REVIEWER:** Mouna P. Selvam, Ph.D., **DATE COMPLETED:** 08/30/2000

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-289

BIOEQUIVALENCE REVIEW

Nifedipine
60 mg Extended-Release Tablet
ANDA # 75-289
Reviewer: Andre Jackson
WP # 75-289SD.D97

Biovail Incorporated
Mississauga, Ontario , Canada
Submission Date:
December 24, 1997

Review of In-Vivo Single Dose Fasting , Post-Prandial and Multiple Dose Bioequivalence Studies and Dissolution Data

BACKGROUND

Nifedipine, is a prototype calcium channel blocker. The drug is rapidly and completely absorbed after oral administration of the immediate-release formulation *(Physicians' Desk Reference, 47th Edition. Medical Economics Data, 1993, pp 1838)*. However, the absolute biovailability of an oral dose ranges from 45-75 % due to first-pass effect (Kelly, J.G. & O'Malley: Clinical Pharmacokinetics, of Calcium Antagonists, *Clin. Pharmacokinet. 1992;22(6):416-433; AHFS Drug Information 1994, pp 1043)*. The half-life of nifedipine is approximately 2 hours.

Procardia XL is the Extended-Release (ER) formulation of the drug and is marketed as 30 mg, 60 mg and 90 mg tablets. The biovailability of this ER tablet at steady-state is 86% relative to the immediate-release capsules and linear pharmacokinetics have been demonstrated for Procardia XL over the dose range of 30-180 mg.*(Physicians'Desk Reference, 47th Edition. Medical Economics Data, 1993, pp 1840)*.

FOUR-WAY CROSSOVER SINGLE DOSE STUDIES FASTING AND FED

OBJECTIVES

This study was designed to compare the rate and extent of absorption of the following nifedipine products under fasting and fed conditions:

1) Nifedipine XL 60 mg Tablets, (Biovail Corporation International, Research and Development Division, Toronto, Ontario, Canada)

2) Procardia XL 60 mg Tablets (Pfizer Inc., New York, NY, U.S.A.)

Bioequivalence between formulations was evaluated based on the statistical comparisons of the areas under the plasma nifedipine concentration versus time curves (AUCs), and peak concentrations. The GITS expulsion time was determined, and is used to identify outliers only.

METHODS

The study was done as a randomized, four-period, single-dose fasting and food-effect cross-over design in (40) normal, healthy, non-smoking male volunteers. The clinical portion of the study was conducted at Biovail Contract Research, Ontario Canada under the direction of Paul Y. Tam, M.D. The analytical study was done at the same facility under the direction of David McDonald, Ph.D. Study dates were:

Phase I	September 11, 1997
Phase II	September 18, 1997
Phase III	September 25, 1997
Phase IV	October 2, 1997

Samples were analyzed from October 7, 1997 to October 27, 1997. Therefore the total sample storage time was approximately 50 days.

INCLUSION/EXCLUSION CRITERIA

Characterization of Volunteers

40 normal, healthy, non-smoking male volunteers between the ages of 20 to 35, inclusive, were selected for inclusion in the study, no more than thirty (30) days prior to the first drug administration. Subjects who had donated or given blood within 30 days preceding this study, including blood withdrawals during the conduct of any clinical study, were excluded from participation in this trial. Subjects who had taken any investigational drug within thirty (30) days of study entry were also excluded.

Before having the following procedures performed, each prospective subject agreed by signing a Consent To Medical Form. An Inclusion/Exclusion Check List was completed for each subject to assess their suitability for inclusion. Subjects were ruled to be of good health following a physical examination, ECG and medical history by a registered (Ontario) physician. The physician also reviewed pre-clinical laboratory test data from

Constipation and conditions in which constipation was a problem (i.e. hemorrhoids and spastic bowel).

Frequent use of antidiarrheal drugs.

Concurrent Medication

Subjects were informed not to take any drugs for at least fourteen (14) days prior to the study. They were specifically reminded that this included cold preparations, Aspirin, Bufferin, Excedrin, Anacin, etc., vitamin and antacid (magnesium and aluminum hydroxides) preparations. In addition, no concomitant medication was permitted during the study period. Each subject was specifically questioned as to these points by BCR's professional staff prior to each study phase. If a subject admitted to drug ingestion, the Principal Investigator and/or Sponsor decided whether the subject was permitted to remain in the study, depending on the drug used, but the type of drug and dose was noted and reported.

Subjects were requested to abstain from alcohol and xanthine-containing foods and fluids for 48 hours prior to each study phase (this included tea, coffee, chocolate and cola drinks). If there was any doubt about alcohol use, a saliva test for alcohol was performed based on the judgment of the Principal investigator, or their appropriate designee.

EXPERIMENTAL PLAN

Experimental Drug

Treatment Test Nifedipine XL 60 mg tablets
Lot # 97G051, potency, 99.3% label claim, lot size not reported

Treatment Reference Procardia XL 60 mg tablets
Lot Number 57P153A,potency 110% (based on 60mg) , expiration date November 2000

APPEARS THIS WAY
ON ORIGINAL

Negative for drugs of abuse, hepatitis C, hepatitis B-surface antigen and HIV.

No clinical laboratory values outside of the Investigator's acceptable range, unless the Investigator decides they were not clinically significant and records this on the case report form.

Exclusion Criteria

Subjects meeting any of the following criteria were excluded:

Known history of hypersensitivity to nifedipine (Procardia® XL, and/or related drugs.

Known history or presence of cardiac, pulmonary, gastrointestinal, endocrine, neuromuscular, neurological, hematological, liver or kidney disease, or any condition known to interfere with the absorption, distribution, metabolism or excretion of drugs.

Known history of asthma, chronic bronchitis or other bronchospastic condition.

Any clinically significant illness during the last four (4) weeks prior to entry into this study.

Presence of any significant physical or organ abnormality.

Any subject that required maintenance therapy with any drug, or a history of drug dependency, or serious psychological disease.

Regular use of medication, abuse of alcoholic beverages, or participation in a clinical trial with an investigational drug, including MAO inhibitors, within 30 days preceding the study.

Use of enzyme-inducing and enzyme-inhibiting drugs such as phenobarbital, carbamazepine and cimetidine within 30 days prior to entry into this study.

Use of any drugs similar to the one under study, or administration of any medication (including over-the-counter preparations) within 14 days preceding entry into this study.

Blood donation exceeding 250 mL within the previous 30 days.

each subject. In addition, a urine sample provided at the time of the medical had to be free from drugs of abuse. The latter included complete biochemical and hematological screens as well as urinalyses, as follows:

Biochemical Profile - serum electrolytes (sodium, potassium, chloride),serum calcium, urea nitrogen, glucose, total bilirubin, alkaline phosphatase, lactate dehydrogenase, AST (SGOT) and creatinine.

Hematology - hemoglobin, hematocrit, total white blood cell and differential counts, erythrocyte and platelet count and morphology.

Urinalysis - specific gravity, pH, protein, glucose, ketones, bilirubin, blood and microscopic examination, if necessary.

Urine Drug Screen - marijuana, amphetamines, barbiturates, cocaine, opiates, benzodiazepines and alcohol.

HIV, hepatitis C and hepatitis B-surface antigen screen.

Inclusion Criteria

Subjects meeting the following criteria were included in the study.

Non-smoking males between 20 and 35 years of age, inclusive.

Regular bowel habit, i.e. at least one (1) bowel movement in the morning, but not more than two (2) per day.

Body weight not more than ±10% of the ideal weight for the subject's height and frame as determined by the Table of Desirable Weights for Men, recorded in pounds and inches.

Availability of subject for the entire study period and willingness to adhere to protocol requirements, as evidenced by a signed, written Informed Consent Form.

Normal findings in the physical examination, vital signs and ECG (blood pressure $\geq$ 100/60 mm/Hg, pulse rate $\geq$ 50 beats per minute).

Compositions Statement
Formulation for Nifedipine Extended-Release Tablets, 60 mg

	Components	Extended-release Tablet (mg/tablet)
1	Nifedipine. USP	60.000 mg/tablet
2	Hydroxypropylmethyl Cellulose [redacted] USP	[redacted]
3	Hydroxyethylcellulose [redacted], NF	[redacted]
4.	Anhydrous Lactose, NF	[redacted]
5.	Silicon Dioxide, NF	[redacted]
6.	Microcrystalline Cellulose [redacted], NF	[redacted]
7.	Sodium Lauryl Sulphate [redacted] NF	[redacted]
8.	[redacted]	[redacted]
9.	Ethylcellulose N- 100, NF	[redacted]
10.	Magnesium Stearate. NF	[redacted]
11.	Methacrylic Acid Copolymer Type A [redacted] NF	[redacted]
12.	Polyethylene Glycol 600 [redacted] NF	[redacted]
13.	Talc [redacted] USP	[redacted]
14.	Titanium Dioxide. USP	[redacted]
15.	Red Ferric Oxide, NF	[redacted]
16.	[redacted]	[redacted]
17.	[redacted]	[redacted]
18.	Methacrylic Acid Copolymer Type B [redacted] NF	[redacted]

[redacted]

Treatment Plan

The subjects were required to report to the clinic two (2) days prior to drug administration on each phase of the study for diet equilibration.

Subjects received one (1) nifedipine extended-release tablet (total dose 60 mg) with 240 mL water during each study phase, according to the randomized sequence shown in Appendix VI as follows:

Regimen A: (Test product) One (1) 60 mg tablet at 7 AM with 240 mL water 5 minutes following complete ingestion of a standard high fat content breakfast.

Regimen B: (Reference product) One (1) 60 mg tablet at 7 AM with 240 mL water 5 minutes following complete ingestion of a standard high fat content breakfast.

Regimen C: (Test product) One (1) 60 mg tablet at 7 AM with 240 mL water following an overnight fast.

Regimen D: (Reference product) One (1) 60 mg tablet at 7 AM with 240 mL water following an overnight fast.

DOSAGE REGIMEN

SUBJECT NO.	SUBJECTS INITIALS	PERIOD I	PERIOD II	PERIOD III	PERIOD IV
02	LM	A	C	B	D
03	MC	B	D	A	C
04	JB	C	A	D	B
05	GN	C	A	D	B
07	AP	B	D	A	C
08	DR	D	B	C	A
10	DO	A	C	B	D
11	RJ	D	B	C	A
12	RB	D	B	C	A
13	AG	B	D	A	C
14	LV	A	C	B	D
15	GH	D	B	C	A
16	MK	A	C	B	D
17	JC	A	C	B	D
18	NJ	C	A	D	B
19	NM	C	A	D	B
20	GI	D	B	C	A
21	RK	B	D	A	C
22	MO	D	B	C	A
23	DT	B	D	A	C
25	DC	B	D	A	C
26	CH	C	A	D	B
27	WM	A	C	B	D
28	FD	A	C	B	D
29	IV	C	A	D	B
30	PC	D	B	C	A
31	SO	B	D	A	C
32	CR	B	D	A	C
33	NK	C	A	D	B
34	CK	A	C	B	D
35	SMS	D	B	C	A

36	OB	C	A	D	B
38	GK	D	B	C	A
39	GMU	B	D	A	C
40	GR	C	A	D	B

Subject #01 was dismissed prior to Period III drug administration due to adverse events.
Subject #06 did not show up for Period II of the study.
Subject #09 did not show up for Period III of the study.
Subject # 24 withdrew minus (-) Day 2. Period I due to personal reasons.
Subject #37 withdrew prior to Period II entry due to adverse events that occurred in Period I.

There was a 7-day washout period between study phases.

Dietary and Fluid Control

Drug was administered with 240 mL of water. In addition, subjects drank 240 mL water from minus Day 2 until 40.0 hours post-drug at the following scheduled times: minus 20 min, 0.0, 2.0, 4.0, 8.0, 10.0, 12.0, 14.0, and 16.0 hours relative to the time of drug administration. However, additional fluid (caffeine and xanthine free, non-alcoholic beverages) were taken with meals. The times and volumes of fluids ingested by all subjects were recorded from minus (-) Day 2 until 48 hours post-drug. Diet and fluid intake were controlled and consistent from minus (-) Day 2 through to Day 3 (48.0 hours post-dose).

Subjects received a xanthine-free, low fiber content (15 g/day) diet according to the meal schedule provided in Appendix VIII, pg. 548 at the following times:

> *Day* 1: The subjects fasted for at least ten (10) hours prior to drug administration. However, thirty (30) minutes prior to drug administration the subjects in Regimens A and B ingested a standard high fat content breakfast which was completely consumed five (5) minutes prior to drug administration. The standard high fat content breakfast consisted of the following: one egg (fried), one buttered English muffin, one slice of American cheese, one slice of Canadian bacon, one serving of

hash brown potatoes, eight fluid ounces (240 mL) of whole milk, six fluid ounces (180 mL) of orange juice. The subjects taking Regimens C and D continued fasting until 5.0 hours post-drug.
At 5.0, 10.0, and 14.0 hours post-drug, standardized xanthine-free meals were provided to all the subjects, with a non-caffeine containing beverage.

Day 2: Standardized xanthine free meals with a non-caffeine containing beverage was provided at,24.0, 29.0, 34.0,and 38.0 hours post-drug. All meals and beverages were xanthine and caffeine-free and were identical throughout each study phase.

Subject Safety

In this study, subjects remained ambulatory for the first four (4) hours following drug administration. However, if drowsiness, dizziness, or light-headedness occurred, subjects were permitted to sit upright in suitable chairs or lie down on their right side. Subjects did not engage in strenuous activity at any time during the study session.

The attending physician was present prior to dosing and observed all subjects for the first 4.0 hours following drug administration. For the duration of the study period, the subjects were monitored by BCR's professional staff. IV normal saline was available for intravenous administration in the event of any significant prolonged hypotension.

Details of Study

Blood Sampling Schedule

Nineteen (19) blood samples (7 mL each) were taken on each study phase according to the following schedule:

Day 1: 0 (pre-drug), 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0,12.0 and 16.0 hours post-drug (i.e., 7 AM, 8 AM,9 AM, 10 AM, 11 AM, 12 PM, 1 PM, 3 PM, 5 PM, 7 PM and 11 PM)

Day 2.	20.0, 24.0, 28.0, 32.0, 36.0 and 40.0 hours postdrug (i.e., 3 AM, 7 AM, 11 AM, 3 PM, 7 PM and 11 PM)
Day 3:	44.0 and 48.0 hours post-drug (i.e., 3 AM and 7 AM)

Approximately 586 mL of blood were taken over the four study phases, including the amount taken for pre and post-study clinical blood tests.

Vital Signs Measurement

Vital signs (blood pressure and heart rate) were monitored during each study phase as follows:

Days 1 & 2: 0 (pre-drug), 2.0, 4.0, 8.0, 16.0 and 24.0 hours post-drug.

Monitoring continued at hourly intervals, when required until the measurements returned to within ±10% of baseline.

Days 1& 2: 12-lead ECG monitoring was carried out at the following times: 0 (pre-drug), 2.0, 4.0, 8.0, 16.0 and 24.0 hours post-drug.

Feces Collection

During each phase of the study, subjects were required to report all of their bowel movements to the clinic staff. The following information was recorded by the clinic staff: Date and time of bowel movement Stool Consistency (hard, normal or soft) Stool Volume (large, normal or small)

Following drug administration, all bowel movements of all subjects were collected until 24.0 hours post-drug, or until the first bowel movement of Day 2, whichever was earlier. The bowel movements of the subjects who had ingested Procardia XL Tablets were carefully examined for the GITS. All GITS found were put into amber-colored bottles, labeled with the following information:

Subject #-,

Date and clock time of bowel movement;

Phase and study day;
Feces volume (estimate) and consistency (i.e., hard, normal, soft).

Feces samples were discarded after careful inspection for the GITS. The feces sample from the subjects taking the test product was discarded without inspection. The samples were protected from fluorescent lighting during all transfers.

Sampling and Storage Technique

Adverse Events

All events, both expected (known pharmacological response) and unexpected or unwanted, occurring during the course of the study were reported and included onset, nature, severity, duration, intervention(s) and medication(s) required.

All events experienced by the subjects were recorded in the Adverse Event Report Form. The Principal Investigator listed the nature, duration and severity of the adverse event, as well as any medical action taken and the outcome of the event. If appropriate, comments were included on the form by the Investigator.

If a subject withdrew from the study due to an adverse reaction, the subject was requested to provide a blood sample.

Criteria for Removal from the Study

Participation in this clinical study was discontinued for any of the following reasons:

1) intercurrent or adverse events;
2) intercurrent illness;
3) administrative reasons (uncooperative, non-compliant, etc.);
4) subject's decision not to participate any further; or
5) if, in the Investigator's opinion, it is in the subject's best interest.

The physician removed any subject from the study if the subject had an intercurrent event. Detailed records, including follow-up treatment, etc., was provided in the report for any patients having an intercurrent event due to the drug or the invasive venipuncture technique (hematoma or collapsed veins, etc.).

In addition, the physician or designate removed subjects from the study if it was determined that the subject did not follow pre-study directions relating to alcohol and drug use, fasting, etc., or if the subject was uncooperative during the study. Details of reasons for removal of subjects were recorded and reported.

40 subjects were entered into the study (35 completing) and samples from all completing subjects (unless the subject expels the GITS in 16.0 hours or less post-drug) were assayed for pharmacokinetic and statistical analysis.

Data Analysis

Statistical evaluation of concentration-time data was carried out according to current guidelines as described in Appendix V. pg. 543, vol. 1.2

Institutional Review Board

Guidelines, as drawn up by the Institutional Review Board (hereafter IRB) of BCR, were followed with regard to the treatment of human volunteers in the study. These guidelines meet the requirements of the U.S. Code of Federal Regulations (Title 21, Part 56), the Declarations of Helsinki (Appendix II) and the Canadian MRC Guidelines on Research Involving Human Subjects (1987).

This Protocol and the Informed Consent Form were submitted to the IRB. Prior to initiation of the study, a copy of the IRB's approval letter was provided to the Sponsor.

Informed Consent

Before recruitment and enrollment into the study, each prospective candidate was given a full verbal explanation of the study. Once this essential information has been provided to the subject and the physician assures himself that an individual candidate understands the implications of participating in the study, the subject was asked to give consent to participate in the study by signing the Informed Consent Form. A copy of the Informed Consent Form was provided to the subject upon request. The original copy of the signed and dated Informed Consent Form was maintained by BCR. A copy of the Informed Consent Form was included in the final report.

ANALYTICAL METHOD CHARACTERISTICS
OF NIFEDIPINE IN HUMAN PLASMA

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RESULTS

Table 1. Mean plasma concentrations(±sd) for the 35 subjects in the 4-way crossover study. Concentration units are ng/mL.

	FED TEST		FED REFERENCE		FASTED TEST		FASTED REFERENCE	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
HOUR0	0	0	0.03	0.16	0	0	0	0
HOUR1	0	0	0.03	0.16	0	0	0	0
HOUR2	0	0	0.52	0.56	0	0	1.21	1.32
HOUR3	0	0	8.2	6.57	0.6	1.34	11.65	6.74
HOUR4	0.04	0.16	28.78	12.81	4.34	5.52	22.95	12.44
HOUR5	1.53	4.73	41.52	15.03	11.74	9.37	31.37	16.61
HOUR6	7.33	10.83	49.34	21.78	22.44	11.96	36.53	17.47
HOUR8	17.16	15.66	37.33	17.73	21.68	8.71	27.96	15.51
HOUR10	21.95	16.27	37.99	23.04	27.44	14.01	26.71	19.39
HOUR12	38.96	22.53	43.33	22.5	40.92	23.03	37.37	20.2
HOUR16	42.21	24.68	36.98	15.92	45.75	23.37	39.55	17.06
HOUR20	29.45	20.45	28.92	15.83	30.02	17.05	28.77	17
HOUR24	36.88	26.38	32.56	16.98	34.27	20.38	35.04	19.75
HOUR28	32.34	24.15	29.79	16.48	30.91	23.07	35.48	19.22
HOUR32	26.5	19.24	23.32	15.53	24.17	16.09	31.53	19.02
HOUR36	18.36	14.73	14.72	11.53	16.49	14.37	20.91	15.24
HOUR40	11.53	10.08	9.19	7.86	10.51	9.99	14.19	12.47
HOUR44	7.32	6.28	5.67	5.31	6.58	6.25	8.84	8.13
HOUR48	5.49	5.2	3.79	4.06	4.68	5.01	6.46	6.2

The firm did the study as a 4-way crossover. The data was analyzed by the reviewer using the model Y=SEQ + SUBJ(SEQ)+ PER +TRT+RES to determine if there was a significant residual effect. The p value was 0.7 for this analysis indicating that the residual effect was not significant. This result allowed the fasting and food studies to be separated and analyzed independently after removing the residual term from the model.

Table 2. Plasma parameters for fasting study. Values are Mean(%CV)

Parameter	Test Fasting	Reference Fasting	Ratio (Test/Reference
AUCT(ng/ml)x hr	1075.45(48.66)	1213.49(47.66)	0.88
[1]LAUCT(ng/ml) x hr	986.22	1113.50	0.88
AUCI(ng/ml) x hr	1124.29(50.22)	1287.87(51.45)	0.87
[1]LAUCI(ng/ml) x hr	1026.28	1154.38	0.89
Cmax (ng/ml)	56.22(43.58)	51.77(42.30)	1.08
[1]LCmax (ng/ml)	51.80	48.05	1.08
Half-Life (hrs)	6.13(30.09)	6.15(25.45)	
Tmax (hrs)	16.69(36.99)	16.00(60.23)	
Kel (hrs-1)	0.122(25.80)	0.119(23.48)	

1.Geometric mean based upon LSMEANS

Table 3. 90% Confidence Intervals for the Fasting Study

Parameter	
LAUCT	82-95
LAUCI	82-96
LCmax	99-117

Table 4. Plasma parameters for food study. Values are Mean(%CV)

Parameter	Test Food	Reference Food	Ratio (Test/Reference
AUCT(ng/ml)x hr	1037.00(54.27)	1165.59(40.45)	
[1]LAUCT(ng/ml) x hr	923.76	1088.00	0.85
AUCI(ng/ml) x hr	1117.02(54.22)	1206.35(42.27)	
[1]LAUCI(ng/ml) x hr	976.42	1122.11	0.87
Cmax (ng/ml)	57.27(44.15)	58.42(39.65)	
[1]LCmax (ng/ml)	52.69	54.45	0.97
Half-Life (hrs)	6.11(34.27)	5.88(31.78)	
Tmax (hrs)	17.26(43.46)	8.94(62.49)	
Kel (hrs-1)	0.123(25.04)	0.128(27.61)	

1.Geometric mean based upon LSMEANS

CALCULATIONS WERE VERIFIED BY THE REVIEWER

Adverse Events

Eighty-one adverse events were experienced by 30 subjects. The number of events were 11 for test-food; 14 for reference-food; 17 for test-fast; 14 for reference fast. Adverse effects were evenly distributed and the type of event seemed to be the same for all products.

Subject Drop-outs

See randomization table on page 8 of the review.

Sample Repeats

[redacted] samples out of [redacted] were reanalyzed.

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ON ORIGINAL

MULTIPLE DOSE STUDY

Objective

This study was designed to compare the rate and extent of absorption of the following nifedipine products under steady-state fasting conditions:

1) Nifedipine XL 60 mg Tablets, (Biovail Corporation International, Research and Development Division, Toronto, Ontario, Canada)

2) Procardia XL 60 mg Tablets (Pfizer Inc., New York, NY, U.S.A.)

METHODS

The study was done as a randomized, two-way, multiple-dose cross-over design in (48) normal, healthy, non-smoking male volunteers. The clinical portion of the study was conducted at Biovail Contract Research, Ontario Canada under the direction of Paul Y. Tam, M.D. The analytical study was done at the same facility under the direction of David McDonald, Ph.D. The study was conducted from November 4, 1997 to November 26, 1997.
Samples were analyzed from November 27, 1997 to December 4, 1997. Therefore the total sample storage time was approximately 30 days.

Inclusion and Exclusion Criteria

The criteria were the same as for the fasting and fed studies.

Treatment Plan

Subjects received one (1) nifedipine tablet (total daily dose = 60 mg) on Day 1 to Day 7 with 240 mL water during each study phase, according to the randomized sequence shown presented in the following table.

DOSAGE REGIMEN

Subject No.	*Phase* I	*Phase* II	*Subject* No.	*Phase* 1	*Phase* II
1	B	A	26	A	B
2	A	B	26	A	B
3	A	B	27	A	B
4	B	A	28	A	B
5	B	A	29	B	A
6	B	A	30	A	B
7	A	B	31	B	A
8	A	B	32	A	B
9	A	B	33	B	A
10	B	A	34	B	A
11	B	A	35	B	A
12	A	B	36	B	A
13	A	B	37	A	B
14	B	A	38	B	A
16	B	A	39	B	A
16	A	B	40	A	B
17	A	B	41	A	B
18	A	B	42	B	A
19	B	A	43	A	B
20	B	A	44	A	B
21	A	B	45	A	B
22	B	A	46	B	A
23	B	A	47	B	A
24	A	B	48	B	A

A) Nifedipine XL 60 mg Tablets
(Biovail Corporation International)

Day 1 to Day 7: One (1) 60 mg tablet with 240 mL of water following an overnight fast (total daily dose 60 mg)

B) Procardia@ XL 60 mg Tablets (Pfizer Inc.)

Day 1 to Day 7: One (1) 60 mg tablet with 240 mL of water following an overnight fast (total daily dose = 60 mg)

There was a 7-day washout period between study phases.

Dietary and Fluid Control

Drug was administered with 240 mL water from Day 1 to Day 7. In addition, subjects drank 240 mL water at the following times: minus 1(-) 2.0 , 0.0, 2.0, 4.0, 8.0, 10.0, 12.0, 14.0, and 16.0 hours relative to the time of drug administration. However, additional fluid (caffeine and xanthine free, non-alcoholic beverages) may be taken with meals. The times and volumes of fluids ingested by all subjects were recorded from Day 1 through to Day 7.

Diet and fluid intake were controlled and consistent from Day 1 through to Day 7.

Subjects received a xanthine-free, low fiber content (15 g/day) diet according to the meal schedule provided in Appendix IX pg. 3857, vol.1.11.

In each phase of the study, meals were administered relative to the time of drug administration with a non-caffeine containing beverage at the following times: 4.0 hours, 10.0 hours, and 13.0 hours post-dose. The subjects fasted for at least 10 hours prior to drug administration on each study day, and continued fasting until 4.0 hours post-drug. All meals and beverages were xanthine and caffeine-free and were identical throughout each study phase.

Subject Safety

Same as for single dose studies

Details of Study

Experimental Drugs

Treatment Test Fasting Nifedipine XL 60 mg tablets
Lot # 97G051, potency, 99.3% label claim, lot size not reported.

Treatment Reference Fasting Procardia XL 60 mg tablets
Lot Number 57P153A,potency 110% (based on 60mg) , expiration date November 2000.

Blood Sampling Schedule

Seventeen (17) blood samples (7 mL each) were taken on each study phase according to the following schedule:

Day 1:	0 pre-drug
Day 2:	No blood sampling
Day 3:	No blood sampling
Day 4:	0 pre-drug
Day 5:	0 pre-drug
Day 6:	0 pre-drug
Day 7:	0 pre-drug, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0,12.0 and 16.0 hours post-drug
Day 8:	20.0 and 24.0 hours post-drug

Approximately 292 mL of blood was taken over the two study phases, including the amount taken for pre and post-study clinical blood tests.

Vital Signs Measurement

Vital signs (blood pressure and heart rate) were monitored during each study phase as follows:

Days 1 to 7: 0 (pre-drug), 2.0, 4.0, 8.0 and 12.0 hours post-drug.

Monitoring continued at hourly intervals, when necessary, until the measurements returned within ±10% of baseline.

Days 1 to 7: 12-lead ECG monitoring were carried out at the following times: 0 (pre-drug), 2.0, 4.0, 8.0 and 12.0 hours post-drug.

Sampling and Storage Technique

Same as for the single dose study.

Bowel Movements

During each phase of the study, subjects were required to report all of their bowel movements to the clinic staff. The following information was recorded by the clinic staff:

Date and time of bowel movement

Stool Consistency (hard, normal or soft) Stool Volume (large, normal or small)

As per one of the inclusion criteria, a subject must have had at least one bowel movement a day. If the subject did not have at least one bowel movement a day, the plasma samples of the subject were not analyzed.

Adverse Events

Same as for the single dose studies.

Criteria for Removal from the Study

Same as for single dose study.

Data Analysis

Same as for single dose studies.

Institutional Review Board

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ON ORIGINAL

Same as for single dose studies.

Informed Consent

Same as for single dose studies.

ANALYTICAL METHOD CHARACTERISTICS
OF NIFEDIPINE IN HUMAN PLASMA

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RESULTS

Subject Drop-outs

48 subjects qualified for the study. Subjects dropped-out for the following reasons:

Subject #	Reason
37	Personal reasons
41	Adverse event
23	Adverse event
31	Personal reasons
27	Personal reasons
38	Illness
26	Did not show up for Period II
16	Adverse event
15	Adverse event
36	Adverse event
40	Personal reasons

Table 5 Mean plasma concentrations(±sd) for the 37subjects in the 2-way crossover study. Concentration units are ng/mL.

	Test			Reference	
	Mean	SD		Mean	SD
HOUR0	34.05	24.78		41.92	27.24
HOUR1	35.46	25.29		43.96	25.71
HOUR2	34.41	25.41		46.28	30.66
HOUR3	33.96	24.49		53.26	28.84
HOUR4	36.25	24.95		60.82	29.88
HOUR5	48.65	28.59		71.64	33.51
HOUR6	45.5	24.78		63.49	30.49
HOUR8	38.99	21.24		51.92	26.36
HOUR10	38.21	22.16		46.06	23.46
HOUR12	50.07	22.98		53	24.98
HOUR16	47.18	24.87		49.35	23.57
HOUR20	34.53	21.01		36.7	19.18
HOUR24	36.92	26.28		43.8	26.53

The Cmin values were analyzed using the logs of the differences (ie.,Cmin 5 and Cmin 7) to determine if the study had attained

steady-state. A one-sided confidence interval was constructed for these differences for the test and reference formulations. The one-sided CI value was greater than 1 for both test and reference formulations confirming that steady-state had been attained.

The firm has proposed to drop subjects 3, 6, 7, 10, 14, 21, 34, 42 and 47 because they had bowel movements on day 6 only for the test product. Based upon the mechanism of drug release the firm claims that this resulted in the extra 6 mg of reference drug contained in the GITS system to be absorbed. The firm has presented data to the agency that showed some effect of bowel movement on drug absorption, but the study was not conducted in a fashion that would allow one to definitively conclude that bowel movement was the sole causative factor for higher plasma drug levels. As part of these discussions the Division of Bioequivalence acknowledged that at least one bowel movement is considered acceptable 'as an expanded qualification of health.' However, at no time was there a discussion of deleting subjects that did not have a bowel movement from the final data set.

Further analysis of the data in the current study for subjects that had a bowel movement for test and not reference and those that had a bowel movement for both treatments shows that only 1 subject (#47)from the former group exhibited an extreme test/reference ratio of 0.19 for AUC and 0.24 for Cmax. Otherwise ratios from the two groups were comparable.

Table 6. Subject number Test and Reference AUCT and Cmax values and ratios(T/R) for the subjects that had bowel movements for test and reference formulations.

	OBS	SUBJ	Test AUC	Test CMAX	Ref AUC	Ref CMAX	T/R AUC	T/R CMAX
	1	1	774.33	50.15	924.59	60.26	0.8375	0.8322
	2	2	760.69	44.75	648.5	38.83	1.173	1.1525
	3	4	823.71	52.55	906.78	69.01	0.9084	0.7615
	4	5	1371.4	66.68	1481.2	86.7	0.9258	0.7691
	5	8	1620.2	110.99	2568.8	173.36	0.6307	0.6402
	6	9	1499	87.95	1392.4	110.74	1.0766	0.7942
	7	11	501.49	30.92	772.95	53.47	0.6488	0.5783
	8	12	943.98	76.27	1012.3	72.49	0.9325	1.0522
	9	13	855.93	64.47	1053.5	64.58	0.8125	0.9983

	10	17	1378.1	89.46	2019.9	108.91	0.6823	0.8214
	11	18	1546.7	120.58	1253.2	90.16	1.2342	1.3374
	12	19	731.79	53.83	670.92	50.16	1.0907	1.0732
	13	20	1390.3	79.82	1779	124.13	0.7815	0.643
	14	22	1765.3	111.35	1952.8	108.01	0.904	1.0309
	15	24	768.59	65.74	1132.7	95.1	0.6786	0.6913
	16	25	733.72	82.57	995.79	66.83	0.7368	1.2355
	17	28	755.02	45.4	626.57	43.06	1.205	1.0543
	18	29	1083.5	76.73	1400.7	85.11	0.7736	0.9015
	19	30	961.05	54.2	770.28	44.72	1.2477	1.212
	20	32	628.65	49.18	1329.4	98.53	0.4729	0.4991
	21	33	956.05	71.19	859.77	61.88	1.112	1.1505
	22	35	863.23	64.67	852.27	58.14	1.0129	1.1123
	23	39	440.07	48.95	590.81	55.19	0.7449	0.8869
	24	43	1716.4	109.13	1228.2	76.71	1.3974	1.4226
	25	44	736.23	49	588.6	62.55	1.2508	0.7834
	26	45	2032.8	124.08	2217.7	129.42	0.9166	0.9587
	27	46	1118.7	65.15	1143	80.82	0.9788	0.8061
	28	48	437.18	29.67	496.44	44.45	0.8806	0.6675

Table 7. Subject number Test and Reference AUCT and Cmax values and ratios(T/R) for the subjects that had bowel movements for test but not for reference formulations.

	OBS	SUBJ	Test AUC	Test CMAX	Ref AUC	Ref CMAX	T/R AUC	T/R CMAX
	1	3	841.1	56.88	1051.8	70.35	0.7997	0.8085
	2	6	664.95	47.15	1231.9	70.16	0.5398	0.672
	3	7	903.45	47.72	827.98	67.58	1.0912	0.7061
	4	10	2191.2	103.27	2506.8	170.99	0.8741	0.604
	5	14	703.04	58.56	738.49	43.45	0.952	1.3478
	6	21	738.59	60.99	1209.8	87.04	0.6105	0.7007
	7	34	494.2	43.68	1147.8	62.4	0.4306	0.7
	8	42	173.46	18.39	559.26	41.46	0.3102	0.4436
	9	47	328.22	27.89	1679.5	114.09	0.1954	0.2445

Table 8. Plasma parameters for multiple dose study. Values are Mean(%CV) N=37

Parameter	Test Fasting	Reference Fasting	Ratio Test/Ref
AUC(0-Tau)(ng/ml)x hr	979.25(48.67)	1178.98(45.58)	0.83
[1]LAUCT(ng/ml) x hr	870.76	1076.07	0.81
Cmax (ng/ml)	65.94(40.37)	79.48(41.54)	0.83
[1]LCmax (ng/ml)	60.89	73.85	0.82
Tmax (hrs)	11.22(55.75)	8.38(6.52)	

1.Geometric mean based upon LSMEANS

Table 9 90% Confidence Intervals for the Multiple Dose Study.

Parameter	N=37	N=36(#47 deleted)	N=35(#47 and 42 deleted)
LAUC(0-Tau)	72-90	77-92	79.6-93
LCmax	75-91	78-92	80-93

ALL CALCULATIONS WERE VERIFIED BY THE REVIEWER

Adverse Events

There were numerous adverse events and they are being evaluated by Dr. Fanning.

Sample Repeats

[redacted] samples out of [redacted] were reanalyzed.

In-Vitro Dissolution Testing Results

The method used was:
Apparatus USP 2 paddle

[redacted]

Comments

1.The 90% confidence intervals for the single dose fasting study were within the acceptable range of 80-125% of reference.

2.The test to reference ratios of LAUC and LCmax for the food study were within 0.8-1.25 of the reference.

Deficiencies

1.The preamble to the multiple dose study indicated that there was some uncertainty on the part of the firm related to subjects that did not have a bowel movement. It was initially stated "If the subject does not have at least one bowel movement a day, the plasma samples of the subject will not be analyzed", however the next paragraph stated that the criterion was too strict and samples from all subjects that completed the study would be analyzed with those subjects that did not have a bowel movement being classified as within-subject outliers. **The Division of Bioequivalence believes that the firm's first decision not to analyze samples collected from the subjects that did not have a bowel movement was justified.** On the other hand, analyzing the subjects' samples, including them in the data analysis and then designating those subjects without a bowel movement as within-subject outliers is not acceptable to the Division of Bioequivalence.

2.The Division of Bioequivalence does not agree with the firm that subjects 3,6,7, 10, 14, 21, 34, 42, and 47 can be deleted from the data set for the multiple dose fasting study because they did not have a bowel movement after taking the reference formulation. Other subjects within the population that had bowel movements following both formulations had test/reference ratios for AUC(0-tau) and Cmax comparable to those for the subjects which the firm deleted. Therefore, the multiple dose study is unacceptable since with inclusion of these subjects the CI is outside the acceptable range of 80-125% of reference.

3.The firm did not give the lot size for the bio-batch.

4. The Division of Bioequivalence recommends that before dissolution conditions and specification are established that a

multipoint dissolution profiles should be obtained in three aqueous media, for example, [redacted] for the biobatch or marketed batch. Adequate sampling should be performed, for example, at [redacted] thereafter until either [redacted] of the drug from the drug product is released or an asymptote is reached. A surfactant may be used with appropriate justification. If the application/compendial test apparatus is the rotating basket method (Apparatus 1), a rotation speed of 50, 100, and 150 rpm may be used, and if the application/compendial test apparatus is the rotating paddle method (Apparatus 2), a rotation speed of 50, 75, and 100 rpm may be used.

5. The firm should explain why the ratio of Tmax values for the Test/ Reference products in the post-prandial study was 1.93 while the Tmax ratios for the fasting and multiple dose studies were 1.0 and 1.34 respectively.

Recommendation

1.The single dose fasting bioequivalence study conducted by Biovail on its 60 mg Nifedipine ER Tablet, batch 97G051 has been found to be acceptable.

2.The post-prandial study by Biovail on its 60 mg Nifedipine ER Tablet comparing it to Pfizer's Procardia XL 60 mg tablet has been found to be incomplete by the Division of Bioequivalence.

3.The overall application is unacceptable since the post-prandial study was found to be incomplete and the multiple dose fasting study was found to be unacceptable.

4.The in vitro dissolution testing conducted on the 60 mg strength (batch # 97G051), is incomplete.

/S/

Andre J. Jackson
Division of Bioequivalence
Review Branch I

RD INITIALLED YC HUANG
FT INITIALLED YC HUANG /S/ Date: 6/29/98

Concur:_ /S/ Date: 6/30/98
Dale P. Conner, Pharm.D.
Director,
Division of Bioequivalence
cc:ANDA 75-289 (original, duplicate), HFD-650(Director), HFD-652 (Huang, Jackson), Drug File, Division File.

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ON ORIGINAL

Table8. In Vitro Dissolution Testing

Drug (Generic Name):Nifedipine XL
Dose Strengths:60 mg
ANDA No.:75-289
Firm:Biovail Laboratories
Submission Date: December 24, 1997
File Name:75289SD.D97

I. Conditions for Dissolution Testing:

USP XXIII Basket: Paddle:x RPM: 100
No. Units Tested:
Medium:

Volume:
Specifications: Firm's
Proposed Specifications:

Reference Drug: Procardia
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (HRS)	Test Product Batch # 97G038 Strength(mg) 60			Reference Product Batch # 57P153A Strength(mg) 60		
	Mean	Range	%CV	Mean	Range	%CV
1	14		11.6	4		14.6
2	26		9.2	5		15.6
3	38		7.8			

4	49			6.7	15		19.4
6	70			6.0	26		23.3
8	88			5.6	40		15.6
10	98			3.6	54		9.6
12	101			2.6	68		8.6

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-289 APPLICANT: Biovail Laboratories

DRUG PRODUCT:Nifedipine Extended-Release Tablets

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

1.The preamble you presented to the multiple dose study indicated that there was some uncertainty on your part related to subjects that did not have a bowel movement. You initially stated "If the subject does not have at least one bowel movement a day, the plasma samples of the subject will not be analyzed", however the next paragraph stated that the criterion was too strict and samples from all subjects that completed the study would be analyzed with those subjects that did not have a bowel movement being classified as within-subject outliers. **The Division of Bioequivalence believes that the your first decision not to analyze samples collected from the subjects that did not have a bowel movement was justified.** On the other hand, analyzing the subjects' samples, including them in the data analysis and then designating those subjects without a bowel movement as within-subject outliers is not acceptable to the Division of Bioequivalence.

2.The Division of Bioequivalence does not agree with you that subjects 3,6,7, 10, 14, 21, 34, 42, and 47 can be deleted from the data set for the multiple dose fasting study because they did not have a bowel movement after taking the reference formulation. Other subjects within the population that had bowel movements following both formulations had test/reference ratios for AUC(0-tau) and Cmax comparable to those for the subjects which you deleted. Therefore, the multiple dose study is unacceptable since the CI is outside the acceptable range of 80-125% of reference when these subjects are included.

3.You did not give the lot size for the bio-batch.

4. The Division of Bioequivalence recommends that before dissolution conditions and specification are established that multipoint dissolution profiles should be obtained in three aqueous media, for example, in

[redacted] for the bio-batch or marketed batch. Adequate sampling should be performed, for example, at [redacted] thereafter until either [redacted] of the drug from the drug product is released or an asymptote is reached. A surfactant maybe used with appropriate justification. If the application/compendial test apparatus is the rotating basket method (Apparatus 1), a rotation speed of 50, 100, and 150 rpm may be used, and if the application/compendial test apparatus is the rotating paddle method (Apparatus 2), a rotation speed of 50, 75, and 100 rpm may be used.

5. The firm should explain why the ratio of Tmax values for the Test/ Reference products in the post-prandial study was 1.93 while the Tmax ratios for the fasting and multiple dose studies were 1.0 and 1.34 respectively.

Sincerely yours,

/S/

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

APPEARS THIS WAY
ON ORIGINAL

CC: ANDA 75-289
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)
HFD-652/Reviewer
HFD-652/Bio Team Leade /S/ 6/29/98
HFD-617/Project Manage-
HFD-650/Dale Conner /S/ 6/30/98

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(x:new'biovail,ltrs%rev,75289SD.D97..)
BIOEQUIVALENCY - DEFICIENCIES Submission Date: December 24, 1997

1. **FASTING STUDY** (STF) Strengths: 60 mg
Clinical: Biovail, Ontario Canada **Outcome: AC**
Analytical: Biovail, Ontario Canada

2. **FOOD STUDY** (STP) Strengths: 60 mg
Clinical: Biovail, Ontario Canada **Outcome: ~~AC~~ IN**
Analytical: Biovail, Ontario Canada

3. **MULTIPLE DOSE STUDY** (STM) Strengths: 60 mg
Clinical: Biovail, Ontario Canada **Outcome: UN**
Analytical: Biovail, Ontario Canada

4. ~~**DISSOLUTION DATA** (DIS)~~ All Strengths
Outcome: IC

AD 6/30/98

Outcome Decisions:
UN - Unacceptable

APPEARS THIS WAY
ON ORIGINAL

AUG 4 1998

BIOEQUIVALENCY DEFICIENCIES

ANDA: [redacted] APPLICANT: Biovail Laboratories

DRUG PRODUCT: Nifedipine Extended-Release Tablets, 30 mg

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

1. The statistical model used for the study data did not include the **group effect** and the **residual effect**. The group effect should be assessed, and only when this term is found statistically insignificant should the data from the two groups of subjects be pooled. Similarly, the residual effects should be assessed, and only when they are found statistically insignificant should the term(s) be dropped from the model. The 90% confidence intervals for AUCs and CMAX should be calculated based on the correct statistical model.

2. You have not conducted the *in vitro* dissolution testing for the test product in aqueous media of different [redacted] as recommended in the Division of Bioequivalence Guidance for Oral Extended (Controlled) Release Dosage Forms *In Vivo* and *In Vitro* Dissolution Testing (issued September 9, 1993), with early sampling times of [redacted], included in the sampling schedule to provide assurance against dose dumping from the formulation.

In addition, since the drug product is expected to be in the gastric before the intestinal environment, it is not particularly useful to test the test product at [redacted] and then follow by dissolution at the more acidic pH for the next [redacted] as you did in this current submission. The reverse order of pH dissolution testing is the usual practice for the reasons cited above.

Sincerely yours,

/S/

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

Nifedipine ER Tablets, 30 mg
ANDA # [redacted]
Reviewer: Hoainhon Nguyen
WP # [redacted]sd.298

Biovail Corporation
Ontario, Canada
Submission Date:
February 11, 1998

Review of Two Bioequivalence Studies, Disolution Data

I. Background:

Nifedipine is a calcium-channel blocking agent, used in the treatment of vasospastic angina, chronic stable angina and hypertension. Nifedipine is a calcium ion influx inhibitor (slow-channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac muscle and smooth muscle. The contractile processes of cardiac muscle and vascular smooth 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 or cardiac muscle and vascular smooth muscle without altering serum calcium concentrations. Nifedipine is water-insoluble.

Innovator's nifefipine extended-release tablet, Procardia XL®, also called Nifedipine GITS (Gastrointestinal Therapeutic System), consists of a semipermeable membrane surrounding an osmotically active drug core. The core itself is devided into two layers: an "active" layer containing the drug, and a "push" layer containing pharmacologically inert (but osmotically active) components. As water from the GI tract enters the tablet, pressure increases in the osmotic layer and "pushes" against the drug layer, releasing drug through the precision laser-drilled tablet orifice in the active layer. The product is designed to provide nifedipine at an approximately constant rate over 24 hours. This controlled rate of drug delivery into the gastrointestinal lumen is independent of pH or gastrointestinal motility. The product depends for its action on the existence of an osmotic gradient between the contents of the bi-layer core and fluid in the GI tract. Drug delivery is essentially constant, and then gradually falls to zero. Upon swallowing, the biologically inert components of the tablets remain intact during the GI transit and are eliminated in the feces as an insoluble shell.

Nifedipine is completely absorbed after oral administration. Following oral adminstration of a single dose of the drug as extended-release tablets, plasma nifedipine concentrations increase gradually, reaching a peak at approximately 6 hours, and bioavailability is approximately 55-65% of that achieved with the same doses administered orally as conventional capsules. Following multiple doses, oral bioavailability from the extended-release tablets increases to approximately 75-86% of that achieved with the same doses administered as conventional capsules. Administration of nifedipine extended-release tablets with food can increase the early rate of GI absorption but reportedly does not affect overall bioavailability. With another extended-release tablet formulation (Adalat L®, not commercially available in the US), both the rate and extent (over 12 hours) of absorption of a single dose of nifedipine were increased by administration with food. Pharmacokinetics of the innovator's ER tablets are linear over the dose range of 30 to 180 mg in that plasma drug concentrations are proportional to dose administered. There was no evidence of dose dumping either in the presence or absence of food for over 150 subjects in pharmacokinetic studies.

Nifedipine is extensively metabolized on first pass through the liver to highly water-soluble inactive metabolites accounting for 60 to 80% of the dose excreted in the urine. The elimination half-life of nifedipine is approximately 2 hours. Only traces (less than 0.1% of the dose) of 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. Binding of nifedipine to plasma proteins is concentration dependent and ranges from 92-98%.

Therapy for either hypertension or angina should be initiated with 30 or 60 mg once daily, and the tablets should be taken whole, and not bitten or divided.

Most common adverse effects associated with nifedipine ER tablets include dizziness, lightheadedness, giddiness, flushing or heat sensation, and headache, reportedly occurring in up to 25% of patients.

The firm has submitted the results of one fasting/food four-way single-dose and one fasting multiple-dose bioequivalence study for its Nifedipine ER Tablets, 30 mg, comparing it with Procardia XL® CD, 30 mg Tablets, manufactured by Pratt

Pharmaceutical (a division of Pfizer). Comparative dissolution data for the products were also submitted.

II. Bioequivalence Studies:

A. Fasting and Non-Fasting, Four-Way Single-Dose Bioequivalence Study:
(Study No. S73(B97-333PK-NIFB35)) A Four-Way Single-Dose Open-Label Fasting and Food-Effect Bioavailability Study of Nifedipine XL 30 mg Tablets Versus Procardia® XL 30 mg Tablets in Normal Healthy Non-Smoking Male Volunteers

Study Objective:

The purpose of this study is to evaluate the bioequivalency of Biovail's Nifedipine ER Tablets, 30 mg, and Pratt's Procardia XL® 30 mg Tablets under fasting and non-fasting conditions.

Study Investigators and Facilities:

The study was conducted at [redacted] between October 24 and December 17, 1997. The principal investigator was [redacted]. Plasma samples were assayed by [redacted], under the supervision of [redacted] between November 26, 1997 and January 15, 1998.

Demographics:

Thirty-eight normal, healthy non-smoking male volunteers between 20-35 years of age, and within 10% of their ideal weight according to the Metropolitan Life Insurance Company Bulletin, 1983, participated in a four-treatment, four-period, randomized crossover study. The subjects were selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests. The subjects' weight and height ranged 129 - 199 lbs and 63 - 77 in, respectively. Fourteen subjects were caucasians, 23 blacks and 1 asian.

Inclusion/exclusion criteria:

Subjects did not have any history of: hypersensitivity to nifedipine or related drugs; cardiac, pulmonary, gastrointestinal, endocrine, neuromuscular, neurological, hematological, liver or kidney disease, or any condition known to interfere with the absorption, distribution, metabolism or excretion of drugs; asthma, chronic bronchitis or other bronchospastic condition; use of enzyme-inducing or enzyme-inhibitin drugs such as phenobarbital, carbamazepine and cimetidine within 30 days prior to the study; constipation and conditions in which constipation should be avoided (i.e. hemorrhoids and spastic bowel); frequent use of antidiarrheal drugs. In addition, one of the inclusion criteria was presence of regular bowel habit; i.e. at least one bowel movement in the morning but not more than two per day.

Restrictions:

They were free of all medications for 14 days prior to the study. Forty-eight to ten hours prior to dosing, standardized xanthine-free, low-fiber (15g/day) content meals and non-caffeine-containing beverages were provided to the subjects. For the 2 fasting legs of the study (Treatments C and D), the subjects fasted overnight prior to and 5 hours after each drug administration. For the non-fasting legs, the subjects fasted overnight and then were given a standard high-fat content breakfast 30 minutes prior to the drug administration. The standard breakfast consisted of 1 fried egg, 1 slice American cheese, 1 slice Canadian bacon, 1 buttered English muffin, 1 serving of hash brown potatoes, 8 fluid ounces (240 mL) of whole milk, and 6 fluid ounces (180 mL) of orange juice. The washout duration between the phases was 7 days. Duration of confinement was approximately two days pre-dose to approximately 48 hours post-dose.

Treatments and Sampling:

The four treatments consisted of a single 30 mg dose of either the test product or reference product taken orally with 240 ml of water.

Test Product: Biovail's Nifedipine ER Tablets, 30 mg, Lot No. 97G050 (Batch size of [redacted] units, potency of 100.6%), given under fasting conditions

(**Treatment C**), or non-fasting conditions (**Treatment A**).

Reference product: Pfizer's Procardia XL® 30 mg tablets, lot # 57P219E (Potency of 97.3% (Based on [redacted] label claim with [redacted] or 107.0% (Based on 30 mg label claim)), given under fasting conditions (**Treatment D**), or non-fasting conditions (**Treatment B**).

NOTE 1: Potency of the test product differs from that of the reference product by [redacted] potency is used to determine the potency difference between the test and reference product).

NOTE 2: Due to difficulty in recruitment of a large number of subjects (40 was intended per protocol), subjects were recruited in two stages and dosed as **two groups**, Group A numbered 1 through 22, and Group B numbered 23 through 39. Group A Period 1, 2, 3 and 4 was dosed, respectively, on October 27, November 3, November 10, and November 17, 1997; Group B Period 1, 2, 3 and 4 was dosed, respectively, on November 24, December 1, December 8 and December 15, 1997.

[redacted]

Assay Methodology:

[redacted]

Redacted _____ | _____

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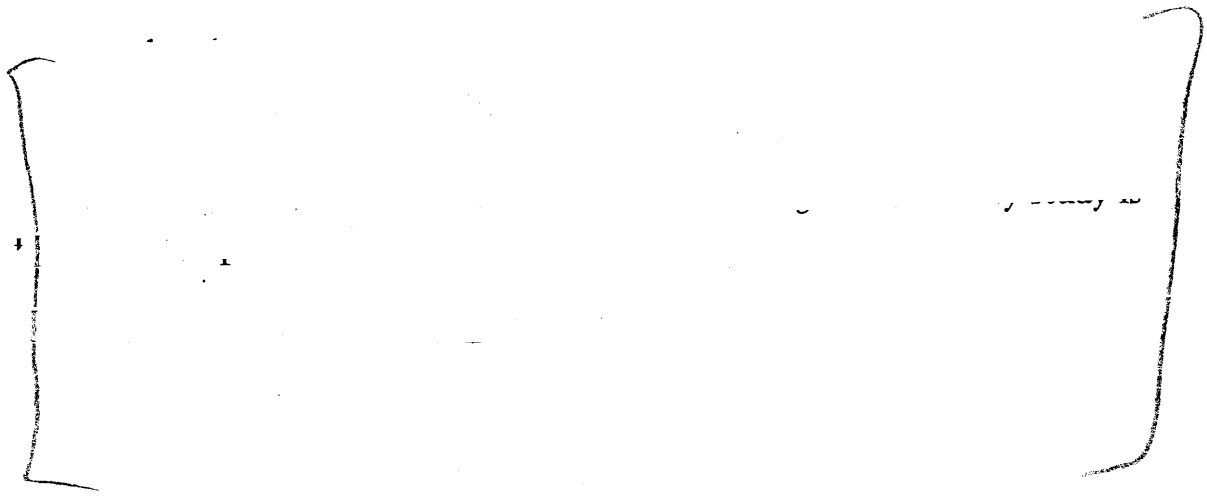

Pharmacokinetic Results:

AUC(0-T) was calculated using the trapezoidal method. AUC(0-Infinity) was calculated by : AUC(0-Infinity) = AUC(0-T) + [last measured concentration/ KEL]. CMAX and TMAX were observed values of the peak plasma concentration and time to peak plasma concentration, respectively. KEL and T1/2 were calculated from the terminal portion of the log concentration versus time curve.

Statistical Analyses:

An analysis of variance and F-test were used to determine statistically significant (p less than 0.05) differences between treatments, sequences of treatment, subjects within sequence, and days of administration for the above pharmacokinetic parameters.

•Deficiency 1: The statistical model used for the study data did not include the *group effect* and the *residual effect*. The group effect should be assessed, and only when this term is found statistically insignificant should the data from the two groups of subjects be pooled. Similarly, the residual effects should be assessed, and only when they are found statistically insignificant should the term(s) be dropped from the model. The 90% confidence intervals for AUCs and CMAX should be calculated based on the correct statistical model.

B. Fasting/Multiple-Dose Bioequivalence Study: (Study No. 1897(B97-330PK-NIFB35)) A Two-Way Multiple-Dose Open-Label Fasting Bioavailabilty Study of Nifedipine XL 30 mg Tablets Versus Procardia® XL 30 mg Tablets in Normal Healthy Non-Smoking Male Volunteers

Study Objective:

The purpose of this study is to evaluate the bioequivalency of Biovail's Nifedipine ER 30 mg Tablets and Pfizer's Procardia XL® 30 mg Tablets under fasting, steady-state conditions using a crossover design.

Study Investigators and Facilities:

The study was conducted at Biovail Contract Research, A Division of Biovail Corp. Int., Ontario, Canada, between October 17 and November 8, 1997. The principal investigators were Paul Y. Tam, M.D.. Plasma samples were assayed at the analytical facility of Biovail, Ontario, Canada, between November 17 and December 5, 1997, under the supervision of David MacDonald, Ph.D..

Demographics:

Forty-eight normal, healthy non-smoking male volunteers between 20-35 years of age, and within 10% of their ideal weight according to the Metropolitan Life Insurance Company Bulletin, 1983, participated in a two-treatment, two-period, randomized crossover study. The subjects were selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests. The subjects' weight and height ranged 126-200 lb and 64-74 in, respectively. Nine subjects were black, 28 caucasians, 2 native americans, 2 asians and 3 hispanics (Note: The demographics are only for 44 subjects who were actually dosed).

Inclusion/exclusion criteria:

See Protocol for Fasting and Non-Fasting/Single-Dose Study above.

Restrictions:

They were free of any medications for 14 days prior to the study and during the study. No alcohol or xanthine-and caffeine-containing beverages and foods for at least 48 hours prior to each study period and throughout the study sessions. The subjects fasted for 10 hours prior to and 4 hours after each drug administration. Diet and fluid intake were controlled and consistent from Day 1 through Day 7. In addition to 240 mL of water taken with each drug administration, the subjects drank 240 mL at the following times: -2.0, 0.0, 2.0, 4.0, 8.0, 10.0, 12.0, 14.0, and 16.0 hours postdose. The subjects also received a xanthine-free, low fiber content (15g/day) diet. The washout duration between phases was 7 days. Duration of confinement was approximately 10 hours prior to Dose 1 and until approximately 24 hours after Dose 7 each period.

Treatments and Sampling:

Each of the two treatments consisted of a single 30 mg dose of either the test product or reference product taken orally with 240 ml of water, once daily for a total of 7 days.

Test Product (Treatment A): Biovail's Nifedipine ER Tablets, 30 mg, Lot No. 97G050 (Batch size of [redacted] units, potency of 100.6%).

Reference product (Treatment B): Pfizer's Procardia XL® 30 mg tablets, lot # 57P219E (Potency of 97.3% (Based on [redacted] label claim with [redacted] or 107.0% (Based on 30 mg label claim)).

Blood samples were collected at pre-Dose 1, pre-Dose 4, pre-Dose 5, pre-Dose 6, pre-Dose 7, and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, and 24 hours following Dose 7 administration. [redacted]

Assay Methodology:

Redacted 1

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Accuracy:

Pharmacokinetic Results:

Steady-state pharmacokinetic parameters for nifedipine were calculated. CMAX and TMAX were determined from the observed plasma concentration-time profile over the sampling interval (Day 7). CMIN was the lowest concentration observed on Day 7 excluding the pre-dose (zero hour) concentration for all formulations. AUC_{0-24} at steady-state was the sum of the linear trapezoidal estimation of the areas from the time of the 7th dose to 24 hours post 7th dose. FLUCT was the percent fluctuation calculated as the difference between CMAX and CMIN divided by $AUC_{0-24}/24$.

Statistical Analyses:

Analysis of variance and F-test were used to determine statistically significant (p less

than 0.05) differences between treatments, sequences of treatment, subjects within sequence, and days of administration for the above pharmacokinetic parameters as well as $LNAUC_{0-24}$ and LNCMAX. The 90% confidence intervals for $lnAUC_{0-24}$ and lnCMAX were calculated, based on least squares means, using the two, one-sided t-test.

Assessment of steady-state: Trough samples were taken prior to the morning dose on Days 4,5, 6 and 7. An analysis of steady-state attainment was performed using concentration data from the pre-dose levels of Day 4,5,6 and 7 and ANOVA model blocking for sequence, subject(sequence), period, and treatment. Steady-state was judged to have been achieved if the time and time*treatment interaction were not significant for either formulation.

Results:

Due to the lack of available subjects, only 47 qualified subjects were entered into the study on October 17, 1997. Subject #3 was dismissed prior to Period I, Day 1 dosing due to an abnormal laboratory result. Subjects #9 and 14 withdrew prior to the start of the study due to personal reasons. Subject #42 withdrew prior to drug administration (Reference treatment) on Day 2 of Period I due to an adverse event (headache). Subject #30 was dismissed prior to drug administration on Day 4 of Period I (Test treatment) due to adverse events consisting of diaphoresis, lightheadedness and nausea. Subjects #21, 17 and 28 withdrew some time after the start of the study due to personal reasons. Subject #10 was dismissed prior to drug administration on Day 5 of Period II (Reference treatment) due to a 1° AV block. Therefore, thirty-eight of 47 enrolled volunteers completed the clinical portion of the study. Data for these 38 subjects were analyzed.

Assessment of steady-state:

The firm's ANOVA results in assessing the attainment of steady-state showed that treatment*time interaction is statistically significant ($p=0.0256$). However, the differences between treatments and between times are not statistically significant.

Additional assessment of the attainment of steady-state was done by the reviewer

using the one-sided t-test comparing pairs of consecutive CMINs for each treatment, a method proposed by Dr. Andre Jackson of the DBE and to be published shortly. The 90% confidence limits were above 1.0 for all pairwise consecutive CMIN comparisons for both treatments, except for the comparison between CMINs of Days 4 and 5 for the Test treatment (The limit was 0.835). The steady-state is therfore considered achieved for the study.

There was significant difference (alpha=0.05) between treatments for lnAUC(p=0.0100) and TMAX(p=0.0371). The results are summarized in the tables below:

Table I
Nifedipine Comparative Pharmacokinetic Parameters
Multiple-Dose Study; Dose = 7x30 mg; n = 38

Parameters	Biovail Mean (CV)	Procardia XL® Mean (CV)	90% C.I.	Ratio T/R
AUC_{0-24} ng.hr/ml	493.8*	566.3*	[0.80;0.95]	0.87
CMAX(ng/mL	34.54*	37.79*	[0.84;0.99]	0.91
CMIN(ng/mL)	17.41*	19.57*	[0.78;1.02]	0.89
TMAX (hrs)	11.82(60)	8.55(71)		
FLUCT(%)	78.29(85)	72.12(67)		
CAVE(ng/mL)	22.39(42)	25.22(38)		

*Geometric, LS Means

Table II
Comparative Mean Plasma Levels of Nifedipine
Multiple-Dose Study; Dose = 7x30 mg; n = 38
ng/ml(CV)

Hour	Test	Reference
0(Day 1)	0	0
0(Day 4)	21.28(50)	20.62(55)
0(Day 5)	16.75(67)	21.61(54)
0(Day 6)	22.78(69)	19.30(58)
0(Day 7)	19.58(53)	20.35(53)
1.0	20.62(55)	21.86(53)
2.0	20.69(56)	22.17(49)
3.0	18.81(53)	25.37(48)
4.0	18.83(55)	30.69(46)
5.0	25.25(46)	37.85(43)
6.0	25.44(53)	32.76(45)
8.0	20.75(57)	29.28(51)
10	19.53(52)	24.52(46)
12	25.00(44)	28.01(43)
16	26.96(49)	24.82(38)
20	19.59(63)	18.07(46)
24	21.72(62)	22.47(51)
$AUC_{0\text{-}24(ng.hr/ml)}$	537.4(42)	605.4(38)
$CMAX_{ng/ml}$	36.74(37)	40.60(39)
$CMIN_{ng/ml}$	21.72(62)	22.47(51)
Fluct(%)	78.29(85)	72.12(67)

Adverse Effects:

There was no serious adverse effect. The mild-to-moderate adverse events included:

lightheadedness, flushing, dry mouth/dry skin, face burning/dryness/reddened, sinus bradycardia, pulse deviation, dry/red eyes, borderline 1° AV block, giddiness, diaphoresis, coolness of the right arm, faintness, diarrhea, hot feeling, chest pain, weakness to knees, dizziness, indigestion, sore left knee, bilateral lower leg/left mid sternal tingling, sinus tachycardia and stomach cramps. Two hundred thirty seven adverse events took place during the Test treatment, and 228 during the Reference treatment. There were 37 possibly or probably drug related adverse events reported by 22 subjects.

III. Dissolution Testing: Presently there is no official USP or FDA dissolution methods and specification for the drug product.

Drug (Generic Name): Nifedipine ER Tablets Firm: Biovail
Dose Strength: 30 mg ANDA # [redacted]
Submission Date: February 11, 1998

In-Vitro Dissolution Testing

Conditions for Dissolution Testing:
USP XXIII Basket__ Paddle X RPM ~~20 dips/min~~ 100 rpm Units Tested [redacted]

Reference Drug: (Manuf.) Procardia XL Tablets, 30 mg (Pratt)
Assay Methodology: [redacted]
Firm's Specification:

Time	Amount Dissolved (%)
[redacted]	NMT [redacted]
[redacted]	NMT [redacted]
[redacted]	[redacted]
[redacted]	NLT [redacted]

●Deficiency 2: The firm has not conducted the *in vitro* dissolution testing for the test product in aqueous media of different *pH ranges:* [redacted] as recommended in the Division of Bioequivalence Guidance for Oral Extended (Controlled) Release Dosage Forms *In Vivo* and *In Vitro* Dissolution Testing (issued September 9, 1993), with early sampling times of [redacted] included in the sampling schedule to provide assurance against dose dumping from the formulation.

In addition, since the drug product is expected to be in the gastric before the

intestinal environment, it is not particularly useful to test the test product at [redacted] for the [redacted] and then follow by dissolution at the more acidic pH for the next [redacted] as did the firm in this current submission. The reverse order of pH dissolution testing is the usual practice for the reasons cited above.

IV. Comment:

The multiple-dose bioequivalence study is acceptable. The test and reference products are equivalent under steady state conditions in the rate and extent of absorption of nifedipine, as measured by log-transformed AUC and CMAX.

V. Recommendations:

1. The **single-dose, fasting/non-fasting** bioequivalence study conducted by Biovail on the test product, Nifedipine ER Tablets, 30 mg, lot # 97G050, comparing it with the reference product, Pfizer 's Procardia XL® Tablets, 30 mg Tablets, lot # 57P219E, have been found **incomplete** by the Division of Bioequivalence due to the reasons cited in the Deficiency No. 1 (Statistical Analysis deficiency) above .

2. The **multiple-dose, fasting** bioequivalence study conducted by Biovail on the test product, Nifedipine ER Tablets, 30 mg, lot # 97G050, comparing it with the reference product, Pfizer 's Procardia XL® Tablets, 30 mg Tablets, lot # 57P219E, has been found **acceptable** by the Division of Bioequivalence.

3. The in-vitro dissolution testing conducted by Biovail on its Nifedipine ER Tablets, 30 mg, and Pfizer 's Procardia XL Tablets, has been found unacceptable due to the Deficiency No. 2 above.

The firm should be informed of the Recommendations and Deficiencies.

/S/

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

BIOEQUIVALENCY DEFICIENCIES

ANDA: [redacted] APPLICANT: Biovail Laboratories

DRUG PRODUCT: Nifedipine Extended-Release Tablets, 30 mg

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

1. The statistical model used for the study data did not include the **group effect** and the **residual effect**. The group effect should be assessed, and only when this term is found statistically insignificant should the data from the two groups of subjects be pooled. Similarly, the residual effects should be assessed, and only when they are found statistically insignificant should the term(s) be dropped from the model. The 90% confidence intervals for AUCs and CMAX should be calculated based on the correct statistical model.

2. You have not conducted the *in vitro* dissolution testing for the test product in aqueous media of different **pH ranges:** [redacted], as recommended in the Division of Bioequivalence Guidance for Oral Extended (Controlled) Release Dosage Forms *In Vivo* and *In Vitro* Dissolution Testing (issued September 9, 1993), with early sampling times of [redacted], included in the sampling schedule to provide assurance against dose dumping from the formulation.

In addition, since the drug product is expected to be in the gastric before the intestinal environment, it is not particularly useful to test the test product at [redacted] for the [redacted] and then follow by dissolution at the more acidic pH for the next [redacted], as you did in this current submission. The reverse order of pH dissolution testing is the usual practice for the reasons cited above.

Sincerely yours,

/S/

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

CC: ANDA
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)
HFD-652/HNguyen /S/ 7/23/98
HFD-652/YHuang /S/ 7/23/98
HFD-617/Project Manager
HFD-650/Dale Conner /S/ 7/23/98

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BIOEQUIVALENCY - DEFICIENCIES Submission Date: February 11, 1998

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

2. **MULTIPLE DOSE STUDY** (STP) Strengths: 30 mg
Clinical: Biovail Contract Research **Outcome: AC**
Analytical: Biovail Contract Research

4. **DISSOLUTION DATA** (DIS) All Strengths
Outcome: UN

Outcome Decisions:
AC - Acceptable
NC - No Action
UN - Unacceptable
IC - Incomplete

WinBio Comments

APPEARS THIS WAY
ON ORIGINAL

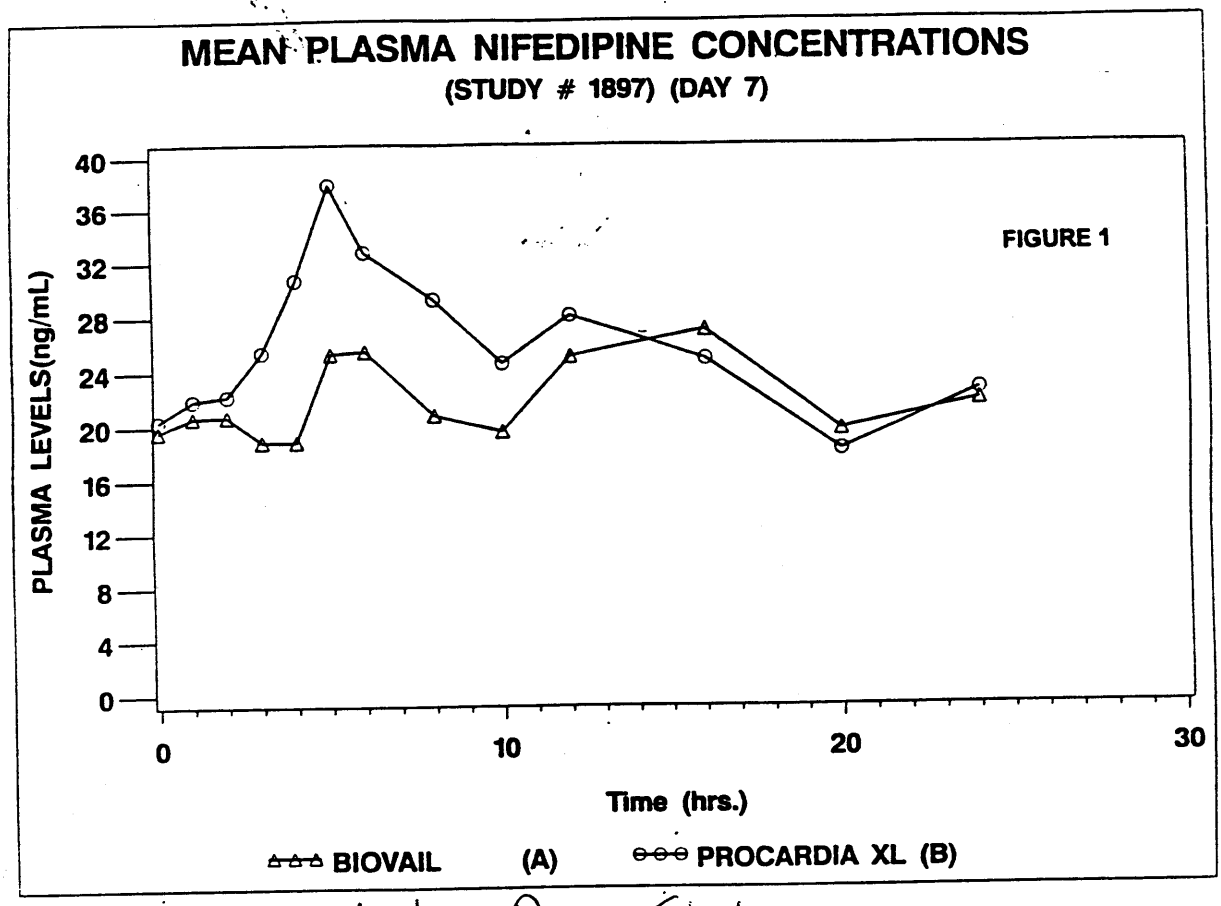
Section 7: Compositions Statement
B35 ANDA
Nifedipine Extended-release Tablets, 30 mg

	Components	Extended-release Tablet (mg/tablet)
1.	Nifedipine, USP	30.000 mg/tablet
2.	Anhydrous Lactose, NF	[redacted]
3.	[redacted]	[redacted]
4.	Ethylcellulose N-100, NF	[redacted]
5.	Hydroxyethylcellulose, NF	[redacted]
6.	Hydroxypropylmethyl Cellulose, USP	[redacted]
7.	[redacted]	[redacted]
8.	Magnesium Stearate, NF	[redacted]
9.	Methacrylic Acid Copolymer Type A, NF	[redacted]
10.	Methacrylic Acid Copolymer Type B, NF	[redacted]
11.	Microcrystalline Cellulose, NF	[redacted]
12.	Polyethylene Glycol 600, NF	[redacted]
13.	[redacted]	[redacted]
14.	Red Ferric Oxide, NF	[redacted]
15.	Silicon Dioxide, NF	[redacted]
16.	Sodium Lauryl Sulphate, NF	[redacted]
17.	Talc [redacted], USP	[redacted]
18.	Titanium Dioxide, USP	[redacted]

[redacted]

WP# [redacted] sd. 298 Attachment (1 of 2)

BIOVAIL CORPORATION INTERNATIONAL
STUDY # 1897 (B97-330PK-NIFB35)



Multiple-Dose Study

APPEARS THIS WAY
ON ORIGINAL

MAY 26

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-289 APPLICANT: Biovail Laboratories

DRUG PRODUCTS: Nifedipine 30 mg and 60 mg ER Tablets

30 mg ER Tablet

The Division of Bioequivalence has completed its review on your 30 mg ER tablet and has no further questions at this time.

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

The dissolution testing should be conducted as follows:

Dissolution Apparatus/Method

Apparatus	USP rotating paddle method (Apparatus 2)
Rotation speed	100 rpm

[redacted]

*For each dosage unit, add the corresponding amount released in [redacted] to the amount released at each time point in [redacted]

APPEARS THIS WAY
ON ORIGINAL

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.

60 mg ER Tablet

The Division of Bioequivalence has completed its review of your 60 mg tablet. The following deficiencies have been identified:

1.You did not give the potency for the reference lot 87T005A used in the multiple dose study.

2.You conducted the multiple dose study using three groups but did not do the statistical analysis with group in the model.

3.You should repeat the statistical analysis using the following model to test if group is significant at p=0.05.

Y= Group Sequence Subjects(Group*Sequence) Period(Group)
Trt Group*Trt

If group is not significant, then group*trt can be dropped from the model and the data reanalyzed.

An ASCII file containing the multiple dose raw plasma data and parameters coded for groups should be submitted with the analysis.

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4. You should explain why subject #42 for the reference had a time zero concentration of [redacted].

Sincerely yours,

/S/

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

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CC: ANDA 75289
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)
HFD-652 /Reviewer
HFD-652 /Bio Team Leader /S/ 5/11/99
HFD-617/Project Manager
HFD-650/Dale Conner /S/ 5/17/99

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BIOEQUIVALENCY - DEFICIENCIES 60 mg
Submission Date: December 29, 1998

1. **MULTIPLE DOSE STUDY** (STM) ✓
Clinical: _____
Analytical: Biovail, Ontario Canada

Strengths: 60 mg
Outcome: IC

2. **STUDY AMENDMENT** (STA) ✓

Strengths: 30 mg
Outcome: AC

Outcome Decisions:

IC - Incomplete

WinBio Comments

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ON ORIGINAL

Nifedipine
60 mg Extended-Release Tablet
30 mg Extended-Release Tablet
ANDA # 75-289
Reviewer: Andre Jackson
WP # 75-289ASD.D98
V:\Firmsam\Biovail\ltrs&rev\75289ASD.D98

Biovail Incorporated
Mississauga, Ontario, Canada
Submission Date:
December 29, 1998
February 23, 1999

Review of An Amendment to the 30 mg ER Tablet In-Vivo Single Dose Fasting Study and a New Multiple Dose Bioequivalence Study on the 60 mg ER Tablet and Dissolution Data

Background:

The firm submitted two ANDA's (i.e., ——— for their 30 mg ER tablet and 75-289 for their 60 mg ER tablet) to the Division of Bioequivalence. ANDA # ——— contained two bioequivalence studies, a single dose fasting and non-fasting four-way crossover and a multiple dose two-way crossover. The single dose study had deficiencies while the multiple dose study was found to be acceptable. The former ANDA has been collapsed into the ANDA # 75-289 (See agency letter dated October 1, 1998). Both dosage strengths had deficiencies. The current submission contains the firm's response to those deficiencies.

30 mg STUDY

FDA Question # 1:

The statistical model used for the study data did not include the group effect and the residual effect. The group effect should be assessed, and only when this term is found statistically insignificant should the data from the two groups of subjects be pooled. Similarly, the residual effects should be assessed, and only when they are found statistically insignificant should the term(s) be dropped from the model. The 90% confidence intervals for AUCs and Cmax should be calculated based on the corrected statistical model.

Firm's Response # 1:

The logarithmic transformed data of AUC_{0-t}, $AUC_{0-\infty}$, and Cmax were analyzed using ANOVA. Specifically, we used the Generalized

Linear Model of the SAS software package. A statistical model was used that incorporated the group effect and carry-over effect. Only the first order carry-over effect is considered in this analysis.

The results of ANOVA are summarized in the attached tables. These results show that both the group and carry-over effect were not significantly different from zero for the pharmacokinetic parameters AUC_{0-t}, $AUC_{0-\infty}$, and Cmax. Since the group effect and the carry-over effect are insignificant ($p>0.05$), they should be dropped from the statistical model, thereby confirming the statistical relevance of the model used in the original analysis for the ANDA submission. Therefore, the conclusions we made based on the results of the statistical analysis in the original submission should be retained: the test product, Nifedipine Extended Release Tablets, 30 mg (Biovail Lot #97G050) is bioequivalent to the reference product, Procardia XL Tablets, 30 mg (Pfizer Lot #57P219E) (see pages 5919 through 5926 of the ANDA submission).

FDA Response-The firm's reply is acceptable.

The dissolution questions asked by the FDA for the combined submissions (i.e., 30 mg and 60 mg) were slightly different, but the firm's response was similar and resulted in the establishment of a dissolution procedure and specifications for both products. Therefore, only the response to the 30 mg tablet will be given. Any details related to the 60 mg tablet can be found in Appendix 3 of ANDA# 75-289.

FDA Question # 2:

You have not conducted the in vitro dissolution testing for the test product in aqueous media of different pH ranges: [redacted] as recommended in the Division of Bioequivalence Guidance for Oral Extended (Controlled) Release Dosage Forms In Vivo and In Vitro Dissolution Testing (issued September 9, 1993), with early sampling times of [redacted] included in the sampling schedule to provide assurance against dose dumping from the formulation.

In addition, since the drug product is expected to be in the gastric before the intestinal environment, it is not particularly useful to test the test product at [redacted] for the [redacted]

and then follow by dissolution at the more acidic pH for the next [redacted], as you did in this current submission. The reverse order of pH dissolution testing is the usual practice for the reasons cited above.

Firm's Response # 2:

To meet the requirements of in-vitro dissolution for quality control, pre-approval dissolution testing has been conducted on 12 (twelve) individual dosage units of the test (Biovail Lot #97G036) and reference (Procardia Lot #57P219E) products used in the bioequivalence studies. Dissolution profiles generated in aqueous [redacted] media of pH [redacted] and water for both the test and reference product have been appended to this response (Appendices 1a - 1e and 2a - 2e, respectively). Furthermore, dissolution data for the test and reference products in [redacted] are also included in Appendices 1f and 2f, respectively.

The test product is comprised of an [redacted] contains, among other items, the following [redacted] Methacrylic Acid Copolymer Type A NF [redacted] Methacrylic Acid Copolymer Type B NF [redacted] and a [redacted] in the form of Polyethylene Glycol 600 NF. The [redacted] media, for up to [redacted]. The tablet [redacted] dissolves within 30 minutes in alkaline media, for example, [redacted] characteristic of our tablet has been identified in our existing Quality Standard Specification Form (QSF) - In-Process, item 6. See Appendix 3 - QSF - In-Process (ANDA [redacted] page 10003).

Although the reverse order of pH dissolution testing is the "usual" practice, we have developed a discriminatory method that fulfills the requirements outlined in the Agency Guidance for Oral Extended (Controlled) Release Dosage Forms: In Vitro Dissolution for Quality Control. The dissolution was performed in [redacted] This order permitted solubilization of the nifedipine and thereby allowed its detection.

The dissolution method proposed for the Nifedipine Extended-release Tablets, 30 mg, is anchored on two scientific grounds:

1. The design of the dosage form

The tablet is designed to reach the intestinal tract prior to complete dissolution. To accomplish this, a [redacted] was applied to the tablet that will withstand the acid pH of the stomach for up to two hours but will dissolve within 30 minutes in the alkaline pH of the intestine. We are able to mimic the in vivo dissolution of the tablet [redacted] in the lab by subjecting the tablet to pH 7.5 medium for one hour. The dissolution specification indicates that not more than [redacted] of the nifedipine can be released at the [redacted] time point. Our results show that at the [redacted] about 5.5% (mean) of the nifedipine is released, with a high of [redacted] and a low of [redacted]

2. **The physico-chemical characteristic of the drug substance**

Nifedipine is practically insoluble in water and in the aqueous buffer media recommended by the FDA for dissolution testing. Using a surfactant such as SLS enhances the solubility of nifedipine in the dissolution medium in order to obtain a sink condition and meaningful dissolution data. [redacted] is [redacted] but it is insoluble in the aqueous buffer solutions of pH [redacted] Hence, the final stage of the dissolution testing is carried out in [redacted] (pH 1.2) with [redacted] or until an asymptote is reached.

The dissolution data on the test product in [redacted] was obtained by initially dissolving the tablets in an aqueous buffer of [redacted] for [redacted] to [redacted] the tablet [redacted] This was followed by dissolution of the extended release [redacted] in SGF with [redacted] The dissolution results reported incorporate the percent dissolved values obtained during the [redacted] testing at [redacted] This [redacted] dissolution method was developed to allow dissolution testing of the product for the purposes of quality control and has been fully validated according to USP Validation of Compendial Methods <1225> monograph. The dissolution validation report is attached as Appendix 4.

FDA Reply:

The firm performed dissolution studies using the aqueous media (i.e., phosphate buffer at pH [redacted] as suggested by the Division of Bioequivalence. However in all cases the per cent dissolved was very low 18-30% within 24

hours. In order to establish a meaningful dissolution specification with this product the reverse method as described by the firm (i.e., 1 hour in base then [redacted] is acceptable to the Division of Bioequivalence. It is noted that the bulk lot number 97G036 is used for this data which is the same as 97G050 in the original submission (see lot history vol. 1.28 pg. 10311).

This amendment will present the summary data for the single dose food fasting four-way crossover study since this data was not presented in the original review.

Subject drop-outs: The study was designed for 40 subjects and was done as two groups. Group I consisted of subjects #1-22, while group II consisted of #23-39. Subject #11 was hospitalized for chronic schizoprenia which was not study related. Subjects # 26 and # 34 withdrew from the study for personal reasons after and before period I, respectively. Therefore there were 36 evaluable subjects. Data for subject #2 had only one detectable level in periods I and II and no concentrations in period IV. His data for period III is reflected in the mean data.

Table 1. Plasma concentrations for the 36 subjects in the study. Values are mean ± sd.

	TEST FED		REFERENCE FED		TEST FASTING		REFERENCE FASTING	
HOUR0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
HOUR1	0.00	0.00	0.00	0.00	0.00	0.00	0.02	0.12
HOUR2	0.00	0.00	0.16	0.28	0.00	0.00	0.22	0.35
HOUR3	0.00	0.00	2.14	1.82	0.80	1.24	3.32	3.03
HOUR4	0.00	0.00	8.73	4.14	3.17	5.17	7.52	4.25
HOUR5	1.18	3.67	11.33	4.90	5.55	5.87	9.49	5.39
HOUR6	4.15	7.67	13.90	6.29	8.16	6.16	11.89	6.57
HOUR8	8.27	8.08	11.56	5.31	8.42	6.04	9.50	5.24
HOUR10	9.65	9.29	10.64	6.97	9.65	5.73	9.78	5.78
HOUR12	13.48	9.87	11.66	6.23	16.48	11.44	13.24	8.18
HOUR16	15.32	9.02	10.99	5.11	16.06	7.39	13.73	6.49
HOUR20	10.69	5.92	8.11	4.22	10.08	4.88	9.77	4.58
HOUR24	9.69	5.12	8.04	4.44	8.59	4.28	8.94	4.59
HOUR28	8.19	4.58	8.52	5.10	7.63	4.31	8.44	4.06
HOUR32	6.50	4.63	6.95	4.33	5.14	3.36	6.58	4.01
HOUR36	3.98	3.40	4.08	2.91	3.33	2.17	4.94	6.78
HOUR40	2.75	2.69	2.61	2.26	1.98	1.62	3.11	3.85
HOUR44	1.62	1.59	1.61	1.57	1.35	1.28	2.11	2.28
HOUR48	1.17	1.22	1.24	1.29	0.85	1.01	1.51	1.87

Table 2. Mean plasma parameters for the 36 subjects. Values are mean ± sd.

	A TEST FED		B REFERENCE FED		C TEST FASTING		D REFERENCE FASTING		RATIO(C/D)
AUCL[1] NG.HR/ML	320.29	146.63	327.29	141.66	326.17	119.90	349.64	147.44	
LAUCL NG.HR/ML	5.62	0.64	5.63	0.71	5.71	0.41	5.81	0.39	0.90[3]
AUCI[2] NG.HR/ML	374.41	136.12	352.04	145.23	363.93	119.30	356.04	159.03	
LAUCI NG.HR/ML	5.86	0.38	5.76	0.54	5.84	0.36	5.84	0.39	1.00
CPEAK NG/ML	19.90	9.00	16.61	6.85	20.83	9.57	18.20	8.52	
LCPEAK NG/ML	2.89	0.46	2.72	0.43	2.94	0.45	2.84	0.44	1.10
TMAX HR	15.00	6.22	9.92	6.35	14.11	5.19	13.86	6.25	
THALF HR	6.60	2.42	6.03	2.79	5.80	2.26	6.22	2.23	
KEL HR-1	0.12	0.05	0.14	0.07	0.14	0.05	0.12	0.04	

1.Area to last measured time point
2.Area to time infinity
3.Ratio of geometric means test fasting/reference fasting

Table 3. 90% CI and Ratio LSmeans for the fasting and food studies.

Parameter	Fasting Studies(C&D) CI	Fasting Studies(C&D) Ratio LSmeans(C/D)	Food Studies(A&B) Ratio LSmeans(A/B)
LCPEAK	100-124	1.12	1.18
LAUCL	82-108	0.94	0.98
LAUCI	81-101	0.91	1.09

ALL CALCULATIONS FOR THE SINGLE DOSE FOUR-WAY CROSSOVER STUDY WERE VERIFIED BY THE REVIEWER

COMMENT:

1.The 90% CI for the single dose fasting study are within the acceptable limits of 80-125 of the reference for all parameters.

2.The ratio of the LSmeans for the food study is within the acceptable limits of 0.8 and 1.25 of the reference.

60 MG STUDY

FDA Question # 1:

The preamble you presented to the multiple dose study indicated that there was some uncertainty on your part related to subjects that did not have bowel movement. You initially stated " If the subject does not have at least one bowel movement a day, the plasma samples of the subject will not be analyzed", however the next paragraph stated that the criterion was too strict and samples from all subjects that completed the study would be analyzed with those subjects that did not have a bowel movement being classified as within-subject outliers. The Division of Bioequivalence believes that your first decision not to analyze samples collected from the subjects that did not have a bowel movement was justified. On the other hand, analyzing the subjects' samples, including them in the data analysis and then designating those subjects without a bowel movement as within-subject outliers is not acceptable to the Division of Bioequivalence.

Firm's Response # 1:

In light of the Agency's concern with our multiple-dose study, Study No. 1862-2, Biovail performed another study. This study aimed to confirm whether or not the test product is bioequivalent to the reference listed drug under steady-state, fasting conditions. In the new study, Study No. 109240, the plasma samples from all subjects were analyzed. Results of the study confirmed that the test product is bioequivalent to the reference listed drug under steady-state, fasting conditions.

The complete report of Study No. 109240 has been submitted for your review as appendix 6.

FDA Reply:

The Division of Bioequivalence agrees with the firm's comments related to its initial multiple dose study and will review the new multiple dose study.

FDA Question #2:

The Division of Bioequivalence does not agree with you that subjects 3, 6, 7, 10, 14, 21, 34, 42 and 47 can be deleted from

the data set for the multiple dose fasting study because they did not have a bowel movement after taking the reference formulation. Other subjects, within the population that had bowel movements following both formulations, had test\reference ratios for AUC(0-tau) and Cmax comparable to those for the subjects which you deleted. Therefore, the multiple dose study is unacceptable since the CI is outside the acceptable range of 80-125% of reference when these subjects are included.

Firm's Response # 2:

In light of the Agency's concern with our multiple-dose study, Study No. 1862-2, Biovail performed another study. This study aimed to confirm whether or not the test product is bioequivalent to the reference listed drug under steady-state, fasting conditions. In the new study, Study No. 109240, the plasma samples from all subjects were analyzed. Results of the study confirmed that the test product is bioequivalent to the reference listed drug under steady-state, fasting conditions. The 90% geometric confidence intervals for nifedipine AUC and Cmax were 86 - 100 % and 89 - 106 %, respectively.

The complete report of Study No. 109240 has been submitted for your review as appendix 6.

REVIEW OF NEW MULTIPLE DOSE STUDY ON 60 MG ER TABLET

Study Facility Information:

Clinical Facility:	[redacted]
Principal Investigator:	[redacted]
Clinical Study Dates:	**Group 1** Period I-July 30, 1998 Period II-August 12, 1998 Subjects(1-36) **Group 2** Period I-August 6, 1998 Period II-August 19, 1998 Subjects(37-48) **Group 3** Period I-August 19, 1998 Period II-September 1, 1998 Subjects(49-56)
Analytical Facility:	Biovail Contract Research Toronto, Canada
Analytical Study Date:	September 9, 1998-September 21, 1998
Storage Period:	60 days

Study Design:

Protocol No.:	B98-353PK-NIFB35
Design Type:	Crossover
Randomized:	Y
No. of Sequences:	2
No. of Periods:	5 as dates of drug administration
No. of Treatments:	2
Washout Period:	7 days
Single or Multiple dose:	Multiple

Subjects:

Normal; Healthy Volunteers:	Y
IRB Approval:	Y

Informed Consent Obtained:	Y
No. of Subjects Enrolled:	56-all male
Inclusion/Exclusion criteria	Vol.: 2.2; pages 159-162

Treatment Information:

Treatment:	A	B
Test or Reference:	Test	Reference
Product Name:	NIFEDIPINE XL	PROCARDIA XL®
Strength:	60 MG	60 MG
Manufacturer:	BIOVAIL	PFIZER
Batch/Lot no.:	97G051	87T005A
Lot size	[redacted] Tablets	N/A
Expiration Date:	N/A	JUNE 2003
Assay	99.3	
Dose Administered:	60MG	60 MG
Dosing Interval:	24 HRS	24 HRS
Number of Doses:	7	7

Dosing:

After an overnight fast of ten hours, each subject randomly (Randomization Code in Table 4)received either a test product or a reference product with 240 mL of water on Days 1 to 7. Subjects fasted for 4 hours post-dose. Standard meals were provided at 4 hours after dosing and at appropriate times thereafter. Water was not permitted until 2 hours after and 4 hours before dosing in each dosing period.

Table 4. RANDOMIZATION SCHEDULE

Sequence	Subjects
AB	2,3,6,7,8,9,10,15,16,18,29,30, 32,38,39,40,42,44,46,48,49,51, 52,53,56
BA	1,4,5,11,12,14,19,20,21,22,26, 27,31,33,34,35,36,41,45,47,50

STUDY PRODUCTS:
A = (Test Drug Product):
B = (Reference Drug Product):

Blood Sampling

Blood sample volume	7 mL
No. of time points	17
Time points	Days 1, 4, 5, 6 and 7 predose On day 7 at 1, 2,3,4,5,6,8,10,12,16,20 and 24 hr

[

]

Analytical Method

[

]

Statistical Analysis

STATISTICAL ANALYSIS:

The concentration versus time data was used to calculate the areas under the concentration-time curves AUC(0-τ) by linear interpolation between consecutive blood drug levels during the dosing interval 24 hours at steady-state. Maximum concentration attained (Cpeakss) and the time of maximum concentration (Tmaxss) at steady-state were also calculated. Cminss and Cavg were also calculated.

The ANOVA was the same as for the previous fasting study.

Results:

Of the 56 male subjects enrolled, 47 subjects completed both periods of the study. Subjects 17, 23, 24, 25, 28, 43, 54 and 55 withdrew for personal reasons. Subject 13 withdrew due to the occurrence of a headache and vomiting.

Adverse Events

There were numerous adverse events which are summarized in vol. 2.2, Table C2, pages 018-030. 32 subjects receiving the test product experienced adverse effects which were mainly headaches. 28 subjects receiving the reference product experienced adverse effects which were mainly headaches and lightheadedness.

Re-assays

1% of the analytical samples were subjected to reassay.

Table 5. Mean plasma concentrations ± sd for nifedipine in the 47 subjects that completed the study.

	TEST		REFERENCE	
HOUR0	0.00	0.00	0.01	0.10
CMIN1-Day 4	32.50	20.14	37.81	18.56
CMIN2-Day 5	31.03	20.11	36.01	19.10
CMIN3-Day 6	35.32	24.00	37.19	20.81
CMIN4-day 7	34.28	19.13	42.42	24.91
HOUR1	36.81	21.06	44.23	25.94
HOUR2	35.68	19.40	42.44	23.41
HOUR3	35.76	21.11	49.64	26.01
HOUR4	37.02	19.90	58.63	30.10
HOUR5	42.44	22.63	57.20	25.66
HOUR6	47.52	26.90	58.69	24.34
HOUR8	38.99	19.85	47.75	24.40
HOUR10	41.82	26.55	42.70	20.11
HOUR12	57.19	30.46	50.97	23.00
HOUR16	49.11	26.91	45.18	18.55
HOUR20	30.71	16.93	31.43	14.53
HOUR24	34.91	20.47	40.19	20.23

Table 6. Mean nifedipine plasma pharmacokinetic parameters ± sd for the 47 subjects in the multiple dose study.

	TEST		REFERENCE		RATIO(T/R)
AUCTAU[1] ng.hr/ml	999.39	462.28	1082.08	428.06	0.92
LAUCTAU ng.hr/ml	6.82	0.50	6.90	0.43	0.92[3]
CPEAK[2] ng/ml	69.60	32.52	72.14	27.68	0.96
LCPEAK ng/ml	4.17	0.43	4.21	0.39	0.96
Cavg ng/ml	41.64	46.26	45.09	39.56	
CMIN ng/ml	34.91	20.47	40.19	20.23	
TPEAK hr	9.19	5.31	7.85	4.30	

1.Area from time zero to time 24 hours on day 7.
2.Peak concentration
3.Ratio of geometric means

FDA Question #3

You did not give the lot size for the bio-batch.

Firm's Reply #3

The lot size is [redacted] tablets.

FDA Reply:

The firm's reply is acceptable.

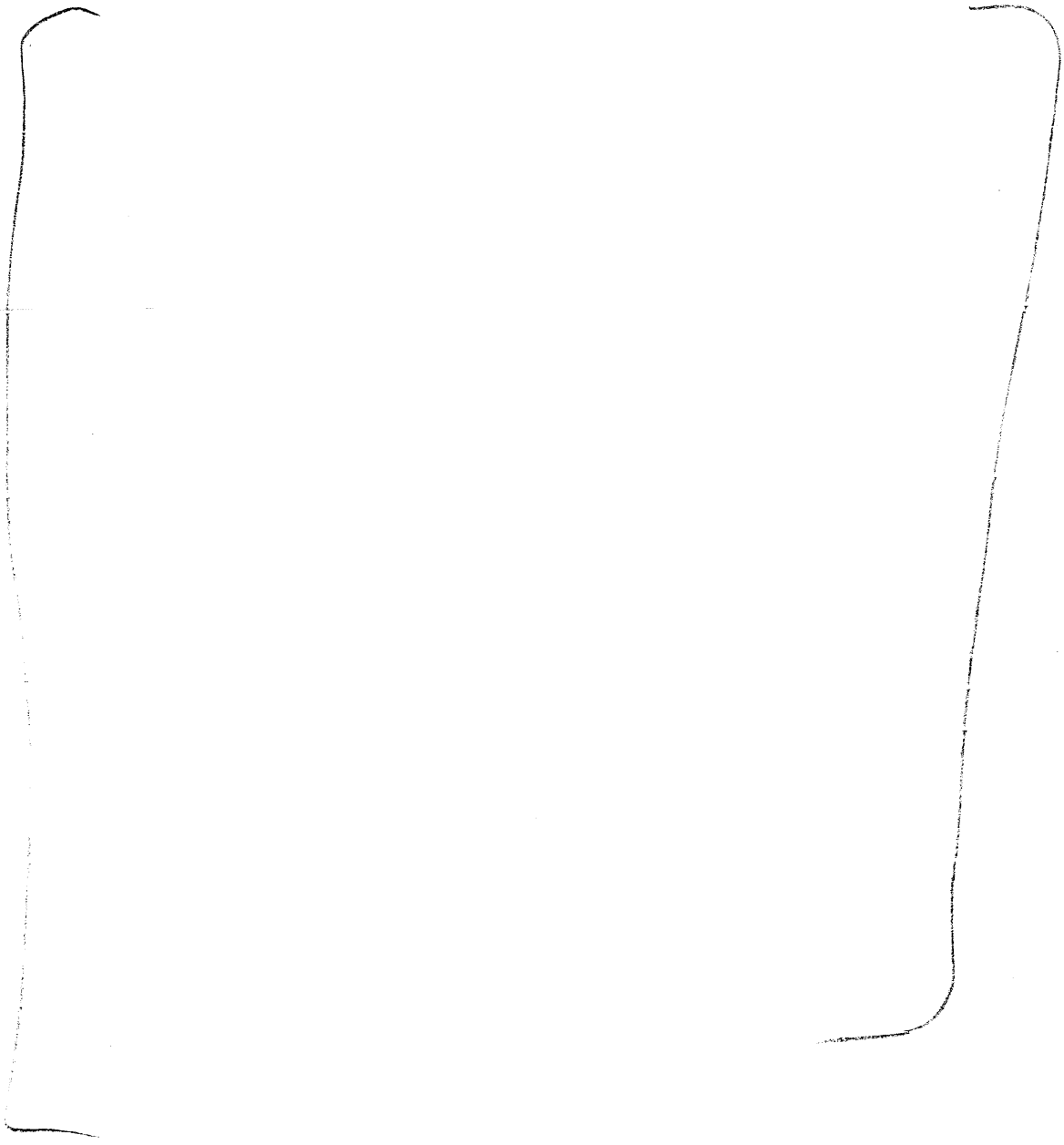
Proposed Dissolution Apparatus/Method-30 mg and 60 mg tablets

Based on the multi-point dissolution profiles for Nifedipine Extended-release Tablets, 30 mg (Lot #97G036) and 60 mg (Lot # 97G051) in various media, the following dissolution test condition and apparatus was proposed for this product:

Dissolution Apparatus/Method

Apparatus USP rotating paddle method (Apparatus 2)

Rotation speed 100 rpm



DEFICIENCIES:

1. The firm did not give the potency for the reference lot 87T005A used in the multiple dose study.

2. The firm conducted the multiple dose study using three groups but did not do the statistical analysis with group in the model.

3. The statistical analysis should be repeated using the following model to test if group is significant at p=0.05

   Y= Group Sequence Subjects(Group*Sequence) Period(Group) Trt Group*Trt

   If group is not significant, then group*trt can be dropped from the model and the data reanalyzed.

   An ASCII file containing the multiple dose raw plasma data and parameters coded for groups should be submitted with the analysis.

4. The firm should explain why subject #42 for the reference had a time zero concentration of [redacted]

RECOMMENDATIONS:

1.The single-dose, fasting/non-fasting bioequivalence study conducted by Biovail on the test product, Nifedipine ER Tablets, 30 mg, lot # 97G050, comparing it with the reference product, Pfizer's Procardia XL® Tablets, 30 mg, lot # 57P219E, has been found to be acceptable by the Division of Bioequivalence. The study demonstrates that Biovail's 30 mg, Nifedipine ER Tablets are bioequivalent to Pfizer's 30 mg Procardia XL® Tablets.

2.The multiple-dose, fasting bioequivalence study conducted by Biovail on the test product, Nifedipine ER Tablets, 60 mg, lot # 97G051, comparing it with the reference product, Pfizer's Procardia XL® Tablets, 60 mg lot # 87T005A, has been found to be incomplete by the Division of Bioequivalence.

3.The <u>in vitro</u> dissolution testing conducted on the 30 mg and 60 mg strengths (lots # 97G050 and #97G051 respectively), is acceptable.

4.The in vitro dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted as follows:

Dissolution Apparatus/Method

Apparatus	USP rotating paddle method (Apparatus 2)
Rotation speed	100 rpm

APPEARS THIS WAY
ON ORIGINAL

[redacted]

*For each dosage unit, add the corresponding amount released in [redacted] to the amount released at each time point in [redacted]

/S/

André J. Jackson, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang
FT INITIALED YCHuang /S/ Date 4/1/99

Concur: /S/ Date 5/17/99

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

cc: ANDA # 75289(original), HFD-652 (Huang, Jackson), HFD-650(Director), Drug File, Division File

APPEARS THIS WAY
ON ORIGINAL

Table 7. In Vitro Dissolution Testing

Drug (Generic Name): Nifedipine ER Tablet
Dose Strengths:30 mg, 60 mg
ANDA No.:75-289
Firm: Biovail Laboratories
Submission Date: December 29, 1998
File Name:75289ADS.D98

I. Conditions for Dissolution Testing:

Part 1:Pre-Conditioning -1 hr pH [redacted]
Part 2: USP XXIII Basket: Paddle: x RPM: 100
No. Units Tested: [redacted]
Medium: [redacted]
Volume: Not Given
Specifications:

Time	Amount Dissolved
[redacted]	NMT [redacted]
[redacted]	[redacted]
[redacted]	NLT [redacted]
[redacted]	NLT [redacted]

Reference Drug: Procardia®
Assay Methodology: [redacted]

II. Results of In Vitro Dissolution Testing:

Sampling Times (hr)	Test Product Lot #97G036(same as bio-lot 97G050) Strength(30mg)			Reference Product Lot # 57P219E Strength(30mg)		
	Mean	Range	%CV	Mean	Range	%CV
1	15	[redacted]	6.3	5	[redacted]	9.5
2	25	[redacted]	6.6	6	[redacted]	6.7
4	45	[redacted]	7.4	16	[redacted]	13.1
6	64	[redacted]	6.2	28	[redacted]	10.5
8	81	[redacted]	4.7	40	[redacted]	11.2
10	95	[redacted]	3.7	53	[redacted]	10.9
12	103	[redacted]	2.3	65	[redacted]	10.4
14	106	[redacted]	2.2	77	[redacted]	9.8
16	107	[redacted]	2.2	88	[redacted]	9.0
Sampling Times (Minutes)	Test Product Lot # 97G051 Strength(60mg)			Reference Product Lot #87T005A Strength(60mg)		
	Mean	Range	%CV	Mean	Range	%CV
1	20	[redacted]	19	3	[redacted]	0
2	34	[redacted]	11	4	[redacted]	17.5

4	58		7.2	14			13.6
6	80		5	25			10.4
8	96		3.2	37			8.6
10	100		4.6	49			8.2
12	101		4.8	61			7.7
14	101		4.8	73			6.7
16	101		4.5	83			6.3

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-289 APPLICANT: Biovail

DRUG PRODUCT: Nifedipine 60 mg ER Tablet

The Division of Bioequivalence has completed its review on your 60 mg ER tablet and has no further questions at this time.

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

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

The dissolution testing should be conducted as follows:

Dissolution Apparatus/Method

Apparatus	USP rotating paddle method (Apparatus 2)
Rotation speed	100 rpm

*For each dosage unit, add the corresponding amount released in [redacted] to the amount released at each time point in [redacted]

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

Sincerely yours,

/S/

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

APPEARS THIS WAY
ON ORIGINAL

File 75-289
(8)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75-289

SPONSOR : Biovail

DRUG AND DOSAGE FORM : **Nifedipine ER Tablet**

STRENGTH(S) : **60 mg**

TYPES OF STUDIES : Multiple Dose

CLINICAL STUDY SITE(S) : [redacted]

ANALYTICAL SITE(S) : **Biovail Contract Research**
Toronto, Canada

STUDY SUMMARY : See Review

DISSOLUTION : See Review

DSI INSPECTION STATUS

Inspection needed: YES / NO	Inspection status:	Inspection results:
First Generic __X___	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause __ ___		
Other _____		

PRIMARY REVIEWER : Andre Jackson BRANCH : I

INITIAL : /S/ DATE : 8/16/99

for TEAM LEADER : Y.C Huang BRANCH : I

INITIAL : /S/ DATE : 8/16/99

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

INITIAL : /S/ DATE : 8/23/99

Nifedipine
60 mg Extended-Release Tablet
ANDA # 75-289
Reviewer: Andre Jackson
WP # 75-289A.799
V:\Firmsam\Biovail\ltrs&rev\75289A.799

Biovail Incorporated
Mississauga, Ontario, Canada
Submission Date:
July 2, 1999
July 23, 1999(Diskette)

Review of An Amendment to the New Multiple Dose Bioequivalence Study on the 60 mg ER Tablet

Background:

The firm completed a new multiple dose bioequivalence study to support their application. The study was found to be incomplete and the firm's current submission addresses the deficiencies for the multiple dose study.

DEFICIENCIES:

1. The firm did not give the potency for the reference lot 87T005A used in the multiple dose study.

Firm's Response

RESPONSE #1:

Biovail agrees with the Agency regarding the need to include the potency of the reference lot 87T005A used in the multiple dose study.

A complete analysis determining the retention time, potency, uniformity of dosage units and drug related impurities was performed to compare the reference lot, 87T005A, with the test product exhibit lot, 97G051. A table summarizing these results is presented overleaf.

The manufacturer of the reference product, Pfzier Inc., designed the Procardia XL tablet with a [redacted] (60 mg [redacted]) for a total theoretical tablet strength of [redacted] to ensure that 60 mg of the Nifedipine is delivered to the patient. The determined potency value for the reference product varies

depending if the calculated value is based on 66 mg label claim or 60 mg label claim. For the reference lot (87T005A) in question the determined potency value was 97.8% **based on a** label claim. The potency calculated based on a 60 mg label claim is 107.6%.

Unlike the innovator reference product, Biovail has formulated the proposed test product to include the exact amount of Active Pharmaceutical Ingredient to be delivered to the patient. The determined potency value for Nifedipine Extended release Tablets, 60 mg (lot #97C051) is 102.3%.

FDA REPLY:

The firm's response is acceptable.

2. The firm conducted the multiple dose study using three groups but did not do the statistical analysis with group in the model.

RESPONSE #2:

The original analysis submitted did include a group effect in the ANOVA model. In this ANOVA model, "group" was given the label "study". Biovail regrets any confusion this may have caused.

The ANOVA model analysis of group effect was presented in pages 144 - 146 (Volume 1), of study number 109240. This data is also attached in Appendix 1 of this amendment for ease of reference.

FDA REPLY:

The firm's response is acceptable **AND THE CALCULATIONS WERE VERIFIED BY THE REVIEWER.**

3. The statistical analysis should be repeated using the following model to test if group is significant at p=0.05

Y= Group Sequence Subjects(Group*Sequence) Period(Group)
Trt Group*Trt

If group is not significant, then group*trt can be dropped

from the model and the data reanalyzed.

An ASCII file containing the multiple dose raw plasma data and parameters coded for groups should be submitted with the analysis.

RESPONSE #3:

In response to the Agency's request Biovail has repeated the statistical analysis based on the suggested model. The reanalysis confirmed that the group effect is significant as was originally reported in the study analysis. As such the group * trt was maintained in the model. The statement noted on page 43, Volume 1 of study number 109240, "...the group effect was not significant..." was a typographical error that was inadvertently overlooked. The group effect was in fact noticeable as indicated by the original model analysis. A summary of the repeated analysis and the ANOVA outputs are presented in Appendix 2.

Although the group effect is not negligible, the error estimates from the ANOVA of the three separate groups and formulation by study interaction are not significant. These results were included on pages 139 - 143, Volume 1 of study number 109240 and are also attached in Appendix 3 of this amendment for ease of reference.

FDA REPLY:

The firm erroneously tested group for significance while the deficiency requested that they test for group*trt and if it was not significant at the 0.05 level then that parameter could be excluded from the model. Since the firm followed the incorrect procedures the ANOVA was calculated by the reviewer.

The group*trt interaction was not significant so it was dropped from the model and the data reanalyzed. The 90% CI were:

LAUCT 80.8-98.0
LCPEAK 84.1-106.3

4. The firm should explain why subject #42 for the reference had a time zero concentration of [redacted]

RESPONSE #4:

The data was reviewed closely to verify that the observation was not due to an analytical error.

Based on a number of preliminary studies conducted by the applicant the mean half-life ranged between 5 to 8 hours. The washout period for the subject in question was based on ten times the upper limit of this observed range and took into consideration the accumulation ratio for the test product. The accumulation ratio was calculated using a mean half-life value of 6.11 hours, determined from the single-dose fasting study (Study No. 1895) filed in support of this application. The established washout period of seven days was sufficient for all other subjects in this study.

FDA REPLY:

The firm's response is acceptable.

RECOMMENDATIONS:

1.The multiple-dose, fasting bioequivalence study conducted by Biovail on the test product, Nifedipine ER Tablets, 60 mg, lot # 97G051, comparing it with the reference product, Pfizer's Procardia XL® Tablets, 60 mg lot # 87T005A, has been found to be acceptable by the Division of Bioequivalence. The study demonstrates that Biovail's 60 mg, Nifedipine ER Tablets are bioequivalent to Pfizer's 60 mg Procardia XL® Tablets.

2.The in vitro dissolution testing conducted on the 60 mg strength (lot #97G051), was previously found to be acceptable.

André J. Jackson, Ph.D.
Division of Bioequivalence
Review Branch I

for RD INITIALED YCHuang
for FT INITIALED YCHuang

Date 8/16/99

Date 8/23/99

Concur:

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

cc: ANDA # 75289(original), HFD-652 (Huang, Jackson), HFD-650(Director), Drug File, Division File

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-289 APPLICANT: Biovail

DRUG PRODUCT: Nifedipine 60 mg ER Tablet

The Division of Bioequivalence has completed its review on your 60 mg ER tablet and has no further questions at this time.

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

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

The dissolution testing should be conducted as follows:

Dissolution Apparatus/Method

Apparatus	USP rotating paddle method (Apparatus 2)
Rotation speed	100 rpm

[redacted]

*For each dosage unit, add the corresponding amount released in [redacted] to the amount released at each time point in [redacted].

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

Sincerely yours,

/S/

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

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75-289 SPONSOR : Biovail Incorporated

DRUG AND DOSAGE FORM : Nifedipine ER Tablet

STRENGTH(S) : **30 mg and 60 mg**
TYPES OF STUDIES : Single Dose, Multiple Dose, Food Study

CLINICAL STUDY SITE(S) ~~[redacted]~~

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

STUDY SUMMARY : See Review

DISSOLUTION : See Submission

DSI INSPECTION STATUS

Inspection needed: YES / NO	Inspection status:	Inspection results:
First Generic _____	Inspection requested: (date)	
New facility ___	Inspection completed: (date)	
For cause _____		
Other _____		

PRIMARY REVIEWER : Andre Jackson BRANCH : I

INITIAL : /S/ DATE : 3/22/2000

TEAM LEADER : Y.C. Huang BRANCH : I

INITIAL : /S/ DATE : 3/22/2000

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

INITIAL : /S/ DATE : 3/28/00

Nifedipine
60 mg Extended-Release Tablet
30 mg Extended-Release Tablet
ANDA # 75-289
Reviewer: Andre Jackson
V:\Firmsam\Biovail\ltrs&rev\75289AD.799

Biovail Incorporated
Mississauga, Ontario, Canada
Submission Date:
July 2, 1999

Addendum to a Review Recommendation on the 30 mg ER Tablet Dissolution Data

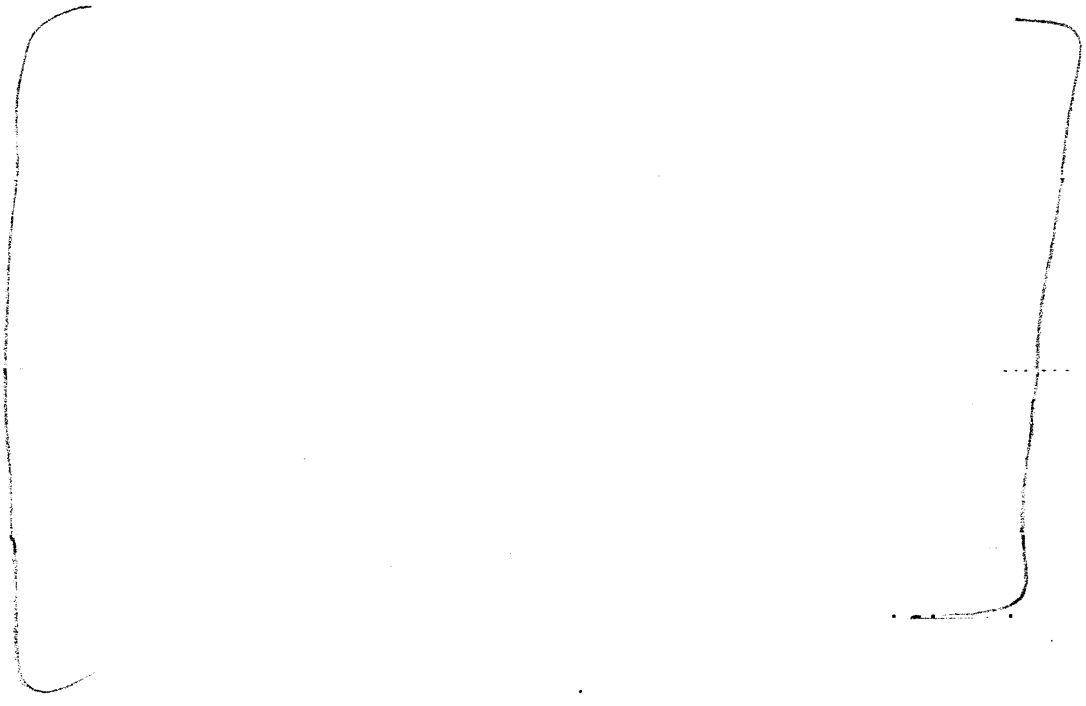
Background:

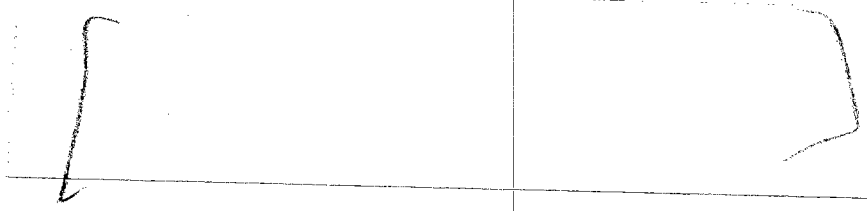
The firm replied to deficiencies on their new 60 mg multiple dose bioequivalence study on July 2, 1999. Included in that submission was stability data for the 30 mg tablet. The Division of Bioequivalence had recommended the following specifications for the 60mg and 30 mg tablets.

The in vitro dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted as follows:

Dissolution Apparatus/Method

Apparatus	USP rotating paddle method (Apparatus 2)
Rotation speed	100 rpm





*For each dosage unit, add the corresponding amount released in [redacted] to the amount released at each time point in [redacted]

THE FOLLOWING IS THE FIRM'S REPLY TO THE DIVISION OF BIOEQUIVALENCE RECOMMENDATIONS RELATED TO THE DISSOLUTION OF THEIR PRODUCT.

In the amendment to the 60 mg multiple dose study, Biovail noted the recommendation posed by the Agency to alter the dissolution specifications for the 30 mg ER tablet so that it is consistent with the dissolution specifications proposed for the 60 mg ER tablet. The firm has noted that the Nifedipine Hydrochloride Extended-release Tablets, 30 mg and 60 mg ER tablets are non-proportional formulations with the dissolution profiles being similar but not identical. The two formulations do not display the same rate of release. Thus, the dissolution specifications proposed for the 60 mg ER tablet are not appropriate for the 30 mg tablet, as suggested.

FDA Comment on Results:

The firm presents room temperature and accelerated stability data to support their request for a change in the dissolution specification. The data is appended to this review. The data presented by the firm demonstrates that at the [redacted] sampling timepoint the majority of results obtained would not meet the specification proposed by the Agency. The mean at the [redacted] sampling timepoint consistently borders the low end of the proposed specification and as such the recommended specification at [redacted] does not adequately represent the drug product release profile.

THE FOLLOWING IS THE FIRM'S REPLY TO THE DIVISION OF BIOEQUIVALENCE RECOMMENDATIONS RELATED TO THE DISSOLUTION OF THEIR PRODUCT.

To comply with the Agency's recommendation to sample at four separate timepoints the firm has proposed the addition of a fourth

sampling timepoint, at [redacted]. The specification for the [redacted] timepoint has been set at not less than (NLT) [redacted] dissolved.

Comments:

1.The Division of Bioequivalence has reviewed the stability data submitted by the firm and now proposes the following specifications for the 30 mg product based upon the new data.

The test product should meet the following specification:

[redacted]

2. The "current specifications" in the appended tables are those proposed by the firm.

Recommendation:

1.The in vitro dissolution testing conducted on the 30 mg strength is acceptable.

2.The in vitro dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted as follows:

Dissolution Apparatus/Method

Apparatus	USP rotating paddle method (Apparatus 2)
Rotation speed	100 rpm

[redacted]

/S/

André J. Jackson, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang
FT INITIALED YCHuang /S/ Date 3/22/2000

Concur: /S/ Date 3/28/00

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

cc: ANDA # 75289(original), HFD-652 (Huang, Jackson),
HFD-650(Director), Drug File, Division File

Nifedipine Extended-release Tablet, 30 mg, Dissolution Stability Data
Packaged in Bottles of 100, 300 and 1000 Stored under Room Temperature Conditions

	Initial				3 months				6 months				9 months			
30 mg	1hr	4hr	8hr	12hr	1hr	4hr	8hr	12hr	1hr	4hr	8hr	12hr	1hr	4hr	8hr	12hr
Current Specifications	NMT	[illegible]	NLT	NLT	NMT	[illegible]	NLT	NLT	NMT	[illegible]	NLT	NLT	NMT	[illegible]	NLT	NLT
in 100 97GO50 Range	[illegible]															
in 300 97HOO4 Range	[illegible]															
in 1000 97HOO5 Range	[illegible]															
Agency Proposed Specifications	NMT	[illegible]	NLT	NLT	NMT	[illegible]	NLT	NLT	NMT	[illegible]	NLT	NLT	NMT	[illegible]	NLT	NLT

	12 months				18 months				24 months				36 months			
30 mg	1hr	4hr	8hr	12hr	1hr	4hr	8hr	12hr	1hr	4hr	8hr	12hr	1hr	4hr	8hr	12hr
Current Specifications	NMT	[illegible]	NLT	NLT	NMT	[illegible]	NLT	NLT	NMT	[illegible]	NLT	NLT	NMT	[illegible]	NLT	NLT
in 100 97GO50 Range	[illegible]						N/T									
in 300 97HOO4 Range	[illegible]						N/T									
in 1000 97HOO5 Range	[illegible]						N/T									
	[illegible]						N/T									
Agency Proposed Specifications	NMT	[illegible]	NLT	NLT	NMT	[illegible]	NLT	NLT	NMT	[illegible]	NLT	NLT	NMT	[illegible]	NLT	NLT

[illegible] PEARS THIS WAY
ON ORIGINAL

Nifedipine Extended-release Tablet, 30 mg, Dissolution Stability Data
Packaged in Bottles of 100, 300 and 1000 Stored under Accelerated Conditions

	Initial				1 months				2 months				3 months			
30 mg	1hr	4hr	8hr	12hr	1hr	4hr	8hr	12hr	1hr	4hr	8hr	12hr	1hr	4hr	8hr	12hr
Current Specifications	NMT	[redacted]	NLT	NLT	NMT	[redacted]	NLT	NLT	NMT	[redacted]	NLT	NLT	NMT	[redacted]	NLT	NLT
in 100 97GO56 Range	[redacted]															
in 300 97HOO4 Range	[redacted]															
in 1000 97HOO5 Range	[redacted]															
Agency Proposed Specifications	NMT	[redacted]	NLT	NMT	NMT	NLT	[redacted]	NLT	NLT	NMT	[redacted]	NLT	[redacted]	NLT	NMT	[redacted]

	6 months			
30 mg	1hr	4hr	8hr	12hr
Current Specifications	NMT	[redacted]	NLT	NLT
in 100 97GO50 Range	[redacted]			
in 300 97HOO4 Range	[redacted]			
in 1000 97H005 Range	[redacted]			
Agency Proposed Specifications	NMT	[redacted]	NLT	NLT

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75289 APPLICANT: Biovail

DRUG PRODUCT: Nifedipine 30 mg ER Tablet

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

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

The dissolution testing should be conducted as follows:

Dissolution Apparatus/Method

Apparatus	USP rotating paddle method (Apparatus 2)
Rotation speed	100 rpm

APPEARS THIS WAY
ON ORIGINAL

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

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-289 APPLICANT: Biovail Laboratories

DRUG PRODUCT: Nifedipine 30 mg and 60 mg ER Tablets

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

The following interim dissolution testing will need to be incorporated into your stability and quality control programs for the 30 mg tablet:

Dissolution Apparatus/Method

Apparatus	USP rotating paddle method (Apparatus 2)
Rotation speed	100 rpm

[redacted]

The following interim dissolution testing will need to be incorporated into your stability and quality control programs for the 60 mg tablet:

Dissolution Apparatus/Method

Apparatus	USP rotating paddle method (Apparatus 2)
Rotation speed	100 rpm

*For each dosage unit, add the corresponding amount released in [redacted] to the amount released at each time point in [redacted]

APPEARS THIS WAY
ON ORIGINAL

In your April 3, 2000 letter you had different sampling times for your 30 mg and 60 mg tablets in the part II dissolution medium. The times were: 30 mg- [redacted] and 60 mg- [redacted] You should clarify whether the times in part II includes the time in the part I dissolution medium [redacted] for 30 mg and 60 mg, respectively) or is this for only the time in the part II dissolution medium.

Final dissolution specifications will be determined based on the data submitted from 3 production batches.

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

APPEARS THIS WAY
ON ORIGINAL

Nifedipine
60 mg Extended-Release Tablet
30 mg Extended-Release Tablet
ANDA # 75-289
Reviewer: Andre Jackson
V:\Firmsam\Biovail\ltrs&rev\75289A.300

Biovail Incorporated
Mississauga, Ontario, Canada
Submission Date:
April 3, 2000
April 10, 2000

Study Amendment to the 30 mg ER Tablet and the 60 mg ER Tablet and Dissolution Data

Background:

The firm submitted two ANDA's (i.e. [redacted] for their 30 mg ER tablet and 75-289 for their 60 mg ER tablet) to the Division of Bioequivalence. ANDA # [redacted] contained two bioequivalence studies, a single dose fasting and non-fasting four-way crossover and a multiple dose two-way crossover. The single dose study had deficiencies while the multiple dose study was found to be acceptable. The former ANDA has been collapsed into the ANDA # 75-289 (See agency letter dated October 1, 1998). The studies were reviewed and found to be acceptable to the Division of Bioequivalence. However, the dissolution conditions recommended to the firm by the Division of Bioequivalence were the same for both strengths. This recommendation was incorrect since the firm had previously requested that the time for [redacted] should be [redacted] for the 30 mg tablet and [redacted], for the 60 mg tablet. This addendum acknowledges the change in the dissolution procedure.

The dissolution testing for the 30 mg tablet should be conducted as follows:

Dissolution Apparatus/Method

Apparatus USP rotating paddle method (Apparatus 2)
Rotation speed 100 rpm

[redacted]

[redacted]

*For each dosage unit, add the corresponding amount released in [redacted] to the amount released at each time point in [redacted]

The dissolution testing for the 60 mg tablet should be conducted as follows:

Dissolution Apparatus/Method

Apparatus	USP rotating paddle method (Apparatus 2)
Rotation speed	100 rpm

[redacted]

The test product should meet the following specification:

[ ]

*For each dosage unit, add the corresponding amount released in [redacted] to the amount released at each time point in [redacted].

Comment : (To be issued to the Firm)

In your April 3, 2000 letter you had different sampling times for your 30 mg and 60 mg tablets in the part II dissolution medium. The times were: 30 mg- [redacted] and 60 mg- [redacted]. You should clarify whether the time in part II includes the time in part I dissolution medium [redacted] for 30 mg and 60 mg, respectively) or is this for only the time in the part II dissolution medium.

/S/

André J. Jackson, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang
FT INITIALED YCHuang

/S/ Date 4/14/2000

Concur: /S/ Date 4/17/00

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

cc: ANDA # 75289(original), HFD-652 (Huang, Jackson), HFD-650(Director), Drug File, Division File

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75-289 SPONSOR : Biovail Incorporated

DRUG AND DOSAGE FORM : Nifedipine ER Tablets

STRENGTH(S) : **30 mg and 60 mg**
TYPES OF STUDIES : N/A
CLINICAL STUDY SITE(S) : N/A
ANALYTICAL SITE(S) : **N/A**

STUDY SUMMARY : See Review

DISSOLUTION : See Submission (4/3/2000 & 4/10/2000)

DSI INSPECTION STATUS

Inspection needed: YES / NO	Inspection status:	Inspection results:
First Generic _____ New facility __ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Andre Jackson BRANCH : I

INITIAL : ___ /S/ _____ DATE : 4/14/2000

TEAM LEADER : Y.C. Huang BRANCH : I

INITIAL : /S/ _____ DATE : 4/14/2000

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

INITIAL /S/ _____ DATE : 4/17/00

5 FF

Nifedipine
30 and 60 mg Extended-Release Tablet
ANDA # 75-289
Reviewer: Andre Jackson

Biovail Incorporated
Mississauga, Ontario, Canada

Submission Date:
May 10, 2000

V:\Firmsam\Biovail\ltrs&rev\75289A.500

Review of An Amendment to the 30 mg and 60 mg ER Tablet

Background:

The firm completed submitted an amendment on May 10, 2000 in response to a telephone communication from the Division of Chemistry II related to the dissolution on their products. One of the questions related to [redacted] had possible bioequivalence implications. Therefore, the Division of Chemistry II requested input from the Division of Bioequivalence.

The question raised by the Division of Chemistry II for the firm to reply was as follows:

[redacted]

Biovail Response:

[redacted]

Redacted 1

pages of trade secret and/or confidential commercial information

[redacted]

30 mg Tablet
Dissolution Apparatus/Method

Apparatus	USP rotating paddle method (Apparatus 2)
Rotation speed	100 rpm

[redacted]

*For each dosage unit, add the corresponding amount released in [redacted] to the amount released at each time point in [redacted]

60 mg Tablet
Dissolution Apparatus/Method

Apparatus	USP rotating paddle method (Apparatus 2)
Rotation speed	100 rpm

[redacted]

*For each dosage unit, add the corresponding amount released in [redacted] to the amount released at each time point in [redacted].

The dissolution studies should be done at the [redacted] and [redacted] levels of [redacted] for the 30 mg and 60 mg ER tablets.

André J. Jackson, Ph.D.
Division of Bioequivalence
Review Branch I

/S/

RD INITIALED YCHuang
FT INITIALED YCHuang

/S/

Date 5/23/2000

Concur: /S/

Date 5/26/2000

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

cc: ANDA # 75289(original), HFD-652 (Huang, Jackson), HFD-650(Director), Drug File, Division File

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75-289 SPONSOR : Biovail Incorporated

DRUG AND DOSAGE FORM : Nifedipine ER Tablets

STRENGTH(S) : **30 mg and 60 mg**
TYPES OF STUDIES : Amendment to Bioequivalence Study

CLINICAL STUDY SITE(S) : N/A
ANALYTICAL SITE(S) : **N/A**

STUDY SUMMARY : See Review

DISSOLUTION : See Submission

DSI INSPECTION STATUS

Inspection needed: YES / NO	Inspection status:	Inspection results:
First Generic _____ New facility _____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Andre Jackson BRANCH : I

INITIAL : _____ DATE : 6/28/2000

TEAM LEADER : Y.C. Huang BRANCH : I

INITIAL : _____ DATE : 6/29/2000

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

INITIAL _____ DATE : 6/29/00

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75-289 SPONSOR : Biovail Incorporated

DRUG AND DOSAGE FORM : Nifedipine ER Tablets

STRENGTH(S) : **30 mg and 60 mg**
TYPES OF STUDIES : N/A
CLINICAL STUDY SITE(S) : N/A
ANALYTICAL SITE(S) : **N/A**

STUDY SUMMARY : See Review

DISSOLUTION : See Submission (4/3/2000 & 4/10/2000)

DSI INSPECTION STATUS

Inspection needed: YES / NO	Inspection status:	Inspection results:
First Generic _____ New facility __ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Andre Jackson BRANCH : I

INITIAL : __ /S/ _____ DATE : 4/14/2000

TEAM LEADER : Y.C. Huang BRANCH : I

INITIAL : /S/ ___ DATE : 4/14/2000

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

INITIAL : /S/ ___ DATE : 4/17/00

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-289 APPLICANT: Biovail Laboratories

DRUG PRODUCT: Nifedipine 30 mg and 60 mg ER Tablets

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

The following interim dissolution testing will need to be incorporated into your stability and quality control programs for the 30 mg tablet:

Dissolution Apparatus/Method

Apparatus USP rotating paddle method (Apparatus 2)
Rotation speed 100 rpm

[redacted]

*For each dosage unit, add the corresponding amount released in [redacted] to the amount released at each time point in [redacted]

The following interim dissolution testing will need to be incorporated into your stability and quality control programs for the 60 mg tablet:

Dissolution Apparatus/Method

Apparatus USP rotating paddle method (Apparatus 2)
Rotation speed 100 rpm

[redacted]

*For each dosage unit, add the corresponding amount released in [redacted] to the amount released at each time point in [redacted]

In your April 3, 2000 letter you had different sampling times for your 30 mg and 60 mg tablets in the part II dissolution medium. The times were: 30 mg- [redacted] and 60 mg- [redacted]. You should clarify whether the times in part II includes the time in the part I dissolution medium [redacted] for 30 mg and 60 mg, respectively) or is this for only the time in the part II dissolution medium.

Final dissolution specifications will be determined based on the data submitted from 3 production batches.

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

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75-289 SPONSOR : Biovail Incorporated

DRUG AND DOSAGE FORM : Nifedipine ER Tablet

STRENGTH(S) : **30 mg and 60 mg**
TYPES OF STUDIES : Single Dose, Multiple Dose, Food Study

CLINICAL STUDY SITE(S) [redacted]

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

STUDY SUMMARY : See Review

DISSOLUTION : See Submission

DSI INSPECTION STATUS

Inspection needed: YES / NO	Inspection status:	Inspection results:
First Generic _____ New facility _____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : /S/ Andre Jackson BRANCH : I

INITIAL : _____ DATE : 3/22/2000

TEAM LEADER : Y.C. Huang BRANCH : I

INITIAL : /S/ DATE : 3/22/2000

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

INITIAL : /S/ DATE : 3/28/00

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-289 APPLICANT: Biovail Laboratories

DRUG PRODUCT: Nifedipine 30 mg and 60 mg ER Tablets

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 for the 30 mg tablet:

Dissolution Apparatus/Method

Apparatus USP rotating paddle method (Apparatus 2)
Rotation speed 100 rpm

[redacted]

*For each dosage unit, add the corresponding amount released in [redacted] to the amount released at each time point in [redacted]

The following dissolution testing will need to be incorporated into your stability and quality control programs for the 60 mg tablet:

Dissolution Apparatus/Method

Apparatus	USP rotating paddle method (Apparatus 2)
Rotation speed	100 rpm

*For each dosage unit, add the corresponding amount released in [redacted] to the amount released at each time point in [redacted]

APPEARS THIS WAY
ON ORIGINAL

In your April 3, 2000 letter you had different sampling times for your 30 mg and 60 mg tablets in the part II dissolution medium. The times were: 30 mg- [redacted] and 60 mg- [redacted] You should clarify whether the times in part II includes the time in the part I dissolution medium ([redacted] for 30 mg and 60 mg, respectively) or is this for only the time in the part II dissolution medium.

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

APPEARS THIS WAY
ON ORIGINAL

Nifedipine	Biovail Incorporated
30 and 60 mg Extended-Release Tablet	Mississauga, Ontario, Canada
ANDA # 75-289	Submission Date:
Reviewer: Andre Jackson	June 12, 2000

V:\Firmsam\Biovail\ltrs&rev\75289A.600

Review of An Amendment to the 30 mg and 60 mg ER Tablet

Background:

The firm submitted an amendment on May 10, 2000 in response to a telephone communication from the Division of Chemistry II related to the dissolution on their products. One of the questions related to [redacted] had possible bioequivalence implications. Therefore, the Division of Chemistry II requested input from the Division of Bioequivalence.

The question raised by the Division of Chemistry II for the firm to reply was as follows:

[redacted]

30 mg Tablet

Dissolution Apparatus/Method

Apparatus	USP rotating paddle method (Apparatus 2)
Rotation speed	100 rpm

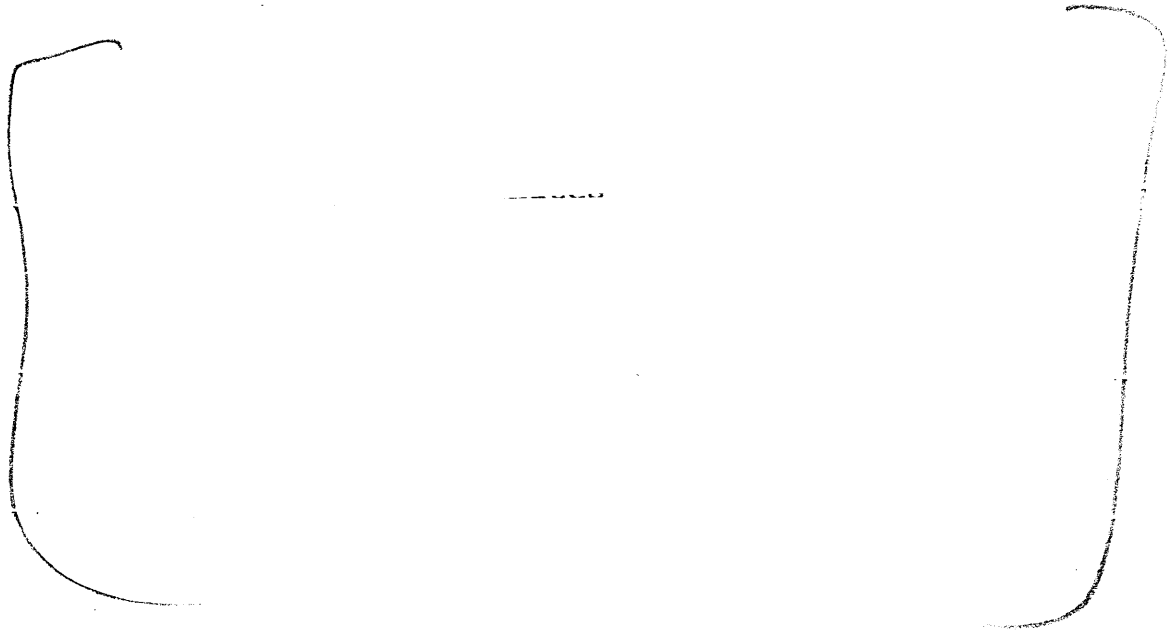
[redacted]

*For each dosage unit, add the corresponding amount released in [redacted] to the amount released at each time point in [redacted]

60 mg Tablet

Dissolution Apparatus/Method

Apparatus	USP rotating paddle method (Apparatus 2)
Rotation speed	100 rpm



[redacted]

*For each dosage unit, add the corresponding amount released in [redacted] to the amount released at each time point in [redacted]

Biovail Response:

The firm has conducted the requested dissolution studies and have presented the following data to the Division of Bioequivalence for review.

Nifedipine XL 30 mg - Lot No. **N-XL30 [redacted]-C(60)**

Tablet Dissolution

[redacted]

Part I of Dissolution Test - % Released at [redacted]

[redacted]	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Mean	S.D.
60 minutes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4.7	0.2

[redacted]

Part 2 of Dissolution test - % Release at [redacted]

[redacted]	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Mean	S.D.
1 hour	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	8.2	0.58
2 hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	16.4	1.05
4 hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	32.4	1.95
8 hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	93.8	3.52
10 hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	77.5	4.32
12 hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	88.9	4.26

[redacted]

Part 1 + Part 2 of Dissolution Test - Total % Released in Both Buffers

[redacted]	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Mean	S.D.
1 hour	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12.9	0.55
2 hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21.1	0.95
4 hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	37.1	2.00
8 hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	68.5	3.39
10 hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	82.2	4.20
12 hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	93.6	4.56

Nifedipine XL 30 mg - Lot No. 97GO36

Tablet Dissolution

[redacted]

Part 1 of Dissolution Test - % Released at [redacted]

	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Mean	S.D.
60 minutes							4.5	1.0

Part 2 of Dissolution Test - % Release at

	Vessel I	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Mean	S.D.
1 hour							9.6	0.6
4 hours							39.3	2.1
8 hours							75.1	3.0
12 hours							95.4	0.7

Part 1 + Part 2 of Dissolution Test - Total % Released in Both Buffers

	Vessel I	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Mean	S.D.
I hour							14.0	1.5
4 hours							43.8	2.8
8 hours							79.6	3.7
12 hours							100.9	1.6

APPEARS THIS WAY
ON ORIGINAL

Nifedipine XL 60 mg - Lot No. 00E165

Tablet Dissolution

Part 1 of Dissolution Test - % Released at [redacted]

[redacted]	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Mean	S.D.
25 minutes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2.8	0.41

Part 2 Of Dissolution Test - Release at [redacted]

[redacted]	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Mean	S.D.
1 hour	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	11,7	1.38
4 hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	46.8	4.57
8 hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	87.5	7.06
12 hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	96.9	1.80

Part I + Part 2 of Dissolution Test - Total % Released in Both Buffers

[redacted]	Vessel I	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Mean	S.D.
I hour	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14.5	1.60
4 hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49.6	4.83
8 hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	90.3	7.31
12 hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	99.7	1.85

Nifedipine XL 60 mg - Lot No. 97GO38

Tablet Dissolution

Part 1 of Dissolution Test - % Released at [redacted]

[redacted]	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Mean	S.D.
25 minutes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	3.5	0.8

Part 2 Of Dissolution Test - % Release at [redacted]

[redacted]	Vessel I	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Mean	S.D.
I hour	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13,1	1.4
4 hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	48.1	2.7
8 hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	85.7	5.7
12 hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95.4	3.6

Part 1 + Part 2 of Dissolution Test - Total % Released in Both Buffers

[redacted]	Vessel I	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Mean	S.D.
1 hour	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	16.6	2.0
4 hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	51.6	3.1
8 hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	89.2	5.8
12 hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	98.9	3.1

Comments:

1.The firm's dissolution studies on the 30 mg and 60 mg ER tablets supports thier claim that the per cent [redacted] does not effect the dissolution profile. Therefore the dissolution data is acceptable to the Division of Bioequivalence.

/S/

for André J. Jackson, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang
FT INITIALED YCHuang /S/ Date 6/20/2000

Concur /S/ Date 6/20/00

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

cc: ANDA # 75289(original), HFD-652 (Huang, Jackson), HFD-650(Director), Drug File, Division File

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-289 APPLICANT: Biovail Incorporated

DRUG PRODUCT: 30 mg and 60 mg ER Tablets

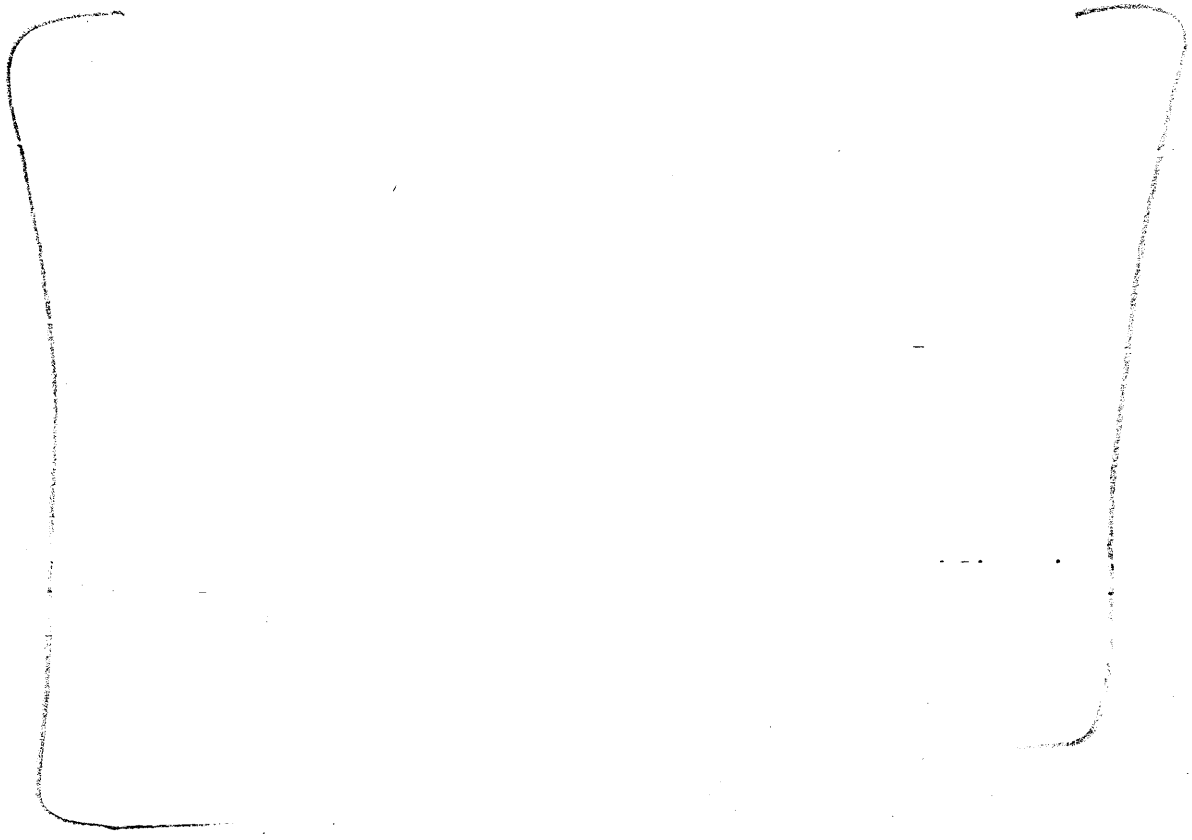
The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

30 mg Tablet

Dissolution Apparatus/Method

Apparatus	USP rotating paddle method (Apparatus 2)
Rotation speed	100 rpm

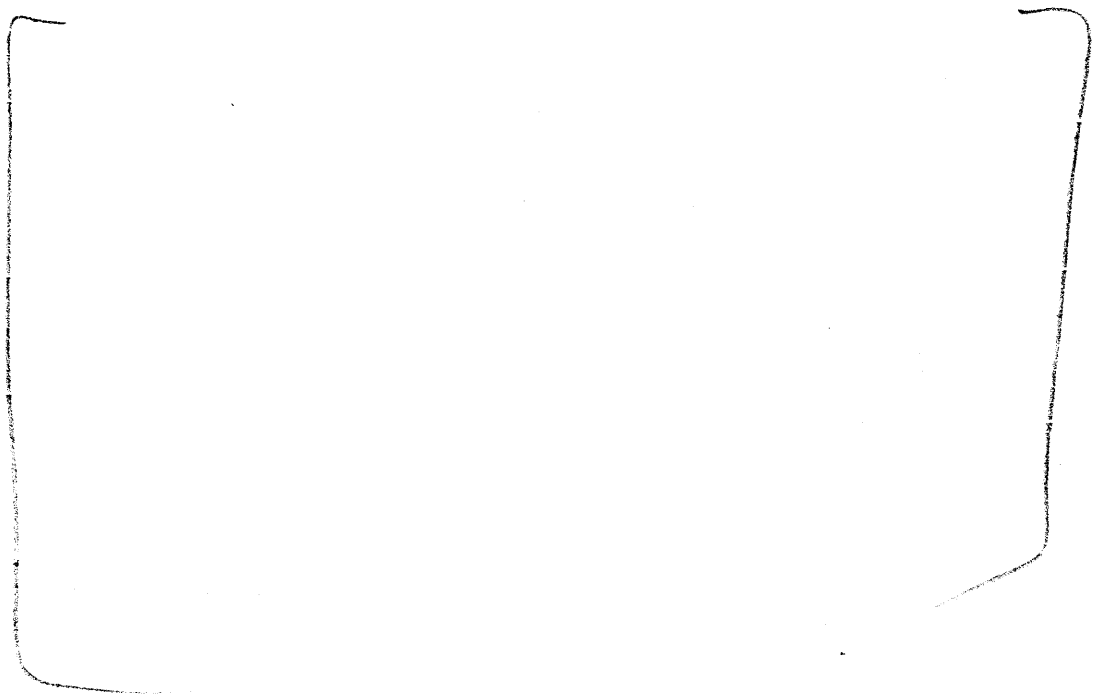


*For each dosage unit, add the corresponding amount released in [redacted] to the amount released at each time point in [redacted]

60 mg Tablet

Dissolution Apparatus/Method

Apparatus	USP rotating paddle method (Apparatus 2)
Rotation speed	100 rpm



*For each dosage unit, add the corresponding amount released in [redacted] to the amount released at each time point in [redacted]

APPEARS THIS WAY
ON ORIGINAL

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for

additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

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

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-289 APPLICANT: Biovail Incorporated

DRUG PRODUCT: 30 mg and 60 mg ER Tablets

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

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

30 mg Tablet

Dissolution Apparatus/Method

Apparatus	USP rotating paddle method (Apparatus 2)
Rotation speed	100 rpm

[redacted]

*For each dosage unit, add the corresponding amount released in [redacted] to the amount released at each time point in [redacted].

60 mg Tablet

Dissolution Apparatus/Method

Apparatus	USP rotating paddle method (Apparatus 2)
Rotation speed	100 rpm

*For each dosage unit, add the corresponding amount released in to the amount released at each time point in

APPEARS THIS WAY
ON ORIGINAL

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

APPEARS THIS WAY
ON ORIGINAL

APR 3 2000

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75289 APPLICANT: Biovail

DRUG PRODUCT: Nifedipine 30 mg ER Tablet

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

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

The dissolution testing should be conducted as follows:

Dissolution Apparatus/Method

Apparatus	USP rotating paddle method (Apparatus 2)
Rotation speed	100 rpm

APPEARS THIS WAY
ON ORIGINAL

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

Sincerely yours,

/S/

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

Nifedipine
60 mg Extended-Release Tablet
ANDA# 75-289
Reviewer: Andre Jackson
V:\firmsam\Biovail\ltrs&rev\75289A.D98

Biovail Incorporated
Mississauga, Ontario, Canada
Submission Date:
December 29, 1998

Addendum to A Review

The firm responded to deficiencies in their submission of December 24, 1997 in a letter to the Division of Bioequivalence dated December 29, 1998. There were 5 deficiencies to which the firm responded. However, the response to deficiency 5 was overlooked by the reviewer and is formally addressed in the current addendum.

Deficiency #5:

The firm should explain why the ratio of Tmax values for the Test/Reference products in the post-prandial study was 1.93 while the Tmax ratios for the fasting and multiple dose studies were 1.0 and 1.34 respectively.

Firm's Response to Deficiency #5:

The relatively higher nifedipine Tmax ratio in the fed state as compared to the two fasting states is attributable to differences in the mean Tmax values of the reference-listed drug. In Study No. 1895, the fasting and limited food-effect study, the mean nifedipine Tmax values for the reference listed drug in fasting and fed states were 16.0 h and 8.94 h, respectively. The corresponding Tmax values for the test product in fasting and fed states were 16.7 h and 17.3 h, respectively. It is therefore evident that within the group of subjects who participated in the study, the Tmax of the test product was similar in fasting and fed states while that of the reference listed drug was influenced significantly by the high-fat meal.

In addition, Tmax is known to be a discrete variable and well known statistical tests are not applicable to it. It is of limited value in the characterization of extended-release formulations that exhibit multiple releases (multiple peaks) or where flat peaks are observed. For the above reasons, and in accordance with the Agency's current acceptance criteria for

bioequivalence studies, Tmax values were not subjected to any statistical tests in the bioequivalence studies.

FDA Reply:

The firm's response is acceptable since as they noted the FDA does not evaluate this parameter to determine the bioequivalence of generic formulations.

Recommendation:

1.The single dose post-prandial study by Biovail on its 60 mg Nifedipine ER Tablet lot # 97G051 comparing it to Pfizer's Procardia XL 60 mg tablet, lot # 57P153A has been found to be acceptable by the Division of Bioequivalence.

2.The prior recommendations for the acceptable single dose 30 mg study and for the acceptable 60 mg multiple and single dose fasting studies submitted by Biovail are unchanged.

André J. Jackson, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang
FT INITIALED YCHuang

Date 7/24/2000

Concur:

Date 7/24/00

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

cc: ANDA # 75289(original), HFD-652 (Huang, Jackson), HFD-650(Director), Drug File, Division File

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-289

ADMINISTRATIVE DOCUMENTS

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

ANDA Number: 75-289 Date of Submission: December 24, 1997

Applicant's Name: Biovail Laboratories Incorporated

Established Name: Nifedipine Extended-release Tablets, 60 mg

Labeling Deficiencies:

1. GENERAL COMMENTS:

   a. Section 126 of Title I of the FDA Modernization Act of 1997, amends Section 503(b)(4) of the Federal Food, Drug, and Cosmetic Act to require at a minimum, that prior to dispensing, the label of prescription products contain the symbol "Rx only". A GUIDANCE FOR INDUSTRY entitled "Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 - Elimination of Certain Labeling Requirements", was revised July 1998 and posted at Internet site http://www.fda.gov/cder/guidance/index.htm. Please note that Section IV, "Frequently Asked Questions" offers guidance on placement of the symbol on all labels and labeling.

   b. Revise your storage temperature recommendations to read "Store below 30°C (86°F)" throughout your labels and labeling.

2. CONTAINER - 100's, 300's & 1000's

   a. See GENERAL COMMENTS.

   b. Revise the established name to read "Nifedipine Extended-release Tablets". [Delete ——— and add "Tablets"]

   c. We encourage the use of boxing, contrasting colors, or other means to differentiate the strength of this drug product from the 30 mg strength (ANDA ———.

   d. Revise " ——— " to read "USUAL DOSAGE".

e. Please include the following statement:

Tablets should be swallowed whole, not bitten or divided.

f. We note that you intend to include desiccant in each package container. We encourage you to declare so on the labels.

3. INSERT

a. GENERAL

i. Revise to read "nifedipine extended-release tablets" throughout the text. Please note that USAN names are common nouns and should be treated as such in the text of labeling (*i.e.*, lower case). Upper case may be used when the USAN name stands alone as on labels or in the title of the package insert.

ii. We note that you have submitted a sister application ANDA [redacted] for 30 mg strength. We encourage that you may consider combining the package inserts for your two different products as does the reference listed drug. However, please note that if you choose to propose the combined insert, these applications must be approved at the same time, or further revisions may be necessary.

iii. It is preferable to delete the terminal zero when referencing a dosage throughout the text. [e.g., "2" rather than [redacted]]

b. TITLE

Please note that "for oral use" is not part of the established name of your drug product. Please delete or italicize to distinguish from the established name.

c. DESCRIPTION

i. Second paragraph, first sentence:

Revise to be in accordance with the reference listed drug and/or comment.

ii. Second paragraph, third sentence - Combine

with the third paragraph and revise to read as follows. Let this begin a new last paragraph:

Each extended-release tablet, formulated as a once-a-day controlled-release tablet for oral administration, delivers 60 mg of nifedipine. In addition, each extended-release tablet contains the following inactive ingredients:...

iii. Revise the molecular weight to read "346.34" to be in accordance with USP 23.

iv. Inactive ingredients:

A) Please alphabetize the listing.

B) You may delete the terms

C) "sulfate" rather than "

D) "red ferric oxide" rather than "

d. PRECAUTIONS - Include the following as the last subsection.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

e. ADVERSE EXPERIENCES

i. "REACTIONS" rather than "

ii. Include the following as the last sentence of the last paragraph:

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

f. OVERDOSAGE

i. Second paragraph, third sentence:

...18 hours post-ingestion. [rather than

ii. Third paragraph, penultimate sentence:

... dictated the prophylactic... [rather than "

g. HOW SUPPLIED

i. First sentence:

Please specify the imprinting of your drug product. We refer you to 21 CFR 206. [e.g., "imprinted with..." or "debossed with...", etc.]

ii. Refer to the GENERAL COMMENT (b).

iii. Refer to the comment (f) under CONTAINER.

Please revise your labels and labeling, as instructed above, and submit in final print.

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

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

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter? Firm using CC in the name (Proprietary?)		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?	X		
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
	Yes	No	N.A.
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present? Proposing Nifedipine CC - includes entire USAN stem			x
Has the name been forwarded to the Labeling and Nomenclature Committee? NO - Feeling is that it would be summarily rejected. If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	x		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		x	

Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		x	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
	Yes	No	N.A.
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed) DON'T KNOW IF TABLET IS IMPRINTED OR NOT		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? YES If so, are the recommendations supported and is the difference acceptable? NO - SEE COMMENTS IN REVIEW		x	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T ½ and date study acceptable)			
Insert labeling references a food effect or a no-effect? YES If so, was a food study done? YES	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. This review was based on the most recently approved labeling of Procardia XL® ([S-014] Approved 8/12/97; Revised 4/97).

2. Storage/Dispensing recommendations

   RLD - Store below 86°F (30°C); PROTECT FROM MOISTURE AND HUMIDITY; Dispense in tight containers (USP).

ANDA - Same as RLD

3. The inactives are accurately listed in the description section. See p.9710, vol.1.27.

4. The tablet description is accurate as seen in the HOW SUPPLIED section. See 10206, vol.1.29.

5. Container Sizes

RLD	30 mg - 100s, 300s, 5000s, UD 100s
	60 mg - 100s, 300s, 5000s, UD 100s
	90 mg - 100s & UD 100s
ANDA	60 mg - 100s, 300s, 1000s

6. The containers are made of White [redacted]; the 100s & 300s size has a CRC while the 1000s size does not (v 1.28 p 10047).

7. There are 5 patents for this drug product:

5264446	11/23/10
4783337	9/16/03
4765989	9/16/03
4612008	9/16/03
4327725	11/25/00

The firm's statement is accurate. However, the firm has filed Paragraph IV Certification.

8. The following statements are found in the innovator's insert labeling, which specifically pertains to the RLD formulation. We will NOT ask the generic firm to include similar information because this information is not related to safety and we have not asked to include this information in the past for other generic products.

a. DESCRIPTION - System Components and Performance

PROCARDIA XL® Extended-Release... in the feces as an insoluble shell.

b. PRECAUTIONS - Information for Patients

[redacted]

Date of Review: July 31, 1998 Date of Submission: 12/24/97

Primary Reviewer: Chan Park Date: 8/10/98 (for C. Park)

Team Leader: Charlie Hoppes Date: 9/10/98

cc:

ANDA: 75-289
DUP/DIVISION FILE
HFD-613/CPark/CHoppes (no cc)
X:\NEW\FIRMSAM\BIOVAIL\LTRS&REV\75289NA1.L
Review

APPEARS THIS WAY
ON ORIGINAL

CDER Establishment Evaluation Report for February 11, 1998

Application: **ANDA 75289/000**
Stamp: **29-DEC-1997** Regulatory Due:
Applicant: **BIOVAIL LABS**
CHELSTON PARK,BLDG 2,COLLYM
SAINT MICHAEL, , BB

Priority:
Action Goal:
Brand Name:
Established Name: **NIFEDIPINE**
Generic Name:
Dosage Form: **EXT (EXTENDED-RELEASE TABLET**
Strength: **60 MG**

Org Code: **600**
District Goal: **28-FEB-1999**

FDA Contacts: **J. WILSON III** **(HFD-617)** **301-827-5848 , Project Manager**
V. SAYEED **(HFD-629)** **301-827-5848 , Team Leader**

Overall Recommendation:

Establishment: **9615235**
BIOVAIL LIFESCIENCES
100 LIFESCIENCES PARKWAY
STEINBACH, MANITOBA, CA

DMF No:
AADA No:

Profile: **TTR** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC**
Milestone Date **11-FEB-1998**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Establishment: [redacted]

DMF No: [redacted]
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC**
Milestone Date **11-FEB-1998**

Responsibilities: [redacted]

Establishment: [redacted]

DMF No:
AADA No:

Profile: **NEC** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC**
Milestone Date **11-FEB-1998**

Responsibilities: [redacted]

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

ANDA Number: 75-335 Date of Submission: February 11, 1998

Applicant's Name: Biovail Laboratories Incorporated

Established Name: Nifedipine Extended-release Tablets, 30 mg

Labeling Deficiencies:

1. GENERAL COMMENTS:

   a. Section 126 of Title I of the FDA Modernization Act of 1997, amends Section 503(b)(4) of the Federal Food, Drug, and Cosmetic Act to require at a minimum, that prior to dispensing, the label of prescription products contain the symbol "Rx only". A GUIDANCE FOR INDUSTRY entitled "Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 - Elimination of Certain Labeling Requirements", was revised July 1998 and posted at Internet site http://www.fda.gov/cder/guidance/index.htm. Please note that Section IV, "Frequently Asked Questions" offers guidance on placement of the symbol on all labels and labeling.

   b. Revise your storage temperature recommendations to read "Store below 30°C (86°F)" throughout your labels and labeling.

2. CONTAINER - 100's, 300's & 1000's

   a. See GENERAL COMMENTS.

   b. Revise the established name to read "Nifedipine Extended-release Tablets". [Delete " [redacted] and add "Tablets"]

   c. We encourage the use of boxing, contrasting colors, or other means to differentiate the strength of this drug product from the 60 mg strength (ANDA 75-289).

   d. Revise [redacted] to read "USUAL DOSAGE".

e. Please include the following statement:

Tablets should be swallowed whole, not bitten or divided.

f. We note that you intend to include desiccant in each package container. We encourage you to declare so on the labels.

3. INSERT

a. GENERAL

i. Revise to read "nifedipine extended-release tablets" throughout the text. Please note that USAN names are common nouns and should be treated as such in the text of labeling (*i.e.*, lower case). Upper case may be used when the USAN name stands alone as on labels or in the title of the package insert.

ii. We note that you have submitted a sister application ANDA 75-289 for 60 mg strength. We encourage that you may consider combining the package inserts for your two different products as does the reference listed drug. However, please note that if you choose to propose the combined insert, these applications must be approved at the same time, or further revisions may be necessary.

iii. It is preferable to delete the terminal zero when referencing a dosage throughout the text. [e.g., "2" rather than ~~2.0~~

b. TITLE

Please note that "for oral use" is not part of the established name of your drug product. Please delete or italicize to distinguish from the established name.

c. DESCRIPTION

i. Second paragraph, first sentence:

Revise to be in accordance with the reference listed drug and/or comment.

ii. Second paragraph, third sentence - Combine

with the third paragraph and revise to read as follows. Let this begin a new last paragraph:

Each extended-release tablet, formulated as a once-a-day controlled-release tablet for oral administration, delivers 30 mg of nifedipine. In addition, each extended-release tablet contains the following inactive ingredients:...

iii. Revise the molecular weight to read "346.34" to be in accordance with USP 23.

iv. Inactive ingredients:

You may delete the terms [redacted]

d. PRECAUTIONS - Include the following as the last subsection.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

e. ADVERSE EXPERIENCES

i. "REACTIONS" rather than "EXPERIENCES"

ii. Include the following as the last sentence of the last paragraph:

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

f. OVERDOSAGE

Third paragraph, penultimate sentence:

... dictated the prophylactic... [rather than

g. HOW SUPPLIED

i. First sentence:

Please specify the imprinting of your drug product. We refer you to 21 CFR 206.

[e.g., "imprinted with..." or "debossed with...", etc.]

ii. Refer to the GENERAL COMMENT (b).

iii. Refer to the comment (f) under CONTAINER.

Please revise your labels and labeling, as instructed above, and submit in final print.

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

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

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

Biovail submitted four separate ANDAs for Nifedipine Extended-release tablets. These ANDAs were all submitted at different times and were not in conformance with OGD Policy and Procedure Guide (P&PG) #20-90. All four ANDAs were inadvertently accepted and filed as individual applications. Based on OGD P&PG #20-90, and to keep consistency in our filing process, the four ANDAs will be administratively collapsed into two ANDAs. ANDA ——— will be collapsed into ANDA **75-269** (ANDA ——— will be withdrawn). All future submissions to ANDA ——— should be submitted as amendments to ANDA 75-269. ANDA ——— will be collapsed into ANDA 75-289 (ANDA ——— will be withdrawn). All future submissions to ANDA ——— should be submitted as amendments to ANDA 75-289.

Nasser Mahmud /S/
September 23, 1998

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

ANDA Number: 75-335 Date of Submission: February 11, 1998

Applicant's Name: Biovail Laboratories Incorporated

Established Name: Nifedipine Extended-release Tablets, 30 mg

Labeling Deficiencies:

1. GENERAL COMMENTS:

   a. Section 126 of Title I of the FDA Modernization Act of 1997, amends Section 503(b)(4) of the Federal Food, Drug, and Cosmetic Act to require at a minimum, that prior to dispensing, the label of prescription products contain the symbol "Rx only". A GUIDANCE FOR INDUSTRY entitled "Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 - Elimination of Certain Labeling Requirements", was revised July 1998 and posted at Internet site http://www.fda.gov/cder/guidance/index.htm. Please note that Section IV, "Frequently Asked Questions" offers guidance on placement of the symbol on all labels and labeling.

   b. Revise your storage temperature recommendations to read "Store below 30°C (86°F)" throughout your labels and labeling.

2. CONTAINER - 100's, 300's & 1000's

   a. See GENERAL COMMENTS.

   b. Revise the established name to read "Nifedipine Extended-release Tablets". [Delete " [redacted] and add "Tablets"]

   c. We encourage the use of boxing, contrasting colors, or other means to differentiate the strength of this drug product from the 60 mg strength (ANDA 75-289).

   d. Revise ' [redacted] " to read "USUAL DOSAGE".

e. Please include the following statement:

Tablets should be swallowed whole, not bitten or divided.

f. We note that you intend to include desiccant in each package container. We encourage you to declare so on the labels.

3. INSERT

a. GENERAL

i. Revise to read "nifedipine extended-release tablets" throughout the text. Please note that USAN names are common nouns and should be treated as such in the text of labeling (*i.e.*, lower case). Upper case may be used when the USAN name stands alone as on labels or in the title of the package insert.

ii. We note that you have submitted a sister application ANDA 75-289 for 60 mg strength. We encourage that you may consider combining the package inserts for your two different products as does the reference listed drug. However, please note that if you choose to propose the combined insert, these applications must be approved at the same time, or further revisions may be necessary.

iii. It is preferable to delete the terminal zero when referencing a dosage throughout the text. [e.g., "2" rather than [redacted]

b. TITLE

Please note that "for oral use" is not part of the established name of your drug product. Please delete or italicize to distinguish from the established name.

c. DESCRIPTION

i. Second paragraph, first sentence:

Revise to be in accordance with the reference listed drug and/or comment.

ii. Second paragraph, third sentence - Combine

with the third paragraph and revise to read as follows. Let this begin a new last paragraph:

Each extended-release tablet, formulated as a once-a-day controlled-release tablet for oral administration, delivers 30 mg of nifedipine. In addition, each extended-release tablet contains the following inactive ingredients:...

iii. Revise the molecular weight to read "346.34" to be in accordance with USP 23.

iv. Inactive ingredients:

You may delete the terms "

d. PRECAUTIONS - Include the following as the last subsection.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

e. ADVERSE EXPERIENCES

i. "REACTIONS" rather than "

ii. Include the following as the last sentence of the last paragraph:

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

f. OVERDOSAGE

Third paragraph, penultimate sentence:

... dictated the prophylactic... [rather than

g. HOW SUPPLIED

i. First sentence:

Please specify the imprinting of your drug product. We refer you to 21 CFR 206.

[e.g., "imprinted with..." or "debossed with...", etc.]

ii. Refer to the GENERAL COMMENT (b).

iii. Refer to the comment (f) under CONTAINER.

Please revise your labels and labeling, as instructed above, and submit in final print.

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

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

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter? Firm using CC in the name (Proprietary?)		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?	X		
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
	Yes	No	N.A.
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present? Proposing Nifedipine CC - includes entire USAN stem			x
Has the name been forwarded to the Labeling and Nomenclature Committee? NO - Feeling is that it would be summarily rejected. If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	x		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		x	

Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		x	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
	Yes	No	N.A.
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed) DON'T KNOW IF TABLET IS IMPRINTED OR NOT		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? YES If so, are the recommendations supported and is the difference acceptable? NO - SEE COMMENTS IN REVIEW		x	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T ½ and date study acceptable)			
Insert labeling references a food effect or a no-effect? YES If so, was a food study done? YES	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. This review was based on the most recently approved labeling of Procardia XL® ([S-014] Approved 8/12/97; Revised 4/97).

2. Storage/Dispensing recommendations

   RLD - Store below 86°F (30°C); PROTECT FROM MOISTURE AND HUMIDITY; Dispense in tight containers (USP).

ANDA - Same as RLD

3. The inactives are accurately listed in the description section. See p.9510, vol.1.26.

4. The tablet description is accurate as seen in the HOW SUPPLIED section. See p.9995, vol.1.28.

5. Container Sizes

RLD	30 mg - 100s, 300s, 5000s, UD 100s
	60 mg - 100s, 300s, 5000s, UD 100s
	90 mg - 100s & UD 100s
ANDA	30 mg - 100s, 300s, 1000s

6. The containers are made of White [redacted] the 100s & 300s size has a CRC while the 1000s size does not (v 1.27 p 9836).

7. There are 5 patents for this drug product:

5264446	11/23/10
4783337	9/16/03
4765989	9/16/03
4612008	9/16/03
4327725	11/25/00

The firm's statement is accurate. However, the firm has filed Paragraph IV Certification.

8. The following statements are found in the innovator's insert labeling, which specifically pertains to the RLD formulation. We will NOT ask the generic firm to include similar information because this information is not related to safety and we have not asked to include this information in the past for other generic products.

a. DESCRIPTION - System Components and Performance

PROCARDIA XL® Extended-Release... in the feces as an insoluble shell.

b. PRECAUTIONS - Information for Patients

Do not be concerned if you... eliminated from your body.

Date of Review: August 7, 1998 Date of Submission: 2/11/98

Primary Reviewer: Chan Park /S/ Date: v (for C.Park) 8/10/98

Team Leader: Charlie Hoppes /S/ Date: 8/10/98

cc:

ANDA: 75-335
DUP/DIVISION FILE
HFD-613/CPark/CHoppes (no cc)
X:\NEW\FIRMSAM\BIOVAIL\LTRS&REV\75335NA1.L
Review

APPEARS THIS WAY
ON ORIGINAL

CDER Establishment Evaluation Report
for March 10, 1998

Application: **ANDA 75335/000**
Stamp: **12-FEB-1998** Regulatory Due:
Applicant: **BIOVAIL LABS**
CHELSTON PARK,BLDG 2,COLLYM
SAINT MICHAEL, , BB

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

Org Code: **600**
District Goal: **12-APR-1999**

FDA Contacts: **T. AMES (HFD-617) 301-827-5849 , Project Manager**
U. VENKATARAM (HFD-647) 301-827-5849 , Team Leader

Overall Recommendation:

Establishment: **9615235**
BIOVAIL LIFESCIENCES
100 LIFESCIENCES PARKWAY
STEINBACH, MANITOBA, CA

DMF No:
AADA No:

Profile: **TTR** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC**
Milestone Date **10-MAR-1998**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Establishment: [redacted]

DMF No: [redacted]
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC**
Milestone Date **10-MAR-1998**

Responsibilities: [redacted]

Establishment: [redacted]

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC**
Milestone Date **10-MAR-1998**

Responsibilities: [redacted]

FYI

M E M O R A N D U M

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

DATE : December 30, 1997

TO : Director
Division of Bioequivalence (HFD-650)

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

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

Mylan Pharmaceuticals has submitted ANDA 75-108 for Nifedipine Extended-release Tablets, 30 mg. The ANDA contains a certification pursuant to 21 USC 355(j)(2)(A)(vii)(iv) stating that a patent expiring November 23, 2010 will not be infringed by the manufacture or sale of the proposed product. In order to accept an ANDA for filing that contains such a patent certification, the Agency must formally make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the study submitted by Mylan on April 7, 1997 for its Nifedipine product satisfies the statutory requirements of "completeness" so that the ANDA may be filed and that a period of six months of market exclusivity can be granted to the applicant who submitted the first substantially complete ANDA under 21 USC 355(j)(4)(B)(iv).

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

ANDA 75-108 Nifedipine Extended-release Tablets, 30 mg Mylan

In determining whether a bio study is "complete" to satisfy statutory requirements, the following items are examined:

1. Study design

   (a) Appropriate number of subjects
   (b) Description of methodology

2. Study results

   (a) Individual and mean data is provided
   (b) Individual demographic data
   (c) Clinical summary

The issue raised in the current situation revolves around whether the study can purport to demonstrate bioequivalence to the listed drug.

We would appreciate a cursory review and your answers to the above questions as soon as possible so we may take action on this application.

DIVISION OF BIOEQUIVALENCE:

_____ Study meets statutory requirements

_____ Study does **NOT** meet statutory requirements

Reason:

APPEARS THIS WAY
ON ORIGINAL

_____ _____

Director, Division of Bioequivalence Date

TELEPHONE MEMO

To: Martin Levy, Regulatory Affairs
Dr. Eradiri, Pharmacokineticist
Dr. Huang, Statistician
(416) 285-6000 X 213

REF # ANDA 75-335

From: Lizzie Sanchez
Hoainhon Nguyen

Date: 9/2/98

Subject: **Nifedipine Extended Release Tablets**

Requested by: Martin Levy

The firm requested clarification of the term "residual effect". Dr. Nguyen explained that it is the same thing as carryover effect. The study submitted included 4 treatments without replication. The carryover effect of the preceding treatment should be accounted for in ANOVA. If the carryover is not significant, this factor can be excluded from the analysis. If it is significant, it should remain in the analysis.

TELEPHONE MEMO

TO: **Martin Levy**
Biovail
(416) 285-6000

REF# **ANDA 75-289**

FROM: **Elaine Hu and Andre Jackson**

DATE: **2/18/1999**

SUBJECT: **Nifedipine Extended-Release Tablets, 60 mg**

REQUESTED BY: **Andre Jackson**

We requested that the firm submit the following information:

1. Bioequivalence data diskette in ASCII format including: subject/sequence/treatment/period/plasma concentration pharmacokinetic parameters (AUC, C_{max}, etc.)

2. Need dosing dates for each subject in the study

3. Need the lot size of the biobatch (number of tablets)

The firm will have 10 business days to respond to this Telephone Bioequivalence Amendment. The firm may fax the information, followed by a hard copy (must receive no later than 3/4/1999).

APPEARS THIS WAY
ON ORIGINAL

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

ANDA Number: **75-289** Date of Submission: **April 5, 1999**

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

Established Name: **Nifedipine Extended-release Tablets 30 mg and 60 mg**

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

Do you have 12 Final Printed Labels and Labeling? No

Container Labels: 30 mg and 60 mg (100s, 300s, 1000s)
Satisfactory (in draft) as of April 5, 1999 submission.

Professional Package Insert Labeling:
Satisfactory (in draft) as of April 5, 1999 submission.

Revisions needed when go to FPL: CONTAINER - Increase prominence of "Rx only", place period after "Store below ..." PI - TITLE - include "Rx only", DESCRIPTION - Third paragraph, last sentence - delete extra space between "copolymer" and "type A" - HOW SUPPLIED - place period after "Store below ..." **These changes were relayed to the firm by telephone by A. Vezza on 4-27-99.**

BASIS OF APPROVAL:

Add "USP" to Label. Tested with test, with which it complies.

Was this approval based upon a petition? No

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

NDA Number: 19-684

NDA Drug Name: Procardia XL® (nifedipine extended-release) Tablets

NDA Firm: Pfizer

Date of Approval of NDA Insert and supplement #: 8/12/97 (S-014)

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

Was this approval based upon an OGD labeling guidance? No

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

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter? Firm using CC in the name (Proprietary?)		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?	X		
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	x		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		x	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		x	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	

Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed) DON'T KNOW IF TABLET IS IMPRINTED OR NOT		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? YES If so, are the recommendations supported and is the difference acceptable? NO - SEE COMMENTS IN REVIEW		x	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T ½ and date study acceptable)			
Insert labeling references a food effect or a no-effect? YES If so, was a food study done? YES	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD: (taken from previous review)

1. This review was based on the most recently approved labeling of Procardia XL® ([S-014] Approved 8/12/97; Revised 4/97).

2. Storage/Dispensing recommendations

   RLD - Store below 86°F (30°C); PROTECT FROM MOISTURE AND HUMIDITY; Dispense in tight containers (USP).

   ANDA - Same as RLD

3. The inactives are accurately listed in the description section. See p.9710, vol.1.27.

4. The tablet description is accurate as seen in the HOW SUPPLIED section. See 10206, vol.1.29.

5. Container Sizes

   RLD 30 mg - 100s, 300s, 5000s, UD 100s
   60 mg - 100s, 300s, 5000s, UD 100s
   90 mg - 100s & UD 100s

   ANDA 60 mg - 100s, 300s, 1000s

6. The containers are made of White [redacted]; the 100s & 300s size has a CRC while the 1000s size does not (v 1.28 p 10047).

7. There are 5 patents for this drug product:

5264446	11/23/10
4783337	9/16/03
4765989	9/16/03
4612008	9/16/03
4327725	11/25/00

The firm's statement is accurate. However, the firm has filed Paragraph IV Certification.

8. The following statements are found in the innovator's insert labeling, which specifically pertains to the RLD formulation. We will NOT ask the generic firm to include similar information because this information is not related to safety and we have not asked to include this information in the past for other generic products.

a. DESCRIPTION - System Components and Performance

PROCARDIA XL® Extended-Release... in the feces as an insoluble shell.

b. PRECAUTIONS - Information for Patients

Do not be concerned if you... eliminated from your body.

9. Firm plans to differentiate their container labels (p 340).

10. Teva to market - new labeling statement.

Date of Review: 4-14-99 Date of Submission: 4-7-99

Primary Reviewer: Adolph Vezza /S/ Date: 4/27/99

Team Leader: Charlie Hoppes /S/ Date: 4/27/99

---

cc:

ANDA: 75-289
DUP/DIVISION FILE
HFD-613/AVezza/CHoppes (no cc)
aev/4/14/99|V:\FIRMSAM\BIOVAIL\LTRS&REV\75289TAP.L
Review

Telephone Conversation Memorandum

ANDA: 75-289

DRUG: Nifedipine Extended-release Tablets, 30 mg and 60 mg

FIRM: Biovail Laboratories, Inc.

PERSONS INVOLVED: Ken Albert, Biovail
Tim Ames, Ubrani Venkataram, FDA

PHONE NUMBER: 703-995-2400

DATE: May 31, 2000

Background:

Firm's Telephone amendment dated May 10, 2000 prompted more concern about the firm's in-process specification of the theoretical for the

Firm was contacted and requested to provide the following:

1. Quantitative data showing amount of drug product released in acidic medium after for both drug products with both the of the theoretical

2. Comparative dissolution profiles for both drug products with of the theoretical. Dissolution testing should be conducted as per the finished product dissolution methods specified in the ANDA with the addition of a quantitative analysis done for the amount of drug release in Part 1 of each method.

KAlbert questioned whether a tightening of the specification would be acceptable in lieu of providing this requested information. It was pointed out that any in-process specification should be justified with quantitative data. KAlbert indicated he would address these requests and get back with a response as soon as possible.

Timothy W. Ames, R.Ph., M.P.H.
Project Manager, Div Chem II, Team 8, OGD

cc: ANDA 75-289
Division file (1)

File: V:\firmsam\biovail\telecons\75289tc2.doc

Telephone Conversation Memorandum

ANDA: 75-289

DRUG: Nifedipine ER Tablets 30 & 60 mg

FIRM: Biovial

PERSONS INVOLVED: Mr. Wayne Krepner,

PHONE NUMBER: 703 665-2000

DATE: May 8, 2000

Called the firm and requested for the following information:

Provide the pharmaceutical function of the excipients.

Dissolution data to support the lower limit on

For 30 mg tablets

Clarify the difference between the test methods 0037.00 (No disintegration within and all disintegrated within and method 0021.11

For 60 mg tablets

Clarify the difference between the test methods 0037.00 (No disintegration within and all disintegrated within and method 0021.11

Also clarify the difference in time between the disintegration and for both strengths.

Firm was requested to submit the information as a telephone amendment.

Vilayat Sayeed, Ph.D.
Deputy Directory, Div Chem II, OGD

/S/ 5/8/00

cc: ANDA 75-515
Division file (1)

File: V:\firmsam\biovail\telecons\75289.may8.2000.doc

File 75-289

Telephone Conversation Memorandum

ANDA: 75-289

DRUG: Nifedipine EXT Tablets

FIRM: Biovail Laboratories, Inc.

PERSONS INVOLVED: Wayne Kreppner, Biovail
Ubrani V. Venkataram, FDA

PHONE NUMBER: 703-995-2400

DATE: April 12, 2000

Background:

I had called Mr. Kreppner on 4/10/00 to ask Biovail to submit revised DP release and stability specifications that included all the revised limits for residual solvents, impurities, and dissolution (including limits recommended by DOB). The firm submitted a telephone amendment on the same day. They had also left a voice message. Review of the amendment indicated that the firm had not implemented the DOB recommendation for dissolution in total but had changed the time point for stage I testing (pH 7.5 buffer; sampling changed from ——— Mr. Kreppner called later that day (about 1:00 p.m.) to discuss this variance. He also suggested that they wish to change the dissolution limit for the ——— tablet to be consistent with the finished product testing. I replied that:

1. The change in dissolution testing proposed by the firm will need to be reviewed and accepted by the Bio reviewer. I will call him back when we have more information.
2. The firm should submit all changes together and not piece meal.

Mr. Kreppner wanted to resolve the issue right away. I called him back today (4/12/00) to let him know that the bio reviewer is currently busy with another application and we will respond later.

Ubrani V. Venkataram, Ph. D.
Team Leader, Div Chem II, Team 8, OGD

4/14/00

---

cc: ANDA 75-289
Dup

ANDA APPROVAL SUMMARY

ANDA: [redacted]

DRUG PRODUCT: Nifedipine USP

FIRM: Biovail Laboratories

DOSAGE FORM: Tablets

STRENGTHS: 30 mg and 60 mg

CGMP STATEMENT/EIR UPDATE STATUS:

Manufacturer-Finished Dosage Form:

The dosage form will be manufactured, controlled and processed, packaged and labeled at

Biovail Corporation International
Manufacturing Division
100 Life Science Parkway
Steinbach, Manitoba
Canada ROA 2T3

EER Attached, Acceptable - November 10, 1999.

Manufacturer-Active Ingredients:

The drug substance, Nifedipine USP is manufactured by:

The drug substance will be —— by:

[redacted]

The U.S. Agent for ———— is:

[redacted]

The firm included authorization to refer to DMF # —— for the synthesis of the drug substance. DMF #—— as amended was found to be Adequate per M.P. Selvam 09/25/99.

And thereafter there is no update.

Contract Laboratories:

The firm indicated that the following contract Laboratories will be used during commercial production:

[redacted]

Certification of GLP/GMP compliance was submitted for each laboratory:

Biovail Corporation International
Manufacturing Division
100 Life Science Parkway
Steinbach, Manitoba
Canada ROA 2T3

[redacted]

BIO STUDY:

The new amendment reviewed by Dr. A. Jackson and the approval letter sent on 04-03-2000 for 30 and 60 mg Tablets. The 04-10-00 amendment was also reviewed and DOB has accepted the dissolution specifications proposed by the firm.

Dissolution Apparatus/Method

Apparatus	USP rotating paddle method (Apparatus 2)
Rotation speed	100 rpm

The test product should meet the following specification:

VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

Drug Substance

The Firm's specifications for drug substance indicate compendial procedures as well as in-house procedures. Review of the listed in-house procedures showed each to be based on current compendial procedures with any modification within acceptable limits. Additional information should not be considered necessary at this time.

Drug Product

The drug product is not compendial, and the firm submitted an in-house ~ method for Assay and Impurities based on the current USP method for the drug substance. The firm submitted a methods validation study and it is satisfactory. MV package has been submitted to the District Lab and is pending evaluation.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?:

Stability protocol: Satisfactory

Lots used in Stability study:

Nifedipine Xl ER 30 mg tablets in 100's:	Lot # 97G050
Nifedipine Xl ER 30 mg tablets in 300's:	Lot # 97H004
Nifedipine Xl ER 30 mg tablets in 1000's:	Lot # 97H005
Nifedipine Xl ER 60 mg tablets in 100's:	Lot # 97G051
Nifedipine Xl ER 60 mg tablets in 300's:	Lot # 97H006
Nifedipine Xl ER 60 mg tablets in 1000's:	Lot # 97H006

3 month accelerated (40°C/75% RH) are included for the 30 mg and 60 mg tablets packaged in the proposed market containers. Room temperature testing will be performed at 25°C ± 2°C and 60% ± 5% RH. Specifications same as at release.

LABELING:

The name, structure, molecular formula and molecular weight are as the same as the Innovator's.

The inactive ingredients' list appears to be Satisfactory.

The HOW SUPPLIED section appears to be Satisfactory

Final Amendment Reviewed by Adolph Vezza on 4/27/1999 and it is satisfactory.

STERILIZATION VALIDATION (IF APPLICABLE):

N/A

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?): Satisfactory

The firm included authorization to refer to DMF # —— for the ———————————— DMF # —— as amended was found to be Adequate per M.P. Selvam 09/25/99. And thereafter there is no update.

Completed batch records were included for the following test batches of finished drug product:

30 mg tablet: Lot # 97G036 ——— tablets
60 mg tablet: Lot # 97G038 ——— tablets

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):

The stability batch size:

30 mg tablet: Lot # 97G036 ——— tablets
60 mg tablet: Lot # 97G038 ——— tablets

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?:

The manufacturing process used for the test batches were the same as the manufacturing process described in the blank batch records.
A commitment to perform process validation studies on the first three post approval production lots is included.

CHEMIST: **Mouna P. Selvam, Ph.L.,** /S/ **DATE 04/26/2000**
SUPERVISOR: **Ubrani V. Venkataram, Ph.D.,** **DATE 04/26/2000**

/S/ 5/1/00.

V:\Firmsam\Biovail\ltrs&rev\75289appl.rms

Patent and Exclusivity Search Results from query on 019684 001.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code
019684	001	4327725	NOV 25,2000	
019684	001	4612008	SEP 16,2003	
019684	001	4765989	SEP 16,2003	
019684	001	4783337	SEP 16,2003	
019684	001	5264446	NOV 23,2010	

Exclusivity Data

There is no unexpired exclusivity for this product.

Thank you for searching the Electronic Orange Book

Patent and Exclusivity Terms

Return to Electronic Orange Book Home Page

APPEARS THIS WAY
ON ORIGINAL

Verified 1/19/00 Rw

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **ANDA 75289/000**
Stamp: **29-DEC-1997** Regulatory Due:
Applicant: **BIOVAIL LABS**

SAINT MICHAEL, , BB

Priority:
Action Goal:
Brand Name:
Established Name: **NIFEDIPINE**
Generic Name:
Dosage Form: **EXT (EXTENDED-RELEASE TABLET**
Strength: **60 MG**

Org Code: **600**
District Goal: **28-FEB-1999**

FDA Contacts: **J. WILSON III (HFD-400) 301-770-9299 , Project Manager**
V. SAYEED (HFD-629) 301-827-5848 , Team Leader

Overall Recommendation:

ACCEPTABLE on 10-NOV-1999 by M. EGAS (HFD-322) 301-594-0095
ACCEPTABLE on 24-FEB-1998 by M. EGAS (HFD-322) 301-594-0095

Establishment: **9615235**
BIOVAIL LIFESCIENCES

STEINBACH, MANITOBA, CA

DMF No:
AADA No:

Profile: **TTR** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **04-NOV-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Establishment: [redacted]

DMF No: [redacted]
AADA No.

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **04-NOV-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: [redacted]

Establishment: [redacted]

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **04-NOV-1999**
Decision: **ACCEPTABLE**

Responsibilities: [redacted]

Printed by Pat Beers-Block

Electronic Mail Message

Date: 28-Jun-2000 11:58am
From: krista Scardina
SCARDINAK
Dept: HFD-600 MPNII
Tel No: 301-827-5830

Subject: ANDA 75-289

Hello.

Would you please cancel the inspection ~~for~~ [redacted] regarding ANDA 75-289. The product is close to approval.

Thanks.

Krista

Refer to office level b/o endorsement forms signed by D. Compton 6/29/00, 4/17/00, and 3/28/00. Each indicates that an inspection is not needed

/s/
6/19/00

APPEARS THIS WAY
ON ORIGINAL

Printed by Pat Beers-Block

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 14-Jul-2000 09:00am
From: Jennifer Fan
FANJE
Dept: HFD-617 MPN2
Tel No: 301-827-5847 FAX t-

TO: Pat Beers-Block (BEERSBLOCKP)

Subject: FWD: ANDA 75-289

Hello Pat,

Here is the cancellation that was sent to DSI.

Thanks,

Jen

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS (HFD-600)
7500 STANDISH PLACE, ROCKVILLE, MD 20855

DATE: 9/13/2000

TO: W. Kreppner

PHONE: 703-995-2400

FAX: 703-995-2444

FROM U. Venkataram

PHONE: 301-827-5849

FAX: _____

TOTAL NUMBER OF PAGES: _____
(EXCLUDING COVER SHEET)

To: Mr. W. Kreppner

Date: 13 September 2000

Regarding ANDA 75-289:

As discussed earlier this morning please revise the analytical methods per the attached analytical chemist's comments. Also, separate the dissolution methods for the CC tablets (ANDA 75-269) from that for the XL tablets (ANDA 75-289).

In your commitment please include a commitment to submit the revised methods in 30 days. We request that you also submit a "Methods Validation" package (with the revised methods), with samples from validation batches.

Telephone Conversation Memorandum

ANDA: 75-289

DRUG: Nifedipine EXT Tablets

FIRM: Biovail Laboratories, Inc.

PERSONS INVOLVED: Wayne Kreppner, Biovail
Ubrani V. Venkataram, FDA

PHONE NUMBER: 703-995-2400

DATE: September 13, 2000

Background:

I called Mr. Kreppner to present 2 issues:

1. Similarity of the products presented in ANDAs 75-269 and 75-289. Since the 2 products have the same imprint and the color differentiation did not appear to be sufficient, I requested him to send some samples for our visual examination. He said that he will send the samples right away.

2. The second was the issue of methods validation. I requested Mr. Kreppner to revise the analytical methods per the analytical chemist's comment and resubmit it. He wanted to know whether they can do it by commitment. I verified the request with Dr. V. Sayeed (DD/Div. 2) who agreed to it if there was a time limit placed on such commitment. I conveyed this to Mr. Kreppner. Mr. Kreppner agreed to a 30 day limit post-approval. He also requested me to fax the analytical chemist's comments. After obtaining clearance from Dr. Sayeed, I faxed the material to Biovail.

/S/ 9/13/00

Ubrani V. Venkataram, Ph. D.
Team Leader, Div Chem II, Team 8, OGD

cc: ANDA 75-289
Dup
Division file (1)

June 22, 2001

RE: MSB FILE Number: 2001-01772

To Whom it May Concern
Office of Generic Drugs, FDA

Follow-up Memo: Response to formulation deficiency query of June 7, 2001 by [redacted]

To Whom it May Concern,

This memo is in reference to the questioned formulation submitted on June7, 2001 by [redacted]

RESULTS:

Upon researching original applications for Nifedipine Extended Release 30mg, it was found that the medication in question is actually manufactured by two separate companies (Bioavail. Labs & Elan Inc.) that use different labeling and is ultimately distributed by the same manufacturer, Teva Pharmaceutical Inc. Though, the tablets appearance may differ both are valid and AB rated to Adalat CC. The reporter may have been used to the appearance of the Bioavail tablets, film coated round brownish tablets imprinted with a "B" on one side and a "30" on the other as opposed to the Elan manufactured tablets, hard peach tablets imprinted with "ELN30". This would explain the misunderstanding.

METHODS:

Upon [redacted] report, original applications 75289 and 75269 were retrieved. It was first found that tablets manufactured by Bioavail, with matching NDC provided by RPH did not match the description reported. Field research at nearby pharmacies ([redacted] showed no discrepancies with original applications.

Two Phone conversations with the [redacted] on 06/19 and 06/20 confirmed the pharmacist confusion as of a change in appearance of tablets. The RPH was further concerned with the "delivery system that did not look like usual matrix coating of the AB rated generic for Adalat CC". NDC numbers were provided. We compared the NDC numbers and tablet descriptions for the Elan laboratory tablets and the Bioavail tablets with NDC number and description provided by the pharmacist. Both NDC numbers matched with the NDC number given by the pharmacist. Hence, there was no mix up from the company's end. What might have led to confusion is that TEVA has the same NDC number for the tablets manufactured by both labs, although the tablet description is different. The pharmacist may have been used to the enteric coated tablet manufactured by Biavail as opposed to the hard core tablets manufactured by ELAN.

The tablets described are thus valid and AB rated to Adalat CC. The pharmacist was then contacted and situation was explained. For further references, the pharmacist was recommended to check the manufacturing companies.

If you have any questions or comment, please contact me at (301) 827-5862.

Best Regards,

Batoul Senhaji

Student Intern
Office of Generics, FDA

Prepared by:
Peter Rickman
9/27/00

60 mg BIOVAIL ONLY

1ST TO FILE:

30 mg	75-108	MYLAN
60 mg	75-289	BIOVAIL

RLD - PROCARDIA XL 19-684 PFIZER

4327725	11/25/00	ALZA
4765989	9/16/03	ALZA
5264446	11/23/10	BAYER
4612008	9/16/03	ALZA
4783337	9/16/03	ALZA

PATENT INFRINGEMENT SUIT against BIOVAIL filed by PFIZER and BAYER on '446 PATENT ONLY
CIVIL ACTION NO. 98-1340 District Court of PUERTO RICO

NOTICES REC'd:

BAYER	rec'd	2/18/98
PFIZER	rec'd	2/23/98
ALZA	rec'd	2/20/98

30 MONTH PERIOD EXPIRED 8/23/00 ON 60 mg

30 mg ONLY BIOVAIL

BAYER rec'd NOTICE ON 3/30/98
PFIZER rec'd NOTICE ON 3/26/98

PFIZER INITIATED A PATENT INFRINGEMENT SUIT ON '446
PFIZER AND BAYER SUED BIOVAIL ON 5/5/98
CIVIL ACTION NO. 98-1494 DISTRICT COURT OF PUERTO RICO

30 MONTH PERIOD WILL EXPIRE 9/30/98 30 mg

Telephone Conversation Memorandum

ANDA: [redacted]

DRUG: Nifedipine Extended-release Tablets, 30 mg and 60 mg

FIRM: Biovail Laboratories, Inc.

PERSONS INVOLVED: Wayne Kreppner, Biovail
Tim Ames, FDA

PHONE NUMBER: 703-995-2400

DATE: September 6, 2000

Background:

In preparation of full approval for the 60 mg tablet, firm was requested to make a commitment to provide for methods validation analysis and samples, should they be requested, due to previous confusion with the the methods validation conducted on ANDA 75-269.

Mr. Kreppner agreed to provide a commitment to provide for further methods validation should it be necessary, and send this request in as a telephone amendment.

Timothy W. Ames, R.Ph., M.P.H.
Project Manager, Div Chem II, Team 8, OGD

/S/

cc: ANDA 75-289
[redacted]

File: V:\firmsam\biovail\telecons\75289tc3.doc

Active Ingredient Search Results from "Rx" table for query on "nifedipine."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
019478	AB	No	NIFEDIPINE	Capsule; Oral	10MG	ADALAT	BAYER
019478	AB	No	NIFEDIPINE	Capsule; Oral	20MG	ADALAT	BAYER
072409	AB	No	NIFEDIPINE	Capsule; Oral	10MG	NIFEDIPINE	CHASE LABS NJ
073421	AB	No	NIFEDIPINE	Capsule; Oral	20MG	NIFEDIPINE	CHASE LABS NJ
072781	AB	No	NIFEDIPINE	Capsule; Oral	10MG	NIFEDIPINE	FLEMINGTON PHARM
072651	AB	No	NIFEDIPINE	Capsule; Oral	10MG	NIFEDIPINE	NOVOPHARM
018482	AB	No	NIFEDIPINE	Capsule; Oral	10MG	PROCARDIA	PFIZER
018482	AB	Yes	NIFEDIPINE	Capsule; Oral	20MG	PROCARDIA	PFIZER
072579	AB	No	NIFEDIPINE	Capsule; Oral	10MG	NIFEDIPINE	PUREPAC PHARM
072556	AB	No	NIFEDIPINE	Capsule; Oral	20MG	NIFEDIPINE	PUREPAC PHARM
073250	AB	No	NIFEDIPINE	Capsule; Oral	10MG	NIFEDIPINE	SCHERER RP
074045	AB	No	NIFEDIPINE	Capsule; Oral	20MG	NIFEDIPINE	SCHERER RP
020198	AB	Yes	NIFEDIPINE	Tablet, Extended Release; Oral	30MG	ADALAT CC	BAYER
020198	BC	Yes	NIFEDIPINE	Tablet, Extended Release; Oral	60MG	ADALAT CC	BAYER
020198	BC	Yes	NIFEDIPINE	Tablet, Extended Release; Oral	90MG	ADALAT CC	BAYER
075128	AB	No	NIFEDIPINE	Tablet, Extended Release; Oral	30MG	NIFEDIPINE	ELAN PHARM
019684	BC	Yes	NIFEDIPINE	Tablet, Extended Release; Oral	30MG	PROCARDIA XL	PFIZER
019684	BC	Yes	NIFEDIPINE	Tablet, Extended Release; Oral	60MG	PROCARDIA XL	PFIZER
019684	BC	Yes	NIFEDIPINE	Tablet, Extended Release; Oral	90MG	PROCARDIA XL	PFIZER

Thank you for searching the Electronic Orange Book

Return to Electronic Orange Book Home Page

Search results from the "Rx" table for query on "019684."

Active Ingredient:	NIFEDIPINE
Dosage Form;Route:	Tablet, Extended Release; Oral
Proprietary Name:	PROCARDIA XL
Applicant:	PFIZER
Strength:	30MG
Application Number:	019684
Product Number:	001
Approval Date:	Sep 06, 1989
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	BC
Patent and Exclusivity Info for this product:	Click Here

Active Ingredient:	NIFEDIPINE
Dosage Form;Route:	Tablet, Extended Release; Oral
Proprietary Name:	PROCARDIA XL
Applicant:	PFIZER
Strength:	60MG
Application Number:	019684
Product Number:	002
Approval Date:	Sep 06, 1989
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	BC
Patent and Exclusivity Info for this product:	Click Here

Active Ingredient:	NIFEDIPINE
Dosage Form;Route:	Tablet, Extended Release; Oral
Proprietary Name:	PROCARDIA XL
Applicant:	PFIZER
Strength:	90MG
Application Number:	019684
Product Number:	003
Approval Date:	Sep 06, 1989
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	BC
Patent and Exclusivity Info for this product:	Click Here

Patent and Exclusivity Search Results from query on 019684 001.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code
019684	001	4327725	NOV 25,2000	
019684	001	4612008	SEP 16,2003	
019684	001	4765989	SEP 16,2003	
019684	001	4783337	SEP 16,2003	
019684	001	5264446	NOV 23,2010	

Exclusivity Data

There is no unexpired exclusivity for this product.

Thank you for searching the Electronic Orange Book

Patent and Exclusivity Terms

Return to Electronic Orange Book Home Page

APPEARS THIS WAY
ON ORIGINAL

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **ANDA 75289/000**
Stamp: **29-DEC-1997** Regulatory Due:
Applicant: **BIOVAIL LABS**
C/O KELLER HECKMAN
1001 G ST NORTHWEST STE 500 WES
WASHINGTON, DC 20001

Priority:
Action Goal:
Brand Name:
Established Name: **NIFEDIPINE**
Generic Name:
Dosage Form: **EXT (EXTENDED-RELEASE TABLET**
Strength: **60 MG**

Org Code: **600**
District Goal: **28-FEB-1999**

FDA Contacts: **J. WILSON III (HFD-400) 301-770-9299 , Project Manager**
V. SAYEED (HFD-629) 301-827-5848 , Team Leader

Overall Recommendation:

ACCEPTABLE on 10-NOV-1999 by M. GARCIA (HFD-322) 301-594-0095
ACCEPTABLE on 24-FEB-1998 by M. GARCIA (HFD-322) 301-594-0095

Establishment: **9615235**
BIOVAIL LIFESCIENCES

STEINBACH, MANITOBA, CA

DMF No:
AADA No:

Profile: **TTR** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **04-NOV-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Establishment: [redacted]

DMF No: [redacted]
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **04-NOV-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: [redacted]

Establishment: [redacted]

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **04-NOV-1999**
Decision: **ACCEPTABLE**

Responsibilities: [redacted]

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Reason: **DISTRICT RECOMMENDATION**

APPEARS THIS WAY
ON ORIGINAL

6.1

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

ANDA Number: **75-289** Date of Submission: **September 26, 2000**

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

Established Name: **Nifedipine Extended-release Tablets 30 mg and 60 mg**

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

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: 30 mg and 60 mg (100s, 300s, 1000s)
60 mg - *Satisfactory in FPL as of August 7, 2000 submission.*
30 mg - *Satisfactory in FPL as of September 26, 2000 submission.*

Professional Package Insert Labeling:
60 mg - *Satisfactory in FPL as of August 7, 2000 submission.*
30 mg - *Satisfactory in FPL as of September 26, 2000 submission.*

Revisions needed post-approval: **The firm has committed to making these changes after approval but before distribution for the 60 mg tabs** - "Dispense in tight, light-resistant containers." to labels and labeling; PI label with drug release test to which it complies - The 30 mg labels and labeling have this information as of the September 26, 2000 submission.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

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

NDA Number: 19-684

NDA Drug Name: Procardia XL® (nifedipine extended-release) Tablets

NDA Firm: Pfizer

Date of Approval of NDA Insert and supplement #: 8/12/97 (S-014)

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

Was this approval based upon an OGD labeling guidance? No

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

Other Comments: Per chemist the drug product (30 mg) conforms to USP drug release test # 1.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

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

Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?	X		
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	x		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		x	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		x	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed) DON'T KNOW IF TABLET IS IMPRINTED OR NOT		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? YES If so, are the recommendations supported and is the difference acceptable? NO - SEE COMMENTS IN REVIEW		x	

Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T ½ and date study acceptable)			
Insert labeling references a food effect or a no-effect? YES If so, was a food study done? YES	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD: (portions taken from previous review)

1. This review was based on the most recently approved labeling of Procardia XL® ([S-014] Approved 8/12/97; Revised 4/97).

2. Storage/Dispensing recommendations

   RLD - Store below 86°F (30°C); PROTECT FROM MOISTURE AND HUMIDITY; Dispense in tight containers (USP).

   ANDA - Store below 30°C (86°F); PROTECT FROM MOISTURE AND HUMIDITY;
   60 mg - Dispense in tight containers (USP).
   30 mg - Dispense in tight, light-resistant container (USP).

   USP - Preserve in tight, light-resistant containers

   The firm has committed to add "Dispense in tight, light-resistant containers." to their 60 mg labels and labeling post-approval but before introduction of the drug product into the market. The 30 mg labels and labeling have this on them as of this submission.

3. The inactives are accurately listed in the description section. See p. 9710, vol. 1.27.

4. The tablet description is accurate as seen in the HOW SUPPLIED section. See 10206, vol. 1.29.

5. Container Sizes

   RLD
   30 mg - 100s, 300s, 5000s, UD 100s
   60 mg - 100s, 300s, 5000s, UD 100s
   90 mg - 100s & UD 100s

   ANDA
   60 mg - 100s, 300s, 1000s

6. The containers are made of White [redacted]; the 100s & 300s sizes have a CRC while the 1000s size does not (v 1.28 p 10047).

7. There are 5 patents for this drug product:

5264446	11/23/10
4783337	9/16/03
4765989	9/16/03
4612008	9/16/03
4327725	11/25/00

   The firm's statement is accurate. However, the firm has filed Paragraph IV Certification.

8. **The following statements are found in the innovator's insert labeling, which specifically pertains to the RLD formulation. We will NOT ask the generic firm to include similar information because this information is not related to safety and we have not asked to include this information in the past for other generic products.**

   a. **DESCRIPTION - System Components and Performance**

      PROCARDIA XL® Extended-Release... in the feces as an insoluble shell.

   b. **PRECAUTIONS - Information for Patients**

      Do not be concerned if you... eliminated from your body.

9. **Firm plans to differentiate their container labels (p 340).**

10. **Teva to market – new labeling statement.**

11. **This amendment provides for FPL for the 30 mg strength. The firm has two separate PI's, one for each strength. We have already approved the 60 mg strength. We will now be approving the 30 mg strength because the 30 month period will be expiring soon for the 30 mg strength. Even though this ANDA has both the 30 mg and the 60 mg strength we will currently be approving the 30 mg strength. A precedent had been set for this in the past per Tim Ames.**

Date of Review: 10-3-00 **Date of Submission:** 9-26-00

Primary Reviewer: Adolph Vezza **Date:** /S/ 10/11/00

Team Leader: Charlie Hoppes **Date:** /S/ 10/11/00

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cc:

ANDA: 75-289
DUP/DIVISION FILE
HFD-613/AVezza/CHoppes (no cc)
aev/10/3/00|V:\FIRMSAM\BIOVAIL\LTRS&REV\75289.APL2
Review

APPEARS THIS WAY
ON ORIGINAL

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

ANDA Number: **75-289** Date of Submission: **August 7, 2000**

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

Established Name: **Nifedipine Extended-release Tablets 30 mg and 60 mg**

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

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: 30 mg and 60 mg (100s, 300s, 1000s)
Satisfactory in FPL as of August 7, 2000 submission.

Professional Package Insert Labeling:
Satisfactory in FPL as of August 7, 2000 submission.

Revisions needed post-approval: **The firm has committed to making these changes after approval but before distribution** - Add "USP" and "Dispense in tight, light-resistant containers." to labels and labeling; PI label with drug release test to which it complies

BASIS OF APPROVAL:

Was this approval based upon a petition? No

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

NDA Number: 19-684

NDA Drug Name: Procardia XL® (nifedipine extended-release) Tablets

NDA Firm: Pfizer

Date of Approval of NDA Insert and supplement #: 8/12/97 (S-014)

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

Was this approval based upon an OGD labeling guidance? No

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

Other Comments: Per chemist the drug product conforms to USP drug release test # 1.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

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

If not USP, has the product name been proposed in the PF?	X		
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	x		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		x	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		x	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed) DON'T KNOW IF TABLET IS IMPRINTED OR NOT		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? YES If so, are the recommendations supported and is the difference acceptable? NO - SEE COMMENTS IN REVIEW		x	
Does USP have labeling recommendations? If any, does ANDA meet them?			X

Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T ½ and date study acceptable)			
Insert labeling references a food effect or a no-effect? YES If so, was a food study done? YES	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: PTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD: (portions taken from previous review)

1. **This review was based on the most recently approved labeling of Procardia XL® ([S-014] Approved 8/12/97; Revised 4/97).**

2. **Storage/Dispensing recommendations**

   RLD - Store below 86°F (30°C); PROTECT FROM MOISTURE AND HUMIDITY; Dispense in tight containers (USP).

   ANDA - Same as RLD

   USP - Preserve in tight, light-resistant containers

   The firm has committed to add "Dispense in tight, light-resistant containers." To their labels and labeling post-approval but before introduction of the drug product into the market.

3. **The inactives are accurately listed in the description section. See p. 9710, vol. 1.27.**

4. **The tablet description is accurate as seen in the HOW SUPPLIED section. See 10206, vol. 1.29.**

5. **Container Sizes**

   RLD 30 mg - 100s, 300s, 5000s, UD 100s
   60 mg - 100s, 300s, 5000s, UD 100s
   90 mg - 100s & UD 100s

   ANDA 60 mg - 100s, 300s, 1000s

6. **The containers are made of White ; the 100s & 300s sizes have a CRC while the 1000s size does not (v 1.28 p 10047).**

7. **There are 5 patents for this drug product:**

5264446	**11/23/10**
4783337	**9/16/03**
4765989	**9/16/03**
4612008	**9/16/03**
4327725	**11/25/00**

   The firm's statement is accurate. However, the firm has filed Paragraph IV Certification.

8. **The following statements are found in the innovator's insert labeling, which specifically pertains to the RLD formulation. We will NOT ask the generic firm to include similar information because this information is not related to safety and we have not asked to include this information in the past for other generic products.**

a. **DESCRIPTION - System Components and Performance**

PROCARDIA XL® Extended-Release... in the feces as an insoluble shell.

b. **PRECAUTIONS - Information for Patients**

Do not be concerned if you... eliminated from your body.

9. **Firm plans to differentiate their container labels (p 340).**

10. **Teva to market – new labeling statement.**

11. **This amendment provides for FPL for the 60 mg strength only. The firm has removed the 30 mg strength from the insert labeling because the 30 month period has not expired for the 30 mg strength. Even though this ANDA has both the 30 mg and the 60 mg strength we will currently be approving only the 60 mg strength at this time. A precedent had been set for this in the past per Tim Ames.**

Date of Review: 8-10-00 **Date of Submission:** 8-7-00

Primary Reviewer: Adolph Vezza /S/ **Date:** 8/17/00

Team Leader: Charlie Hoppes **Date:** 8/17/00

cc:

ANDA: 75-289
DUP/DIVISION FILE
HFD-613/AVezza/CHoppes (no cc)
aev/8/10/00|V:\FIRMSAM\BIOVAIL\LTRS&REV\75289.APL
Review

No AA in RLD labeling
OE - 01/22/2001

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-289

CORRESPONDENCE

BIOVAIL
TECHNOLOGIES LTD.

labeling review
drafted 10/3/00
IS!

VIA COURIER

ORIG AMENDMENT
N/AM

September 26, 2000

Adolf Vezza
FOOD AND DRUG ADMINISTRATION
Division of Drug Labelling and Program Support
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Nifedipine Extended-release Tablets, 30 mg, ANDA #75-289
Minor Amendment to Tentative Approval, dated July 24, 2000

Dear Mr. Vezza;

With reference to our conversation of September 19, 2000, please find enclosed twelve (12) original final printed Package Outserts for Nifedipine Extended-release Tablets, 30 mg, ANDA #75-289. Three copies of this submission have been provided; two contain original final printed Package Outserts and the third contains copies.

We apologize for any inconvenience this may have caused. We look forward to 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 LTD.

Encl.

CENTER FOR DRUG
REC'D
SEP 26 2000
OGD
EVALUATION AND RESEARCH

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

BIOVAIL
TECHNOLOGIES LTD

FACSIMILE TRANSMISSION

September 14, 2000

Ubrani Venkataram, Ph.D.
Division of Chemistry II, ANDA Review Branch VI
Office of Generic Drugs, Division of Chemistry II (HFD-647)
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: Nifedipine Extended-release Tablets, 30 and 60 mg
ANDA #75-289

Dear Dr. Venkataram,

With reference to your fax dated September 13, 2000, please accept this letter as a commitment that Biovail will revise the [redacted] and Dissolution methods to address the comments raised by the FDA Northeast Regional Laboratory.

Specifically Biovail commits to the following:

- Revise the Dissolution method (STM 21.11) to include a notification that drug is to be [redacted]
- Revise the [redacted] method (STM 22.07) to address the unknown peak at a retention time of approximately [redacted], in the impurity [redacted]
- Separate the dissolution methods for the CC tablets (ANDA 75-269) from that for the XL tablets (ANDA 75-289).

As requested the revised test methods will be submitted to the FDA no later than 30 days from the date of full approval.

Should you have any questions or comments, please contact the undersigned directly at (703) 995-2400.

Yours respectfully,
BIOVAIL TECHNOLOGIES LIMITED

Wayne Kreppner
Manager, Regulatory Affairs
(on behalf of Biovail Laboratories Incorporated)

CC: Timothy Ames, Project Manager

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

BIOVAIL
TECHNOLOGIES LTD.

MINOR AMENDMENT
VIA OVERNIGHT COURIER

September 12, 2000

FPL

VIA ORIG AMENDMENT

AM

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

Do not approve in this submission
Labeling with the Conform AP/TA letter
A Stamp labeling in the 9/14/00 letter approve

Re: Nifedipine Extended-release Tablets, 30 mg, ANDA #75-289
Minor Amendment to Tentative Approval, dated July 24, 2000

Dear Mr. Buehler;

With reference to the tentative approval letter dated July 24, 2000, Biovail Laboratories Inc. is enclosing a Minor Amendment to ANDA #75-289, in anticipation of full approval of this application on September 26, 2000 (expiry of 30-month period provided for in section 505(j)(5)(B)(iii) of the Act). Although ANDA #75-289 includes the 30 mg and the 60 mg strengths, this minor amendment refers only to the pending full approval of the 30 mg strength as final printed labeling for the 60 mg strength was previously submitted under separate cover on August 7, 2000.

Biovail Laboratories has not made any changes to the Chemistry, Manufacturing and Controls terms of the application since the time of the tentative approval and has included 12 copies of final printed bottle labels and package insert for the 30 mg strength.

We trust that this amendment is complete and satisfactory for review by the Office of Generic Drugs. We look forward to your acceptance of this minor amendment and full approval of our application.

Should you have any questions or comments, please contact the undersigned at (703) 995-2280, or by fax at (703) 995-2444.

/S/
9/25/00

Respectfully,
On Behalf of Biovail Laboratories Incorporated

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
SEP 12 2000
OGD

Wayne Kreppner, M.Sc.
Manager, Corporate Regulatory Affairs
BIOVAIL CORPORATION INTERNATIONAL

Encl.

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3725 Concorde Parkway, Suite 1500, Chantilly, Virginia 20151 (703) 995-2400

2 Pages including this one

Date: September 6, 2000

To: Tim Ames

Company: FDA

FAX No: 301-443-3839

From: Beth Ferguson

Tel: (703) 995-2279

Fax No: (703) 995-2444

Dear Mr. Ames,

Please find attached a letter responding to your telephone request of earlier today.

Thanks,

Beth Ferguson.

BIOVAIL
TECHNOLOGIES LTD.

TELEPHONE AMENDMENT

September 6, 2000

Timothy Ames
Project Manager, Office of Generic Drugs (HFD-640)
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Nifedipine Extended-release Tablets, 30 and 60 mg
ANDA #75-289

Dear Mr. Ames,

With reference to our conversation earlier today please accept this letter as a commitment that Biovail will provide, if requested, the necessary samples and test documentation to the FDA sufficient to allow the District Laboratory to repeat the method validation analysis.

If you have any questions or comments, please contact the undersigned directly at (703) 995-2400 or via fax (703) 995-2444.

Yours respectfully,
BIOVAIL TECHNOLOGIES LIMITED

Wayne Kreppner, M.Sc.
Manager, Regulatory Affairs
(on behalf of Biovail Laboratories Incorporated)

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2 copy

BIOVAIL
TECHNOLOGIES LTD.

FACSIMILE TRANSMISSION

18 August 2000

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

NEW CORRESP

Re: Nifedipine Extended-release Tablets, 60 mg, ANDA #75-289

Dear Mr. Buehler;

With reference to our previous communication on August 16, 2000 and the conversation between Biovail representatives and the Division of Drug Labeling and Program Support on August 17, 2000, this letter confirms that the dispensing statement on both the bottle and package outsert labels will be revised to include the statement "Dispense in a tight, light resistant container".

This revision is in addition to those requested by OGD in their August 14, 2000 communication. Biovail commits that the revised dispensing statement will be incorporated into the bottle labels and package outsert prior to distribution of the product.

Should you have any questions or comments, please contact the undersigned at (703) 995-2400 or by fax at (703) 995-2444.

Respectfully,
On Behalf of Biovail Laboratories Incorporated

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

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AUG 31 2000
OGD
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BIOVAIL
TECHNOLOGIES LTD.

FACSIMILE TRANSMISSION

16 August 2000

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

Re: Nifedipine Extended-release Tablets, 60 mg, ANDA #75-289

Dear Mr. Buehler;

With reference to the conversation between Biovail representatives and the Division of Drug Labeling and Program Support on August 14, 2000, this letter confirms that Biovail will update the Package Outsert for the abovementioned product to include the revisions suggested by OGD.

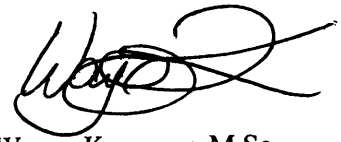
Specifically OGD requested the following revisions:

- The statement "This product meets USP Drug Release Test #1" should be included as the last sentence of the DESCRIPTION section.
- In accordance with the USP Monograph, the dispensing statement should include the statement "Dispense in a tight, light resistant container".

Biovail commits that the suggested changes will be incorporated into the Package Outsert prior to distribution of the product.

Should you have any questions or comments, please contact the undersigned at (703) 995-2400 or by fax at (703) 995-2444.

Respectfully,
On Behalf of Biovail Laboratories Incorporated



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

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BIOVAIL
TECHNOLOGIES LTD.

MINOR AMENDMENT
VIA OVERNIGHT COURIER

07 August 2000

ORIG AMENDMENT
N/AM
labeling review
drafted 8/10/00
/S/

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

Re: Nifedipine Extended-release Tablets, 60 mg, ANDA #75-289
Minor Amendment to Tentative Approval, dated July 24, 2000

Dear Mr. Buehler;

With reference to the tentative approval letter dated July 24, 2000, Biovail Laboratories Inc. is enclosing a Minor Amendment to ANDA #75-289, in anticipation of full approval of this application on August 23, 2000 (expiry of 30-month period provided for in section 505(j)(5)(B)(iii) of the Act). Although ANDA #75-289 includes the 30 mg and the 60 mg strengths, this minor amendment refers only to the pending full approval of the 60 mg strength as the 30-month period has not expired for the 30 mg strength.

Biovail Laboratories has not made any changes to the Chemistry, Manufacturing and Controls terms of the application since the time of the tentative approval and has included 12 copies of final printed bottle labels and package insert for the 60 mg strength.

We trust that this amendment is complete and satisfactory for review by the Office of Generic Drugs. We look forward to your acceptance of this minor amendment and full approval of our application.

Should you have any questions or comments, please contact the undersigned at (416) 285-6000, extension 219 or by fax at (905) 608-1616.

Respectfully,
On Behalf of Biovail Laboratories Incorporated

Wayne Kreppner, M.Sc.
Manager, Corporate Regulatory Affairs
BIOVAIL CORPORATION INTERNATIONAL

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RECD
AUG 09 2000
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Encl.

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BIOVAIL
TECHNOLOGIES LTD.

FACSIMILE TRANSMISSION
TELEPHONE AMENDMENT

June 12, 2000

BIOAVAILABILITY

ORIG AMENDMENT
N/Arr

Tim Ames
Project Manager, Office of Generic Drugs (HFD-640)
Office of Generic Drugs
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

RE: Nifedipine Extended Release Tablets, 30 and 60 mg
Response to June 2, 2000 Telephone Deficiency
ANDA #75-289

Dear Mr. Ames,

Biovail Laboratories Inc. wishes to amend its application, ANDA #75-289, to include responses to the Agency questions raised in a telephone communication on June 2, 2000.

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

We trust that this amendment is acceptable for review and look forward to the completion of the approval process for this product.

If you have any questions or comments, please contact me at telephone number (703) 995-2400, or, at fax number (703) 995-2446.

Yours respectfully,
BIOVAIL TECHNOLOGIES LIMITED

Kenneth S. Albert, Ph.D.,
Vice-President and Chief Scientific Officer
(on behalf of Biovail Laboratories Incorporated)

Encl.

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FACSIMILE TRANSMISSION
TELEPHONE AMENDMENT

May 10, 2000

ORIG AMENDMENT
N/Am

Vilayat Sayeed
Deputy Director, Division of Chemistry II (HFD-641)
Office of Generic Drugs
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

RE: Nifedipine Extended Release Tablets, 30 and 60 mg
Response to May 8, 2000 Telephone Deficiency
ANDA # 75-289

Dear Mr. Sayeed,

Biovail Laboratories Inc. wishes to amend its application, ANDA # 75-289, to include responses to the Agency questions raised in a telephone communication on May 8, 2000.

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

We trust that this amendment is acceptable for review and look forward to the completion of the approval process for this product.

If you have any questions or comments, please contact me at telephone number (703) 995-2400, or, at fax number (703) 995-2446.

Yours respectfully,
BIOVAIL TECHNOLOGIES LIMITED

Kenneth S. Albert, Ph.D.,
Vice-President and Chief Scientific Officer
(on behalf of Biovail Laboratories Incorporated)

Encl.

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TELEPHONE AMENDMNET

April 12, 2000

ORIG AMENDMENT

Ubrani Venkataram, Ph.D.
Division of Chemistry II, ANDA Review Branch VI
Office of Generic Drugs, Division of Chemistry II (HFD-647)
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: Nifedipine Extended-release Tablets, 30 and 60 mg
ANDA #75-289

Dear Dr. Venkataram,

Further to our telephone conversations regarding the revised dissolution specifications for Nifedipine Extended-release Tablets 30 mg and 60 mg, Biovail wishes to clarify the outstanding dissolution method issues:

Part I

As submitted in the original ANDA and all subsequent correspondence dealing with the dissolution methodology (April 5/99, July 2/99 and December 3/99), Biovail has consistently maintained that the time for [redacted] for Nifedipine XL Tablets 30 mg is [redacted] buffer whereas the time for [redacted] for Nifedipine XL Tablets 60 mg is [redacted] in [redacted] The differences in [redacted] time are based on differences in the quantitative [redacted] composition for the 30 mg and 60 mg strengths. This time for [redacted] was detailed in the dissolution test method submitted with the original ANDA and has not been changed for either strength since the time of submission.

In the April 3, 2000 communication from the Division of Bioequivalence, the time for [redacted] proposed for both the 30 mg and 60 mg strengths was [redacted] Biovail agrees with the [redacted] time for the 60 mg strength. However, because Biovail does not have any experience with a [redacted] of less than [redacted] for the 30 mg strength, revision of this test methodology to [redacted] is inappropriate. Please note that the entire stability database for Nifedipine ER Tablets 30 mg is based on a [redacted] in [redacted] Biovail is requesting that the [redacted] time for the 30 mg strength remain at [redacted] in [redacted] as originally proposed.

APPEARS THIS WAY
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Part II

Biovail agrees with the Division of Bioequivalence's recommended dissolution specifications for both the 30 mg and 60 mg strengths of Nifedipine ER Tablets. As proposed in the April 3, 2000 communication Biovail has revised the Part II dissolution specification as follows:

Nifedipine ER Tablets 30 mg

Medium:
Duration of Testing:

Specification:	Time (hours)	Amount dissolved
		not more than
		between and
		not less than
		not less than

Nifedipine ER Tablets 60 mg

Medium:
Duration of testing

Specification:	Time (hours)	Amount dissolved
		not more than
		between and
		not less than
		not less than

Copies of the revised Quality Standard Forms and Interim Stability Report Forms incorporating these dissolution specifications were sent in a separate correspondence dated April 10, 2000.

We trust that this amendment will resolve all of the outstanding dissolution issues raised by the Agency. Should you have any questions or comments, please contact the undersigned directly at (703) 995-2400.

Yours respectfully,
BIOVAIL TECHNOLOGIES LIMITED

For:

Kenneth S. Albert, Ph.D.
Vice President and Chief Scientific Officer
(on behalf of Biovail Laboratories Incorporated)

CC: Timothy Ames, Project Manager

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12 April 2000

NEW CORRESP

NC
the issue of Biovail's use of Federal Express to notify Bayer Aktien in F.R. Germany was discussed with Peter Bickman. In view of the fact that Bayer AG is listed on the patent challenge suit and that Biovail has provided documentation from Fed Ex of receipt of the notice by the office will not object.
IS 1/19/00

Gary Buehler
A/Director, Office of Generic
Centre for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room, HFD-110
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD
USA 20855

RE: ANDA [redacted] and ANDA [redacted]
Nifedipine Extended-release Tablets, 30 mg and 60 mg
Notification Issuance / Receipt of Patent Notice

Dear Mr. Buehler,

On February 11, 1998 and December 24, 1997 Biovail Laboratories Incorporated submitted two separate abbreviated new drug applications for its generic version of Procardia XL 30 mg (ANDA [redacted]) and 60 mg (ANDA 75-289) tablets, respectively. In accordance with Section 314.95(a) of 21CFR, the applicant sent Paragraph IV Certification Notices to each patent holder for the listed drug, Procardia XL.

Notices of Certification were sent to Pfizer Incorporated (USA), Bayer Aktiengesellschaft (Federal Republic of Germany) and to Alza Corporation (USA) for the listed drug, Procardia XL, on [redacted] and February 18, 1998 for ANDA 75-289. During a review of the certification documents the applicant noted that both notices issued to Bayer Aktiengesellschaft were sent by means other than US registered mail (i.e. Federal Express). Bayer Aktiengesellschaft is located in the Federal Republic of Germany as such, delivery of the certification via US registered mail was not an option for the applicant. The Notices of Certification for Pfzier Incorporated and Alza Corporation were sent by US registered mail and domestic receipts are available as proof of delivery. The applicant understands that US registered mail is the only acceptable form of delivery for issuing Notices of Certification to patent holders and its failure to comply with this requirement for this particular case was an administrative error based on previous delivery methods used.

To verify proof of receipt by the patent holders, particularly for Bayer Aktiengesellschaft, the applicant has enclosed Notices of Patent Infringement Action filed against Biovail Laboratories Incorporated by Pfizer Incorporated, Bayer Corporation (USA) and Bayer Aktiengesellschaft. A civil action suit was filed for each application of [redacted] (dated [redacted] and ANDA 75-289 (dated April 2, 1998 for Nifedipine Extended-release Tablets, 60 mg). The 13th paragraph under the subheading:

FIRST CLAIM FOR RELIEF: INFRINGEMENT OF THE '446 PATENT

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of both SUMMONS IN A CIVIL ACTION documents clearly denotes that Pfizer Incorporated and Bayer Aktiengesellschaft received the Notices of Certification issued by Biovail Laboratories Incorporated for the reference listed drug, Procardia XL and the dates on which these notices were received. For ANDA ——, Pfizer Incorporated and Bayer Aktiengesellschaft received their notices on March 26, 1998 and March 30, 2000 respectively. For ANDA 75-289, Pfizer Incorporated and Bayer Aktiengesellschaft received their notice on February 23, 1998.

The applicant apologizes for this error and regrets any inconvenience that it may have caused the Agency. By enclosing the Notices of Patent Infringement Action, which clearly documents that all the patent holders received the Notice of Certification, the requirements for "proof of receipt" are fulfilled. Should you have any concerns or require additional information, please do not hesitate to contact the undersigned by telephone at (703) 995-2280 or by telefax at (703) 995-2444.

Respectfully yours,
On Behalf of Biovail Laboratories Inc.

Kenneth Albert, Ph.D.
Vice President and Chief Scientific Officer
BIOVAIL TECHNOLOGIES, LTD.

APPEARS THIS WAY
ON ORIGINAL

BIOVAIL TECHNOLOGIES LTD.
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BIOVAIL
TECHNOLOGIES LTD.

TELEPHONE AMENDMNET

April 10, 2000

Ubrani Venkataram
Office of Generic Drugs, Division of Chemistry II (HFD-647)
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

NDA DRUG AMENDMENT

Re: Nifedipine Extended-release Tablets, 30 and 60 mg
ANDA #75-289

Dear Dr. Venkataram,

Further to our telephone conversation earlier today regarding the revised dissolution specifications for Nifedipine Extended-release Tablets 30 mg and 60 mg, Biovail has enclosed the following information:

- A revised Quality Standard Specification Form for Nifedipine ER 30 mg Coated Tablets
- A revised Quality Standard Specification Form for Nifedipine ER 60 mg Coated Tablets
- Revised Interim Stability Report Forms for Nifedipine XL Extended Release 30 mg Tablets in package sizes of 100 tablets, 300 tablets and 1000 tablets.
- Revised Interim Stability Report Forms for Nifedipine XL Extended Release 60 mg Tablets in package sizes of 100 tablets, 300 tablets and 1000 tablets.

Please note that the time for [redacted] (Part I) for the 30 mg tablet strength should be [redacted] not [redacted] as originally proposed by the Agency on April 3, 2000. The 30 mg and 60 mg strengths of Nifedipine Extended-release Tablets have different quantitative [redacted] compositions and the time for [redacted] varies accordingly. The differences in [redacted] time are specified in standard test method <0021.11> (attached for review). A copy of this method stipulating the [redacted] time was included in the original Abbreviated New Drug Application for the 30 mg strength.

We trust that this amendment is acceptable for review and approval. Should you have any questions or comments, please contact the undersigned directly at (703) 995-2400.

Yours respectfully,
BIOVAIL TECHNOLOGIES LIMITED

for:

Kenneth S. Albert, Ph.D.
Vice President and Chief Scientific Officer
(on behalf of Biovail Laboratories Incorporated)

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APR 12 2000
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Encl.

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FACSIMILE TRANSMISSION

April 3, 2000

Timothy Ames
Project Manager, Office of Generic Drugs (HFD-640)
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA ORIG AMENDMENT
N/AB

Re: Nifedipine Extended-release Tablets, 30 and 60 mg
ANDA #75-289

Dear Mr. Ames,

Biovail re-confirms that the Nifedipine Extended-release Tablets 30 mg and 60 mg finished product release and stability protocol interim dissolution specifications are in accord with previous recommendations of the Division of Bioequivalence.

The interim dissolution specifications for the 30 mg strength, as proposed in the April 3, 2000 communication from the Division of Bioequivalence are:

Dissolution Apparatus/Method

Apparatus:	USP rotating paddle method (Apparatus 2)
Rotation speed:	100 rpm

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APR 14 2000
OGD

BIOVAIL TECHNOLOGIES LTD.
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The interim dissolution specifications for the 60 mg strength, as proposed in the November 22, 1999 communication from the Division of Bioequivalence are:

Dissolution Apparatus/Method

Apparatus: USP rotating paddle method (Apparatus 2)
Rotation speed: 100 rpm

[redacted]

If you have any questions or comments, please contact the undersigned directly at (703) 995-2400.

Yours respectfully,
BIOVAIL TECHNOLOGIES LIMITED

For:
Kenneth S. Albert, Ph.D.
Vice President and Chief Scientific Officer
(on behalf of Biovail Laboratories Incorporated)

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OVERNIGHT COURIER
MINOR AMENDMENT

December 3, 1999

12/10/99 ORIG AMENDMENT
Am rec'd - N/Am
to CMC Reviewer
for review.
-JS-

Douglas Sporn
Director, Office of Generic Drugs (HFD-600)
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: Nifedipine Extended Release Tablets, 30 and 60 mg
Response to a Minor Amendment dated November 22, 1999
ANDA # 75-289

Dear Mr. Sporn,

Biovail Laboratories Inc. wishes to amend its application, ANDA # 75-289, to include responses to the Agency correspondence of November 22, 1999.

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.

If you have any questions or comments, please contact me at telephone number (416) 285-6000, extension 219 or, at fax number (905) 608-1616.

Yours respectfully,
BIOVAIL CORPORATION INTERNATIONAL

Wayne Kreppner, M.Sc.,
Manager, Corporate Regulatory Affairs
(on behalf of Biovail Laboratories Incorporated)

Encl.

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OGD

12-8-99

BIOVAIL CORPORATION INTERNATIONAL
2488 DUNWIN DRIVE, MISSISSAUGA, ONTARIO, CANADA L5L 1J9 • TEL (416) 285-6000 FAX (416) 285-6499

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BIOEQUIVALENCY AMENDMENT

July 2, 1999

NDA ORIG AMENDMENT
N/AB

Dale P. Conner, Pharm. D.
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Metro Park North II
Document Control Room
7500 Standish Place, Room 150
Rockville, MD 20855

Re: Nifedipine Extended-release Tablets, 30 mg and 60 mg
Response to Bioequivalency Deficiency of May 26, 1999
ANDA # 75-289

Dear Dr. Conner;

Biovail Laboratories Inc. wishes to amend its application, ANDA # 75-289, to include responses to the Agency correspondence of May 26, 1999.

Biovail has addressed all questions and comments posed by the Agency. We look forward to receiving Agency comment on our responses, if any, in due course.

If you have any questions or comments, please contact me at telephone number (416) 285-6000, extension 219 or, at fax number (905) 608-1616.

Yours respectfully,
BIOVAIL CORPORATION INTERNATIONAL

Wayne Kreppner, M.Sc.,
Manager, Corporate Regulatory Affairs
(on behalf of Biovail Laboratories Incorporated)

Encl.

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OVERNIGHT COURIER
MAJOR AMENDMENT

April 5, 1999

Dr Label.
NDA ORIG AMENDMENT
AC

Douglas Sporn
Director, Office of Generic Drugs (HFD-600)
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Nifedipine Extended-release Tablets, 30 and 60 mg
Response to a Major Non-Approvable Letter of November 30, 1998.
ANDA #75-289

Dear Mr. Sporn,

Biovail Laboratories Inc. wishes to amend its application, ANDA 75-289, to include responses to the Agency correspondence of November 30, 1998.

Biovail has responded to all questions posed by the Agency and has included updated Finished Product labeling. Our amendment also includes an appendix containing updated test methods (Appendix 2).

The applicant is also affecting a minor change in the specifications for the Nifedipine [redacted] In particular we are tightening the specifications for [redacted] These non-compendial testing requirements have been included for in-house quality control purposes only. A justification and supporting documentation in the form of an updated Quality Standard Form and Certificate of Analysis from the Nifedipine raw material manufacturer are attached in Appendix 3.

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

If you have any questions or comments, please contact me at telephone number (416) 285-6000, extension 219 or, at fax number (905) 608-1616.

Yours respectfully,
BIOVAIL CORPORATION INTERNATIONAL

Wayne Kreppner, M.Sc.,
Manager, Corporate Regulatory Affairs
(on behalf of Biovail Laboratories Incorporated)

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APR 07 1999
GENERIC DRUGS

Encl.

BIOVAIL CORPORATION INTERNATIONAL
2488 DUNWIN DRIVE, MISSISSAUGA, ONTARIO, CANADA L5L 1J9 • TEL (416) 285-6000 FAX (416) 285-6499

Redacted 2

pages of trade secret and/or confidential commercial information

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BIOVAIL

OVERNIGHT COURIER
AMENDMENT TO A PENDING APPLICATION

December 29, 1998

Douglas Sporn
Director, Office of Generic Drugs (HFD-600)
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA 075289 AMENDMENT
AB

Re: Nifedipine Extended Release Tablets, 30 and 60 mg
Responses to Bioequivalence Deficiencies of July 1 and August 4, 1998.
ANDA #75-289

Dear Mr. Sporn,

In keeping with the Agency's consolidation of our Nifedipine 30 mg and 60 mg applications in your letter dated October 7, Biovail Laboratories Inc. is forwarding responses to the Agency's correspondences of July 1 (for the 60 mg application) and August 4 (for the 30 mg application) in one amendment under ANDA 75-289.

If you have any questions or comments, please contact our U.S. agent, Mr. John Dubeck, at fax number (202) 434-4646.

Yours respectfully,
BIOVAIL CORPORATION INTERNATIONAL

Martin Levy

Martin Levy, M.Sc., FBIRA
Manager, Corporate Regulatory Affairs
(on behalf of Biovail Laboratories Incorporated)

Encl.

RECEIVED
JAN 0 5 1999
[illegible]

ANDA 75-269 (30 mg)
ANDA ——— (60 mg)
ANDA 75-289 (60 mg)
ANDA ——— (30 mg)

Keller & Heckman
Attention: John Dubeck
U.S. Agent for: Biovail Laboratories Inc. OCT 7 1998
1001 G Street N.W.
Suite 500 West
Washington, DC 20001

Dear Sir:

Reference is made to your abbreviated new drug applications (ANDAs) dated December 9, 1997, December 24, 1997, February 11, 1998 and April 15, 1998 for Nifedipine Extended-release Tablets.

It has been the Office of Generic Drugs (OGD) policy to collapse variations of certain drug products into a single application. OGD Policy and Procedure Guide (P&PG) #20-90 lays out the framework for collapsed submissions and describes the benefits to both FDA and the industry. This policy applies to solid oral dosage forms and injectable dosage forms and has been consistently followed since it became effective on October 1, 1990.

Biovail submitted four separate ANDAs for two different reference listed products of Nifedipine Extended-release Tablets. This was not in conformance with OGD P&PG #20-90. These submissions occurred on four different dates ranging from December 9, 1997 to April 15, 1998. All four ANDAs were accepted and filed as individual applications since it was not recognized that other strengths for these drug products had already been filed. Based on OGD P&PG #20-90 and to keep consistency in our filing process, the four ANDAs will be administratively collapsed into two ANDAs as outlined below.

ANDA ——— will be collapsed into ANDA 75-269 and will be given a filing date of December 11, 1997. All data from ANDA ——— will be considered a major amendment to ANDA 75-269.

ANDA ——— will be collapsed into ANDA 75-289 and will be given a filing date of February 5, 1998. All data from ANDA ———

The information in ANDAs ——— and ——— shall be merged into their respective ANDAs as outlined above. ANDA numbers ——— and ——— will be retired in accord with agency procedures.

For purposes of complying with the regulatory requirements related to paragraph IV patent certifications and subsequent 180 day exclusivity provisions, each product strength will retain its date of receipt from the individual submission as listed below.

ANDA 75-269 - December 11, 1997
ANDA ——— ———
ANDA 75-289 - February 5, 1998
ANDA ——— ———

If you have any questions, please contact Mr. Peter Rickman, Chief, Regulatory Support Branch at 301-827-5862.

Sincerely yours,

/S/ 10/4/98

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug and Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

BIOVAIL

BIOVAIL

BIOVAIL

BIOVAIL

BIOVAIL

OVERNIGHT COURIER

AMENDMENT

June 17, 1998

NAI
"New US Agent"
JSr
6/26/98

NEW CORRESP

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
HFD-600
7500 Standish Place, Room 286
Rockville, MD 20855

ATTN: Douglas Sporn
Director, Office of Generic Drugs, Center for Drug Evaluation and Research, Food and Drug Administration

Re: ANDA # 75-289: Nifedipine Extended-release Tablets, 60 mg: Change in US agent

Dear Mr. Sporn:

Biovail Laboratories Inc., a company with offices outside of the United States, wishes to amend the name and address of its US agent.

Effective on June 1, 1998, all correspondences should be sent to the attention of Mr. John Dubeck, Keller and Heckman, 1001 G Street NW, Suite 500 West, Washington, DC 20001. Mr. Dubeck's fax number is 202-434-4646.

If you have any questions or comments, please contact me directly at telephone number (416) 285-6000, extension 213 or at fax number (905) 608-1616.

Kindest regards,
ON BEHALF OF BIOVAIL LABORATORIES INCORPORATED

Martin Levy

Martin Levy, FBIRA
Manager, Worldwide Regulatory Affairs
Biovail Corporation International

Encl.

RECEIVED
JUN 18 1998
GENERIC DRUGS

BIOVAIL
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OVERNIGHT COURIER

August 18, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Metro Park North II
7500 Standish Place
Room E115,HFD-617
Rockville,MD
20855

ATTN: Dr. Aida (Lizzie) Sanchez
Project Manager

Re: Correspondence from FDA dated August 4, 1998: Bioequivalence Deficiency Letter
ANDA —— Nifedipine Extended-release tablets, 30 mg

Dear Dr. Sanchez,

We are in receipt of bioequivalence deficiencies for the aforementioned dossier.

Our statistical and pharmacokinetic departments require clarification on question 1 of the deficiency letter. For ease of reference, this point reads:

> The statistical model used for the study data did not include the group effect and the residual effect. The group effect should be assessed, and only when this term is found statistically insignificant should the data from the two groups of subjects be pooled. Similarly, the residual effects should be assessed, and only when they are found statistically insignificant should the term(s) be dropped from the model.

Our question surrounds the term, "residual effect". We were wondering if this term was used interchangeably with the "carryover effect". It is our opinion that the carryover effect cannot be separated from the true sequence effect and the treatment-by-period interactions (see generally: July 1992 FDA Guidance, "Statistical Procedures for Bioequivalence Studies using a Standard Two-Treatment Crossover Design."). If the Agency meant to say "residual effect", we are unclear as to its definition in the content of average bioequivalence evaluations.

We would appreciate a date and time that the bioequivalence reviewer is available so that we may set up a teleconference.

If you have any questions or comments, please contact me directly at telephone number (416) 285-6000 extension 213 or at fax number (905) 608-1616.

Thank you for your assistance, Dr. Sanchez.

Kindest regards,
BIOVAIL CORPORATION INTERNATIONAL

Martin Levy

Martin Levy, FBIRA
Manager, Corporate Regulatory Affairs
Encl.

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OVERNIGHT COURIER

June 17, 1998

AMENDMENT

NEW CORRESP

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
HFD-600
7500 Standish Place, Room 286
Rockville, MD 20855

ATTN: Douglas Sporn
Director, Office of Generic Drugs, Center for Drug Evaluation and Research, Food and Drug Administration

Re: ANDA # 75-335: Nifedipine Extended-release Tablets, 30 mg: Change in US agent

Dear Mr. Sporn:

Biovail Laboratories Inc., a company with offices outside of the United States, wishes to amend the name and address of its US agent.

Effective on June 1, 1998, all correspondences should be sent to the attention of Mr. John Dubeck, Keller and Heckman, 1001 G Street NW, Suite 500 West, Washington, DC 20001. Mr. Dubeck's fax number is 202-434-4646.

If you have any questions or comments, please contact me directly at telephone number (416) 285-6000, extension 213 or at fax number (905) 608-1616.

Kindest regards,
ON BEHALF OF BIOVAIL LABORATORIES INCORPORATED

Martin Levy

Martin Levy, FBIRA
Manager, Worldwide Regulatory Affairs
Biovail Corporation International

Encl.

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JUN 18 1998
GENERIC DRUGS

JAMES M. MULLIGAN, JR.
ARTHUR G. CONNOLLY, JR.
RUDOLF E. HUTZ
HAROLD PEZZNER
RICHARD M. BECK (D.C. BAR)
PAUL E. CRAWFORD
STANLEY C. MACEL, III
THOMAS M. MESHBESHER
JERRY E. GALLAGHER, JR.
GEORGE PAZUNIAK
W. RICHARD POWERS
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JOHN A. CLARK, III
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COLLINS J. SEITZ, JR.
EDWARD F. EATON
CHARLES J. DURANTE
PATRICIA SMINK ROGOWSKI
MARY W. BOURKE
ROBERT G. McMORROW, JR. (PA.BAR)
R. ERIC HUTZ
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WILLIAM E. McSHANE (PA.BAR)

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TELEPHONE (302) 658-9141
FACSIMILE (302) 658-5614

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PARTNER EMERITUS

WERNER H. HUTZ
1944-1970
JANUAR D. BOVE, JR.
1949-1991

COUNSEL
JOHN D. FAIRCHILD (MI.BAR)
WILLIAM E. LAMBERT III (PA.BAR)
M. EDWARD DANBERG

JOHN C. KAIRIS
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ASHLEY I. PEZZNER
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FRANCIS DiGIOVANNI
KAREN C. BIFFERATO
OLEH V. BILYNSKY (PA.BAR)
JULIE S. DVORAK
ALLAN N. KUTZENCO (N.J.BAR)

May 22, 1998

NEW CORRESP
NC
NAI 6/4/9

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

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

Re: ANDA ——
Notice of Filing Legal Action for Patent Infringement

Dear Sir or Madam:

We represent Bayer AG and Bayer Corporation (collectively "Bayer") who have brought suit against Biovail Corporation International and Biovail Laboratories, Inc. for infringement of US Patent No. 5,264,446 by the submission of the above-referenced ANDA.

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

(i) The ANDA number is ——

(ii) The name of the abbreviated new drug applicant is Biovail Laboratories, Incorporated.

(iii) The notice from Biovail Laboratories, Inc. to Bayer about the ANDA filing did not provide an established name for the ANDA drug product. However, it is referred to as a "...extended release, once daily Nifedipine (30 mg strength)".

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GENERIC DRUGS

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(iv) We certify that the above-referenced patent infringement suit was filed under Civil Action No. 98-1494 JAP in the United States District Court for the District of Puerto Rico on May 5, 1998. A copy of the summons and complaint are enclosed.

Bayer AG received notice on March 30, 1998, pursuant to § 505(j)(2)(B) of the Food, Drug and Cosmetic Act (the "Act") of submission of the above-referenced ANDA. Accordingly, pursuant to § 505(j)(4)(B)(iii) of the Act, approval of the above-referenced ANDA may not be made effective until the expiration of the 30-month period beginning from Bayer AG's receipt of such notice, i.e., until September 2000, or such shorter or longer period as the court may order pursuant to said section of the Act.

Respectfully submitted,

Jeffrey B. Bove

JBB/lwd
Enclosures

APPEARS THIS WAY
ON ORIGINAL

Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 3637 Fax 212 808 8924

Paul S. Miller
Senior Vice President and General Counsel

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

NEW CORRESP
NC
NAI 6/4/98
1ST

May 21, 1998

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

Re: ANDA —
Notice of Filing Legal Action for Patent Infringement

Pfizer Inc ("Pfizer"), Bayer A.G., and Bayer Corporation have brought suit against Biovail Laboratories Incorporated for infringement of US Patent No. 5,264,446 by the submission of the above-referenced ANDA.

Pursuant to 21 CFR § 314.107(f)(2), Pfizer provides notification as follows:

(i) The ANDA number is —

(ii) The name of the abbreviated new drug application applicant is Biovail Laboratories Incorporated ("Biovail").

(iii) The established name of the proposed drug product is "Nifedipine Tablet, Extended Release; Oral"; the strength is 30 mg; and, as described by Biovail, the proposed dosage form is "

(iv) Pfizer certifies that the above-referenced patent infringement suit was filed under Civil Action No. 98-1494, in the United States District Court for the District of Puerto Rico on May 5, 1998. A copy of the summons and complaint is enclosed.

Pfizer received notice pursuant to §505(j)(2)(B) of the Food, Drug and Cosmetic Act (the "Act") of submission of the above-referenced ANDA on March 26, 1998. Accordingly, pursuant to §505(j)(4)(B)(iii) of the Act, approval of the above-referenced ANDA may not be made effective until the expiration of the 30 month period beginning

RECEIVED
MAY 27 1998
GENERIC DRUGS

from Pfizer's receipt of such notice, i.e., until September 26, 2000, or such shorter or longer period as the court may order pursuant to said section of the Act.

Respectfully submitted,

Paul S. Miller

APPEARS THIS WAY
ON ORIGINAL

BIOVAIL
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NAI
Proof of Notification and copy of civil action
Dt 5/5/98

22 April, 1998

PATENT AMENDMENT

NEW CORRESP
NC

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855
USA

Attention: Dr. Jerry Phillips
Director,
Division of Labeling and Program Support

Re: ANDA # 75-289
Nifedipine Extended-release Tablets, 60 mg
(Code Name B35)
Notification Issuance / Receipt of Notice ; Litigation

Dear Dr. Phillips,

This amendment is to notify FDA that

1. In accordance with 21 CFR 314.95(b), the Notice has been provided to each person identified under 314.95 (a) and the notice met the content requirements under 314.95 (c). As such, the applicant certifies that the Notice required pursuant to the provisions of 505(j)(2)(B)(ii) was sent to each of Pfizer Incorporated (USA), holder of the approved application of NDA No. 19-684, Bayer Aktiengesellschaft (Federal Republic of Germany), assignee of U.S. Patent No. 5,264,446, and to Alza Corporation (USA), assignee of U.S. Patent No's. 4,612,008, 4,327,725, 4,783,337, and 4,765,989 for the reference listed Procardia XL brand of once-daily nifedipine on February 20, 1998, for delivery to Pfizer Incorporated and Bayer Aktiengesellschaft on February 23, 1998, and to Alza Corporation on February 25, 1998.

2. In Accordance with 21 CFR 314.95(e), Biovail is providing documentation of receipt of Notice by providing a copy of the return receipt by each person provided the notice:
   - Pfizer Incorporated (USA).
   - Bayer Aktiengesellschaft (Federal Republic of Germany). **Note:** As this site was overseas, a FedEx proof of delivery of the Notice for this product is provided.
   - Alza Corporation (USA).

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3. An action for patent infringement against Biovail concerning the controlled-release, once-daily nifedipine tablets has been filed by Bayer and Pfizer within the 45-day period as provided for in section 505 (j) (4) (B) (iii) of the Act.

Please find attached, in triplicate:

- A signed and dated FDA 356 h Form.
- A copy of the return receipt by each person provided the notice (i.e. from Bayer Aktiengesellschaft (Federal Republic of Germany), Pfizer Incorporated (USA), and Alza Corporation (USA)).
- A copy of the original Patent Certificate Notice that was sent to each of the above stated companies.
- A copy of the notification for a patent infringement action against Biovail filed by Bayer Corporation and Pfizer Incorporated.

If you have any questions or comments, please contact the undersigned at Biovail Corporation International, telephone number 416-285-6000 ext. 212 ; fax number (905) 608-1616.

Sincerely,
BIOVAIL CORPORATION INTERNATIONAL
(on behalf of Biovail Laboratories, Inc.)

George E. Markus, M.Sc.
Manager, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Legal Division
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 3637 Fax 212 573 1445

Paul S. Miller
Senior Vice President and General Counsel

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

April 16, 1998

NEW CORRESP
NC

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

Re: ANDA 75-289
Notice of Filing Legal Action for Patent Infringement

On April 9, 1998, Pfizer notified FDA, pursuant to 21 CFR.107(f)(2), of its filing of a legal action for patent infringement against Biovail Laboratories Incorporated for infringement of U.S. Patent No. 5,264,446.

In that letter, Pfizer certified that the patent infringement suit was filed on April 1, 1998 in the United States District Court for the District of Puerto Rico. Please note, however, that the correct date of the filing of that suit was on April 2, 1998, not April 1, 1998. We apologize for any inconvenience and request that the record be corrected in this regard.

Respectfully submitted,

Paul S. Miller

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APR 21 1998
GENERIC DRUGS

JAMES M. MULLIGAN, JR.
ARTHUR G. CONNOLLY, JR.
RUDOLF E. HUTZ
[illegible]ROLD PEZZNER
[illegible]HARD M. BECK (D.C. BAR)
[illegible]L E. CRAWFORD
[illegible]ANLEY C. MACEL, III
THOMAS M. MESHBESHER
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LAW OFFICES

CONNOLLY, BOVE, LODGE & HUTZ
1220 Market Street
P.O. Box 2207
WILMINGTON, DELAWARE 19899

TELEPHONE (302) 658-9141
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ARTHUR G. CONNOLLY
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JULIE S. DVORAK
ALLAN N. KUTZENCO (N.J.BAR)

April 9, 1998

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

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

Re: ANDA 75-289
Notice of Filing Legal Action for Patent Infringement

Dear Sir or Madam:

We represent Bayer AG and Bayer Corporation (collectively "Bayer") who have brought suit against Biovail Corporation International and Biovail Laboratories, Inc. for infringement of US Patent No. 5,264,446 by the submission of the above-referenced ANDA.

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

(i) The ANDA number is 75-289.

(ii) The name of the abbreviated new drug applicant is Biovail Laboratories, Incorporated.

(iii) The notice from Biovail Laboratories, Inc. to Bayer about the ANDA filing did not provide an established name for the ANDA drug product. However, it is referred to as a "...extended release, once daily Nifedipine (60 mg strength)".

(iv) We certify that the above-referenced patent infringement suit was filed under Civil Action No. 98-1340 JP in the United States District Court for the District of Puerto Rico on April 2, 1998. A copy of the summons and complaint are enclosed.

Bayer AG received notice dated February 18, 1998, pursuant to § 505(j)(2)(B) of the Food, Drug and Cosmetic Act (the "Act") of submission of the above-referenced ANDA. Accordingly, pursuant to § 505(j)(4)(B)(iii) of the Act, approval of the above-referenced ANDA may not be made effective until the expiration of the 30-month period beginning from Bayer AG's receipt of such notice, i.e., until August 2000, or such shorter or longer period as the court may order pursuant to said section of the Act.

Respectfully submitted,

Jeffrey B. Bove

JBB/lwd
Enclosures

APPEARS THIS WAY
ON ORIGINAL

Legal Division
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 3637 Fax 212 573 1445

NEW CORRESP
NC

Paul S. Miller
Senior Vice President and General Counsel

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

April 9, 1998

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

Re: ANDA 75-289
Notice of Filing Legal Action for Patent Infringement

Pfizer Inc ("Pfizer"), Bayer A.G., and Bayer Corporation have brought suit against Biovail Laboratories Incorporated for infringement of US Patent No. 5,264,446 by the submission of the above-referenced ANDA.

Pursuant to 21 CFR § 314.107(f)(2), Pfizer provides notification as follows:

(i) The ANDA number is 75-289.

(ii) The name of the abbreviated new drug application applicant is Biovail Laboratories Incorporated ("Biovail").

(iii) The established name of the proposed drug product is "Nifedipine Tablet, Extended Release; Oral"; the strength is 60 mg; and, as described by Biovail, the proposed dosage form is

(iv) Pfizer certifies that the above-referenced patent infringement suit was filed under Civil Action No. 98-1340, in the United States District Court for the District of Puerto Rico on April 1, 1998. A copy of the summons and complaint is enclosed.

Pfizer received notice pursuant to §505(j)(2)(B) of the Food, Drug and Cosmetic Act (the "Act") of submission of the above-referenced ANDA on February 23, 1998. Accordingly, pursuant to §505(j)(4)(B)(iii) of the Act, approval of the above-referenced ANDA may not be made effective until the expiration of the 30 month period beginning

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APR 10 1998
GENERIC DRUGS

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from Pfizer's receipt of such notice, i.e., until August 23, 2000, or such shorter or longer period as the court may order pursuant to said section of the Act.

Respectfully submitted,

Paul S. Miller

ANDA [redacted]

Biovail Laboratories Incorporated
Biovail Corporation International
Attention: Carmen Reyes
#34 Iturregui Avenue
Sabana Abajo Industrial Park
Carolina, Puerto Rico USA 00983

MAR 10 1998

Dear Madam:

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

NAME OF DRUG: Nifedipine Extended-release Tablets, 30 mg

DATE OF APPLICATION: February 11, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: February 12, 1998

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(I)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

  1) Each owner of the patent or the representative designated by the owner to receive the notice;

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b),provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a final order or judgement from which no appeal may be taken (which might not be the one from the District Court), or a settlement agreement

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

If you have further questions you may contact Peter Rickman, Chief, Regulatory Support Branch, at (301)827-5862.

When submitting applications in the future, it is recommended that applicants follow the accepted format as outlined in the Office of Generic Drugs Policy and Procedure Guide 30-91 (revised 4/97). A copy of this guidance maybe obtained from the Drug information Branch (301) 827-4573 or from the following web site:

http://www.fda.gov/cder/guidance/index.htm

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Tim Ames
Project Manager
(301) 827-5849

Sincerely yours,

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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11 February, 1998

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855
USA

VIA FEDEX

ATTN: Dr. Douglas Sporn
Office of Generic Drug

Re: Abbreviated New Drug Application (ANDA #: Not Assigned Yet)
Nifedipine Extended-release Tablets, 30 mg
(Code Name B35-30 mg)

Dear Dr. Sporn,

In accordance with the provisions of Section 505(j) of the Federal Food, Drug and Cosmetic Act and Section 314.94 of 21 CFR, enclosed please find an Abbreviated New Drug Application for Nifedipine Extended-release Tablets, 30 mg for once daily administration. The listed drug used in the bioavailability / bioequivalence studies is Procardia XL ® manufactured by Pfizer Labs in USA. This product contains nifedipine, a calcium ion influx inhibitor (slow-channel blocker or calcium ion antagonist), and is indicated for :

- The management of vasospastic angina
- The management of chronic stable angina (classic effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and / or organic nitrates or who cannot tolerate those agents
- The treatment of Hypertension.

Biovail Laboratories Incorporated (BLI) in Barbados has sponsored the development of this product and is the ANDA holder. Biovail Laboratories Incorporated (BLI) in Puerto Rico is the US Agent for this application. Biovail Corporation International (BCI), Manufacturing Division, will manufacture the commercial product. Upon approval, BLI will market the product in the USA under the BLI labeling which is submitted in this ANDA. This ANDA submission has been prepared by BCI (Corporate) on behalf of BLI. It should also be noted that BLI has submitted an ANDA (#75-289) for Nifedipine Extended-release Tablets, "60 mg" on December 24, 1997. The Acceptance for Filing date of the ANDA was February 5, 1998.

BIOVAIL CORPORATION INTERNATIONAL
2488 DUNWIN DRIVE, MISSISSAUGA, ONTARIO, CANADA L5L 1J9 • TEL (416) 285-6000 FAX (416) 285-6499

Biovail Laboratories Incorporated is the subsidiary of Biovail Corporation International. Biovail Laboratories Incorporated has its head office at Chelston Park, Building 2, Collymore Rock, St. Michael, BH1, Barbados, W.I., and its manufacturing site at Ave. Iturregui Street B Lot # 34, Sabana Abajo Industrial Park, Carolina, Puerto Rico, 00984, USA.

Biovail Corporation International (Corporate) is located at 2488 Dunwin Drive, Mississauga, Ontario, Canada L5L 1J9. Its manufacturing site is at 100 LifeSciences Parkway, Box 21390, Steinbach, Manitoba, Canada R0A 2T3.

We trust that this ANDA is complete and satisfactory for filing and review by the Office of Generic Drugs. The Archival Copy, the Review Copy, and the Field Copy of this ANDA are included in this package that has been sent via Federal Express.

A total of 64 books are included in this submission. The contents are as follows:

1. Archival Copy :
   - Blue Jackets - 28 books
2. Review Copy :
   - Red Jackets (CMC) - 4 books
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   - one diskette for biostudy 1897 (Book 2 of 28).
   - two diskettes for biostudy S73 (Book 18 of 28).

If you have any questions or comments, please contact the undersigned at Biovail Corporation International, telephone number 1-416-285-6000 extension 218; fax number (905) 608-1616.

Sincerely yours,
BIOVAIL CORPORATION INTERNATIONAL

Mimi Brennan, B.Sc., ART, CIM, P.Mgr
Director Regulatory Affairs and Quality Assurance
(on behalf of Biovail Laboratories Incorporated)

Encl.

\\CA1NT\REGULATORY\projects\Nif-B35 (XL)\US\submission\anda\Original\30 mg\cover-let.doc

ANDA 75-289

FEB 11 1998

Biovail Laboratories Incorporated
Biovail Corporation International
Attention: Carmen Reyes
#34 Iturregui Avenue
Sabana Abajo Industrial Park
Carolina, Peurto Rico USA 00983

Dear Madam:

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

Reference is also made to our "Refuse to File" letter dated February 3, 1998, and your amendments dated February 4 and 5, 1998.

NAME OF DRUG: Nifedipine Extended-release Tablets, 60 mg

DATE OF APPLICATION: December 24, 1997

DATE (RECEIVED) ACCEPTABLE FOR FILING: Feburary 5, 1998

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(I)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

  1) Each owner of the patent or the representative designated by the owner to receive the notice;

  2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

  3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b),provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a final order or judgement from which no appeal may be taken (which might not be the one from the District Court), or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Peter Rickman, Chief, Regulatory Support Branch, at (301)827-5862.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Tim Ames
Project Manager
(301) 827-5849

Sincerely yours,

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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11 February, 1998

VIA FEDEX

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855
USA

ATTN: Dr. Douglas Sporn
Office of Generic Drug

Re: Abbreviated New Drug Application (ANDA #: Not Assigned Yet)
Nifedipine Extended-release Tablets, 30 mg
(Code Name B35-30 mg)

Dear Dr. Sporn,

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We trust that this ANDA is complete and satisfactory for filing and review by the Office of Generic Drugs. The Archival Copy, the Review Copy, and the Field Copy of this ANDA are included in this package that has been sent via Federal Express.

A total of 64 books are included in this submission. The contents are as follows:

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If you have any questions or comments, please contact the undersigned at Biovail Corporation International, telephone number 1-416-285-6000 extension 218; fax number (905) 608-1616.

Sincerely yours,
BIOVAIL CORPORATION INTERNATIONAL

Mimi Brennan, B.Sc., ART, CIM, P.Mgr
Director Regulatory Affairs and Quality Assurance
(on behalf of Biovail Laboratories Incorporated)

Encl.

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9 February, 1998

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855
USA

AMENDMENT

ORIG AMENDMENT
N/AC

ATTN: Dr. Douglas Sporn
Office of Generic Drug

Re: Abbreviated New Drug Application (ANDA # 75-289)
Nifedipine Extended-release Tablets, 60 mg
(Code Name B35-60mg)

Dear Dr. Sporn,

Further to our Refusal to File letter and pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act, enclosed please find this amendment that addresses each of the raised issues.

The following are enclosed:

- 1 x 356h form
- 3 months accelerated stability data for 300s and 1000s package configurations
- 1 Certificate of Analysis for the [redacted] that was used in the production of the Nifedipine XL 60mg bio-batch (Dated July 10/97).

The above information is being sent to you in triplicate (one original and two copies) via Federal Express.

We trust that this amendment is complete and satisfactory for filing and review by the Office of Generic Drugs. We look forward to receiving the "Acceptable for Filing" letter.

If you have any questions or comments, please contact the undersigned at Biovail Corporation International, telephone number 1-416-285-6000 extension 212; fax number (905) 608-1616.

Sincerely yours,
BIOVAIL CORPORATION INTERNATIONAL

George E. Markus, M.Sc.
Manager, Regulatory Affairs
(on behalf of Biovail Laboratories Incorporated)

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FEB 10 1998
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ANDA 75-289

Biovail Laboratories Incorporated
Biovail Corporation International
Attention: Carmen Reyes
#34 Iturregui Avenue
Carolina, Peurto Rico USA 00983

FEB 3 1998

Dear Madam:

Please refer to your abbreviated new drug application (ANDA) dated December 24, 1997 submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Nifedipine Extended-release Tablets, 60 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 file this ANDA under 21 CFR 314.101(d)(3) for the following reason:

> You have failed to provide three months accelerated stability data for your proposed 1000 count containers as required to support a 24-month expiration date. We refer you to the Office of Generic Drugs Policy and Procedure Guide #32-92.

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

You have failed to provide the manufacturer's Certificate of Analysis for your inactive ingredient [redacted] Please note that sources and COAs must be provided for all inactives listed.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(c). If you do so, the application shall be filed over protest under 21 CFR 314.101(b). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call.

Saundra T. Middleton
Project Manager
(301) 827-5862

Sincerely yours,

/s/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-289
DUP/Jacket
Division File
Field Copy
HFD-330
HFD-600/Reading File
HFD-82
HFD-610/J.Phillips
HFD-615/MBennett

Endorsements: HFD-615/PRickman, Chief, /s/ date 2/3/98
HFD-615/SMiddleton, CSO /s/ date 1-26-98
HFD-647/UVenkataram, Sup. Chem. date 2/3/
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FT by/njg/1/26/98
ANDA Acknowledgment Letter!

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December 24, 1997

VIA FEDEX

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Document Control Room
Metro Park North II
7500 Standish Place, Room 150
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Director Regulatory Affairs and Quality Assurance
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Encl.

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VIRUS-FREE CERTIFICATION

Biovail Corporation International certifies that any electronic files associated with this submission, namely:

- Study Number 1895 (B97-328PK-NIFB35)
- Study Number 1862-2 (B97-324PK-NIFB35)

are virus-free. The virus detection software used to in this certification is Norton AntiVirus version 2.0.1 for Windows 95. Any diskette found to contain a virus will be returned to the sponsor.

Markus

George E. Markus, M.Sc.
Manager, Regulatory Affairs
BIOVAIL CORPORATION INTERNATIONAL

Dec 22/97
Date

APPEARS THIS WAY
ON ORIGINAL

BIOVAIL CORPORATION INTERNATIONAL
• TEL (416) 285-6000 FAX (416) 285-6499