CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-401/S-013

Approval Letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

OCT 16 1998

NDA 20-401/S-013

Biovail Laboratories Incorporated
c/o Keller and Heckman
Attention: Mr. John Dubeck
Suite 500 West 1001 G Street, N.W.
Washington, D.C. 20001

Dear Mr. Dubeck:

Please refer to your supplemental new drug application dated February 27. 1998, received March 2, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tiazac (diltiazem HCl) Capsules.

We acknowledge receipt of your submissions dated August 31 and September 15 (two), 1998. Your submissions of September 15, 1998 constituted a full response to our August 28, 1998 action letter.

This supplemental new drug application provides for a new dosage strength, 420 mg Capsules.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert and immediate container and carton labels submitted September 16, 1998). Accordingly, the supplemental application is approved effective on the date of this letter.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Mr. David Roeder
Regulatory Health Project Manager
(301) 594-5313

Sincerely yours,

/S/ 10/16/98

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-401/S-013

Final Printed Labeling

APPROVED

OCT 16 1998

Labeling: ORIGINAL
NDA No: 20-4101 Rc'd. 9-21-98
Reviewed by: [signature] 10-14-98

NDC 0456-2617-30

TIAZAC® (diltiazem HCl)

420 mg

Extended-release Capsules

Rx only

Do not use if bottle closure seal is broken.

30 Capsules

Usual Dosage: Administer once daily, see insert for full prescribing information.
Store at controlled room temperature 20-25°C (68-77°F).
Dispense in well-closed containers with safety closures.
Keep this and all medication out of the reach of children.

Manufactured by:
BIOVAIL LABORATORIES INC.
Carolina, Puerto Rico
Encapsulated and Made in Canada
Rev. 9/98

Manufactured for:
FOREST PHARMACEUTICALS, INC.
Subsidiary of Forest Laboratories, Inc.
St. Louis, Missouri 63045

LL-0149-00
Printed in U.S.A.

NDC 0456-2617-30

PROFESSIONAL SAMPLE - NOT FOR RESALE

TIAZAC® (diltiazem HCl)

420 mg

Extended-release Capsules

Rx only

Do not use if bottle closure seal is broken.

30 Capsules

Usual Dosage: Administer once daily, see insert for full prescribing information.
Store at controlled room temperature 20-25°C (68-77°F).
Dispense in well-closed containers with safety closures.
Keep this and all medication out of the reach of children.

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Rev. 9/98

Manufactured for:
FOREST PHARMACEUTICALS, INC.
Subsidiary of Forest Laboratories, Inc.
St. Louis, Missouri 63045

LL-0160-00
Printed in U.S.A.

NDC 0456-2617-90

TIAZAC® (diltiazem HCl)

420 mg

Extended-release Capsules

Rx only

Do not use if bottle closure seal is broken.

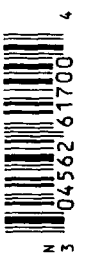
90 Capsules

Usual Dosage: Administer once daily, see insert for full prescribing information.
Store at controlled room temperature 20-25°C (68-77°F).
Dispense in well-closed containers with safety closures.
Keep this and all medication out of the reach of children.

Manufactured by:
BIOVAIL LABORATORIES INC.
Carolina, Puerto Rico
Encapsulated and Made in Canada
Rev. 9/98

Manufactured for:
FOREST PHARMACEUTICALS, INC.
Subsidiary of Forest Laboratories, Inc.
St. Louis, Missouri 63045

LL-0150-00
Printed in U.S.A.



NDC 0456-2617-00

TIAZAC® (diltiazem HCl)

420 mg

Extended-release Capsules

Rx only

Do not use if bottle closure seal is broken.

1000 Capsules

Usual Dosage: Administer once daily, see insert for full prescribing information.
Store at controlled room temperature 20-25°C (68-77°F).
Dispense in well-closed containers with safety closures.
Keep this and all medication out of the reach of children.

Manufactured by:
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Carolina, Puerto Rico
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Rev. 9/98

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Subsidiary of Forest Laboratories, Inc.
St. Louis, Missouri 63045

LL-0151-00
Printed in U.S.A.

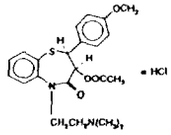
Tiazac®

(diltiazem hydrochloride)

Extended Release Capsules

DESCRIPTION

Tiazac® (diltiazem hydrochloride) is a calcium ion cellular influx inhibitor (slow channel blocker). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)-one,3-(acetyloxy)-5[2-(dimethylamino)ethyl]-2,-3-dihydro-2[4-methoxyphenyl)-, monohydrochloride, (+)-cis. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol and chloroform and has a molecular weight of 450.98. Tiazac® capsules contain diltiazem hydrochloride in extended release beads at doses of 120, 180, 240, 300, 360 and 420 mg.

Tiazac® also contains: Microcrystalline Cellulose NF, Sucrose Stearate, Eudragit, Povidone USP, Talc USP, Magnesium Stearate NF, Hydroxypropylmethylcellulose USP, Titanium Dioxide USP, Polysorbate NF, Simethicone USP, Gelatin NF, FD&C Blue #1, FD&C Red #40, D&C Red #28, FD&C Green #3, Black Iron Oxide USP, and other solids.

For oral administration.

CLINICAL PHARMACOLOGY

The therapeutic effects of diltiazem hydrochloride are believed to be related to its ability to inhibit the cellular influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action.

Hypertension: Diltiazem produces its antihypertensive effect primarily by relaxation of vascular smooth muscle and the resultant decrease in peripheral vascular resistance. The magnitude of blood pressure reduction is related to the degree of hypertension; thus hypertensive individuals experience an antihypertensive effect, whereas there is only a modest fall in blood pressure in normotensives.

Angina: Diltiazem HCl has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal work loads.

Diltiazem has been shown to be a potent dilator of coronary arteries, both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by diltiazem.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of the coronary vascular smooth muscle and dilation of both large and small coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium channel antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure in normotensive individuals and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. Such data have no predictive value with respect to effects in patients with poor ventricular function, and increased heart failure has been reported in patients with preexisting impairment of ventricular function. There are as yet few data on the interaction of diltiazem and beta-blockers in patients with poor ventricular function. Resting heart rate is usually slightly reduced by diltiazem.

Tiazac® produces antihypertensive effects both in the supine and standing positions. Postural hypotension is infrequently noted upon suddenly assuming an upright position. No reflex tachycardia is associated with the chronic antihypertensive effects.

Diltiazem hydrochloride decreases vascular resistance, increases cardiac output (by increasing stroke volume), and produces a slight decrease or no change in heart rate. During dynamic exercise, increases in diastolic pressure are inhibited while maximum achievable systolic pressure is usually reduced. Chronic therapy with diltiazem hydrochloride produces no change or an increase in plasma catecholamines. No increased activity of the renin-angiotensin-aldosterone axis has been observed. Diltiazem hydrochloride reduces the renal and peripheral effects of angiotensin II. Hypertensive animal models respond to diltiazem with reductions in blood pressure and increased urinary output and natriuresis without a change in urinary sodium/potassium ratio. In man, transient natriuresis and kaliuresis have been reported, but only in high intravenous doses of 0.5 mg/kg of body weight.

Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases). Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods by approximately 20%.

In two short term, double-blind, placebo-controlled studies in 256 hypertensive patients with doses up to 540 mg/day, Tiazac® showed a clinically unimportant but statistically significant, dose-related increase in PR interval (0.008 seconds). There were no instances of greater than first-degree AV block in any of the clinical trials (see WARNINGS).

Pharmacodynamics.

Hypertension: In short term, double blind, placebo-controlled clinical trials Tiazac® demonstrated a dose-related antihypertensive response among patients with mild to moderate hypertension. In one parallel-group study of 198 patients Tiazac® was given for four weeks. The changes in diastolic blood pressure measured at trough (24 hours after the dose) for placebo, 90mg, 180mg, 360mg and 540mg were -5.4, -6.3, -6.2, -8.2, and -11.8mm Hg, respectively. Supine diastolic blood pressure as well as standing diastolic and systolic blood pressures also showed statistically significant linear dose response effects.

In another clinical trial that followed a dose-escalation design, Tiazac® also reduced blood pressure in a linear dose-related manner. Supine diastolic blood pressure measured following two week intervals of treatment was reduced by -3.7mm Hg with 120 mg/day versus -2.0mm Hg with placebo, by -7.6mm Hg after escalation to 240 mg/day versus -2.3mm Hg with placebo, by -8.1mm Hg after escalation to 360 mg/day versus -0.9mm Hg with placebo, and by -10.8mm Hg after escalation to 480/540 mg/day versus -2.2mm Hg with placebo.

Angina: In a double-blind parallel group placebo controlled trial (approximately 50 patients/group, in patients with chronic stable angina), Tiazac® at doses of 120-540/day increased exercise tolerance time. At trough, 24 hours after dosing, exercise tolerance times using a Bruce exercise protocol, increased by 14, 26, 41, 33 and 32 seconds over baseline for placebo and the 120 mg, 240 mg, 360 mg, and 540 mg/day treated patient groups, respectively. At peak, 8 hours after dosing, exercise tolerance times relative to baseline were statistically significantly increased by 13, 38, 64, 55 and 42 seconds for placebo and 120 mg, 240 mg, 360 mg, and 540 mg/day Tiazac® treated patients, respectively. Compared to baseline, Tiazac® treated patients experienced statistically significant reductions in anginal attacks and decreased nitroglycerin requirements when compared to placebo treated patients.

Pharmacokinetics and Metabolism. Diltiazem is well absorbed from the gastrointestinal tract but undergoes substantial hepatic first-pass effect. The absolute bioavailability of an oral dose of an immediate release formulation (compared to intravenous administration) is approximately 40%. Only 2% to 4% of unchanged diltiazem appears in the urine. The plasma elimination half-life of diltiazem is approximately 3.0 - 4.5 h. Drugs which induce or inhibit hepatic microsomal enzymes may alter diltiazem disposition. Therapeutic blood levels of diltiazem appear to be in the range of 40 - 200 ng/mL. There is a departure from linearity when dose strengths are increased; the half-life is slightly increased with dose.

The two primary metabolites of diltiazem are desacetyldiltiazem and desmethyldiltiazem. The desacetyl metabolite is approximately 25% to 50% as potent a coronary vasodilator as diltiazem and is present in plasma at concentrations of 10% to 20% of parent diltiazem. However, recent studies employing sensitive and specific analytical methods have confirmed the existence of several sequential metabolic pathways of diltiazem. As many as nine diltiazem metabolites have been identified in the urine of humans. Total radioactivity measurements following single intravenous dose administration in healthy volunteers suggest the presence of other unidentified metabolites. These metabolites are more slowly excreted, (with a half-life of total radioactivity of approximately 20 hours) and attain concentrations in excess of diltiazem.

In vitro binding studies show diltiazem HCl is 70% to 80% bound to plasma proteins. Competitive *in vitro* ligand binding studies have also shown diltiazem HCl binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. A study that compared patients with normal hepatic function to patients with cirrhosis who received immediate release diltiazem found an increase in diltiazem elimination half-life and a 69% increase in bioavailability in the hepatically impaired patients. Patients with severely impaired renal function (creatinine clearance <50 mL/min) who received immediate release diltiazem had modestly increased diltiazem concentrations compared to patients with normal renal function.

Tiazac® Capsules. When compared to a regimen of immediate-release tablets at steady-state, approximately 93% of drug is absorbed from the Tiazac® formulation. When Tiazac® was coadministered with a high fat content breakfast, the extent of diltiazem absorption was not affected; T_{max}, however, occurred slightly earlier. The apparent elimination half-life after single or multiple dosing is 4 to 9.5 hours (mean 6.5 hours).

Tiazac® demonstrates non-linear pharmacokinetics. As the daily dose of Tiazac® capsules is increased from 120 to 540 mg, there was a more than proportional increase in diltiazem plasma concentrations as evidenced by an increase of AUC, C_{max} and C_{min} of 6.8, 6 and 8.6 times, respectively, for a 4.5 times increase in dose.

INDICATIONS AND USAGE

Hypertension:

Tiazac® is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive medications.

Chronic Stable Angina:

Tiazac® is indicated for the treatment of chronic stable angina.

CONTRAINDICATIONS

Diltiazem is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with severe hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

WARNINGS

1. Cardiac Conduction. Diltiazem hydrochloride prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (13 of 3007 patients or 0.43%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.

2. Congestive Heart Failure. Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of diltiazem hydrochloride in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

3. Hypotension. Decreases in blood pressure associated with diltiazem hydrochloride therapy may occasionally result in symptomatic hypotension.

4. Acute Hepatic Injury. Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, and SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to diltiazem hydrochloride is uncertain in some cases, but probable in some (see PRECAUTIONS).

PRECAUTIONS

General. Diltiazem hydrochloride is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters of renal and hepatic function should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of diltiazem hydrochloride. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interactions. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving diltiazem hydrochloride concomitantly with other agents known to affect cardiac contractility and/or conduction (see WARNINGS). Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with Tiazac® (see WARNINGS). As with all drugs, care should be exercised when treating patients with multiple medications. Diltiazem hydrochloride undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of diltiazem hydrochloride with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs such as cyclosporin, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered diltiazem hydrochloride to maintain optimum therapeutic blood levels.

Beta Blockers. Controlled and uncontrolled domestic studies suggest that concomitant use of diltiazem hydrochloride and beta-blockers is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities. Administration of diltiazem hydrochloride concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. *In vitro*, propranolol appears to be displaced from its binding sites by diltiazem. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted (see WARNINGS).

Cimetidine. A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine 1200 mg per day and a single dose of diltiazem 60 mg. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis. Administration of diltiazem hydrochloride with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing diltiazem hydrochloride therapy to avoid possible over- or under-digitalization (see WARNINGS).

Anesthetics. The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Cyclosporine. A pharmacokinetic interaction between diltiazem and cyclosporine has been observed during studies involving renal and cardiac transplant patients. In renal and cardiac transplant recipients, a reduction of cyclosporine dose ranging from 15% to 48% was necessary to maintain cyclosporine trough concentrations similar to those seen prior to the addition of diltiazem. If these agents are to be administered concurrently, cyclosporine concentrations should be monitored, especially when diltiazem therapy is initiated, adjusted, or discontinued.

The effect of cyclosporine on diltiazem plasma concentrations has not been evaluated.

Carbamazepine. Concomitant administration of diltiazem with carbamazepine has been reported to result in elevated serum levels of carbamazepine (40% to 72% increase), resulting in toxicity in some cases. Patients receiving these drugs concurrently should be monitored for a potential drug interaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response *in vitro* or *in vivo* in mammalian cell assays or *in vitro* in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from 4 to 6 times (depending on species) the upper limit of the optimum dosage range in clinical trials (480 mg q.d. or 8 mg/kg q.d. for a 60 kg patient) resulted in embryo and fetal lethality. These studies revealed, in one species or another, a propensity to cause abnormalities of the skeleton, heart, retina, and tongue. Also observed were reductions in early individual pup weights and pup survival, prolonged delivery and increased incidence of stillbirths. There are no well-controlled studies in pregnant women; therefore, use diltiazem hydrochloride in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of Tiazac® is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies with Tiazac®, as well as with other diltiazem formulations. It should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies. A total of 256 hypertensives were treated for between 4 and 8 weeks; a total of 207 patients with chronic stable angina were treated for 3 weeks with doses of Tiazac® ranging from 120-540 mg once daily. Two patients experienced first-degree AV block at 540 mg dose. The following table presents the most common adverse reactions, whether or not drug-related, reported in placebo-controlled trials in patients receiving Tiazac® up to 360 mg and up to 540 mg with rates in placebo patients shown for comparison.

MOST COMMON ADVERSE EVENTS IN DOUBLE-BLIND PLACEBO-CONTROLLED HYPERTENSION TRIALS*

	Placebo	Tiazac®	
		Up to 360 mg	480-540mg
Adverse Events (COSTART Term)	n=57 # pts (%)	n=149 # pts (%)	n=48 # pts (%)
edema, peripheral	1 (2)	8 (5)	7 (15)
dizziness	4 (7)	6 (4)	2 (4)
vasodilation	1 (2)	5 (3)	1 (2)
dyspepsia	0 (0)	7 (5)	0 (0)
pharyngitis	2 (4)	3 (2)	3 (6)
rash	0 (0)	3 (2)	0 (0)
infection	2 (4)	2 (1)	3 (6)
diarrhea	0 (0)	2 (1)	1 (2)
palpitations	0 (0)	2 (1)	1 (2)
nervousness	0 (0)	3 (2)	0 (0)

MOST COMMON ADVERSE EVENTS IN DOUBLE-BLIND PLACEBO-CONTROLLED ANGINA TRIALS*

	Placebo	Tiazac®	
		Up to 360 mg	540 mg
Adverse Events (COSTART Term)	n=50 # pts (%)	n=158 # pts (%)	n=49 # pts (%)
headache	1 (2)	13 (8)	4 (8)
edema, peripheral	1 (2)	3 (2)	5 (10)
pain	1 (2)	10 (6)	3 (6)
dizziness	0 (0)	5 (3)	5 (10)
asthenia	0 (0)	1 (1)	2 (4)
dyspepsia	0 (0)	2 (1)	3 (6)
dyspnea	0 (0)	1 (1)	3 (6)
bronchitis	0 (0)	1 (1)	2 (4)
AV block	0 (0)	0 (0)	2 (4)
infection	0 (0)	2 (1)	1 (2)
flu syndrome	0 (0)	0 (0)	1 (2)
cough increase	0 (0)	2 (1)	1 (2)
extrasystoles	0 (0)	0 (0)	1 (2)
gout	0 (0)	2 (1)	1 (2)
myalgia	0 (0)	0 (0)	1 (2)
impotence	0 (0)	0 (0)	1 (2)
conjunctivitis	0 (0)	0 (0)	1 (2)
rash	0 (0)	2 (1)	1 (2)
abdominal enlargement	0 (0)	0 (0)	1 (2)

* Adverse events occurring in treated patients at 2% or more than placebo-treated patients.

In addition, the following events have been reported infrequently (less than 2%) in clinical trials with other diltiazem products:

Cardiovascular. Angina, arrhythmia, AV block (second- or third-degree), bundle branch block, congestive heart failure, ECG abnormalities, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles.

Nervous System. Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor.

Gastrointestinal. Anorexia, constipation, diarrhea, dry mouth, dysgeusia, mild elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see hepatic warnings), nausea, thirst, vomiting, weight increase.

Dermatological. Petechiae, photosensitivity, pruritus.

Other. Albuminuria, allergic reaction, amblyopia, asthenia, CPK increase, crystalluria, dyspnea, edema, epistaxis, eye irritation, headache, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, neck rigidity, nocturia, osteoarticular pain, pain, polyuria, rhinitis, sexual difficulties, gynecomastia.

In addition, the following postmarketing events have been reported infrequently in patients receiving diltiazem hydrochloride: alopecia, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A number of well-documented cases of generalized rash, characterized as leukocytoclastic vasculitis, have been reported. However, a definitive cause and effect relationship between these events and diltiazem hydrochloride therapy is yet to be established.

OVERDOSAGE

The oral LD50's in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD50's in these species were 60 and 38 mg/kg, respectively. The oral LD50 in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg.

The toxic dose in man is not known. Due to extensive metabolism, blood levels after a standard dose of diltiazem can vary over tenfold, limiting the usefulness of blood levels in overdose cases. There have been 29 reports of diltiazem overdose in doses ranging from less than 1 gm to 10.8 gm. Sixteen of these reports involved multiple drug ingestions. Twenty-two reports indicated patients had recovered from diltiazem overdose ranging from less than 1 gm to 10.8 gm. There were seven reports with a fatal outcome; although the amount of diltiazem ingested was unknown, multiple drug ingestions were confirmed in six of the seven reports.

Events observed following diltiazem overdose included bradycardia, hypotension, heart block, and cardiac failure. Most reports of overdose described some supportive medical measure and/or drug treatment. Bradycardia frequently responded favorably to atropine as did heart block, although cardiac pacing was also frequently utilized to treat heart block. Fluids and vasopressors were used to maintain blood pressure, and in cases of cardiac failure, inotropic agents were administered. In addition, some patients received treatment with ventilatory support, activated charcoal, and/or intravenous calcium. Evidence of the effectiveness of intravenous calcium administration to reverse the pharmacological effects of diltiazem overdose was conflicting.

In the event of overdose or exaggerated response, appropriate supportive measures should be employed in addition to gastrointestinal decontamination. Diltiazem does not appear to be removed by peritoneal or hemodialysis. Based on the known pharmacological effects of diltiazem and/or reported clinical experiences, the following measures may be considered:

Bradycardia: Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockage, administer isoproterenol cautiously.

High-Degree AV Block: Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.

Cardiac Failure: Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.

Hypotension: Vasopressors (e.g. dopamine or levarterenol bitartrate). Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

In a few reported cases, overdose with calcium channel blockers has been associated with hypotension and bradycardia, initially refractory to atropine but becoming more responsive to this treatment when the patients received large doses (close to 1 gram/hour for more than 24 hours) of calcium chloride.

Due to extensive metabolism, plasma concentrations after a standard dose of diltiazem can vary over tenfold, which significantly limits their value in evaluation cases of overdosage.

Charcoal hemoperfusion has been used successfully as an adjunct therapy to hasten drug elimination. Overdoses with as much as 10.8 gm of oral diltiazem have been successfully treated using appropriate supportive care.

DOSAGE AND ADMINISTRATION

Hypertension: Dosage needs to be adjusted by titration to individual patient needs. When used as monotherapy, usual starting doses are 120 to 240 mg once daily. Maximum antihypertensive effect is usually observed by 14 days of chronic therapy; therefore, dosage adjustments should be scheduled accordingly. The usual dosage range studied in clinical trials was 120 to 540 mg once daily. Current clinical experience with 540 mg dose is limited; however, the dose may be increased to 540 mg once daily.

Angina: Dosages for the treatment of angina should be adjusted to each patient's needs, starting with a dose of 120 mg to 180 mg once daily. Individual patients may respond to higher doses of up to 540 mg once daily. When necessary, titration should be carried out over 7 to 14 days.

Concomitant use with Other Cardiovascular Agents.

1. Sublingual Nitroglycerin may be taken as required to abort acute anginal attacks during diltiazem hydrochloride therapy.

2. Prophylactic Nitrate Therapy - Diltiazem hydrochloride may be safely co-administered with short- and long-acting nitrates.

Hypertensive or anginal patients who are treated with other formulations of diltiazem can safely be switched to Tiazac® capsules at the nearest equivalent total daily dose. Subsequent titration to higher or lower doses may, however, be necessary and should be initiated as clinically indicated.

HOW SUPPLIED

Tiazac® (diltiazem hydrochloride) Extended-release Capsules

Strength	Description	Quantity	NDC#
120 mg	#3 lavender/lavender capsule imprinted: Tiazac 120	30's	0456-2612-30
		90's	0456-2612-90
		1000's	0456-2612-00
		HUD's	0456-2612-63
180 mg	#2 white/blue-green capsule imprinted: Tiazac 180	30's	0456-2613-30
		90's	0456-2613-90
		1000's	0456-2613-00
		HUD's	0456-2613-63
240 mg	#1 blue-green/lavender capsule imprinted: Tiazac 240	30's	0456-2614-30
		90's	0456-2614-90
		1000's	0456-2614-00
		HUD's	0456-2614-63
300 mg	#0 white/lavender capsule imprinted: Tiazac 300	30's	0456-2615-30
		90's	0456-2615-90
		1000's	0456-2615-00
		HUD's	0456-2615-63
360 mg	#0 blue-green/blue-green capsule imprinted: Tiazac 360	30's	0456-2616-30
		90's	0456-2616-90
		1000's	0456-2616-00
		HUD's	0456-2616-63
420 mg	#00 white/white capsule imprinted: Tiazac 420	30's	0456-2617-30
		90's	0456-2617-90
		1000's	0456-2617-00

Storage conditions: Store at controlled room temperature 20°-25°C (68°-77°F). Avoid excessive humidity.

Rx Only.

Manufactured by:
Biovail Laboratories Inc.
Carolina, Puerto Rico
Encapsulated and Made in Canada

Manufactured for:
Forest Pharmaceuticals, Inc.
Subsidiary of Forest Laboratories, Inc.
St. Louis, Missouri 63045

Rev: 08/98 LB-0001-05

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-401/S-013

Approvable Letter

AUG 28 1998

NDA 20-401/S-013

Biovail Laboratories Incorporated
c/o Keller and Heckman
Attention: Mr. John Dubeck
Suite 500 West
1001 G Street N.W.
Washington, D.C. 20001

Dear Mr. Dubeck:

Please refer to Biovail's supplemental new drug application dated February 27, 1998, received March 2, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tiazac (diltiazem hydrochloride) Capsules, 120, 180, 240, 300, and 360 mg.

We acknowledge receipt of your submissions dated June 4, 15, 17, 24, and 26; July 16; and August 19 and 21, 1998. The user fee goal date for this application is September 2, 1998.

This supplement provides for a new dosage strength, 420 mg Capsules.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

1. Please revise the commercial product stability commitment as follows:

   The first three commercial production lots will be placed on stability at
   with testing performed at
   months on all package presentations (30, 90, and 1000 capsules). After the initial year, at least one production batch will be added to the stability program at .
   on all package presentations (30, 90, and 1000 capsules).

2. Please revise the certificate of analysis for the drug product to be identical to the quality standard specifications and test methods, e.g., the dissolution specification should include the range at each test interval.

3. Please use the same dissolution method and specifications for the 420 mg strength as approved in NDA 20-401 for the other strengths.

In addition, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to submitted draft labeling (package insert, immediate container and carton labels submitted February 27, 1998).

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit 20 copies of the final printed labeling, ten of which are individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available before we receive the final printed labeling, revision of that labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change prior to approval of this supplemental application.

If you have any questions, contact David Roeder, Regulatory Health Project Manager, at (301) 594-5313.

Sincerely,

/S/ 10-28-98

Kasturi Srinivasachar, Ph.D.
Chemistry Team Leader, DNDC I
Division of Cardio-Renal Drug Products, (HFD-110)
Office of Drug Evaluation I
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-401/S-013

Clinical Pharmacology and Biopharmaceutics Review

21.1

AUG 26 1998

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA:20-401 (SCF-013). Submission Date: August 19, 1998.
Diltiazem Capsules.
Tiazac[R] Capsules
Biovail Corporation.

Reviewer: Patrick J Marroum.

Type of submission: Amendment to a request for a biowaiver for a new dosage strength.

Background:

Tiazac is a once a day diltiazem product approved for the treatment of hypertension.
Currently the approved strengths are the 120, 180, 240, 300 and 360 mg. The sponsor is planning to introduce a new higher strength of 420 mg.
Since the sponsor has developed a level A correlation of acceptable quality, an in vivo bioavailability waiver for this new strength based on comparability of dissolution profiles in the approved media was requested by the firm on February 27, 1998 and was granted by the Office of Clinical Pharmacology and Biopharmaceutics on June 22, 1998. It was discovered subsequently that the dissolution data submitted by the firm was generated using a different dissolution method namely USP basket at rpm in ' of water. The sponsor was asked to resubmit the dissolution data in the approved dissolution method for this product.
Enclosed in Appendix I are the dissolution data that were requested for the new strength in the approved medium using the approved method.

Results:

Figure 1 shows the dissolution profiles for 6 units of the 420 mg new strength while Tables 1 and 2 summarizes the dissolution values at each time point tested for the individual capsules.
From the results submitted (see Table 3 for the dissolution data using the basket method), it can be seen that the dissolution results using the ' method are practically identical to the dissolution results obtained using the ' method. Table 4 gives a comparison of the dissolution results from the 2 different methods.

Comment to the Chemist:

Since the sponsor used a different dissolution methodology without the Agency's consent, the Division of Pharmaceutical Evaluation I suggests that an inspection of the manufacturing facility be undertaken.

Recommendation:

In view of the fact that an acceptable level A ` for this product has been established and the dissolution profiles are similar across the different strengths in the approved medium where the correlation exists, the Office of Clinical Pharmacology and Biopharmaceutics recommends granting an in vivo bioavailability waiver for the new 420 mg strength of Tiazac capsules. Moreover, the Office recommends the same dissolution methodology with the same dissolution specifications for the 420 mg strength as approved in the original application. Any modification of the methodology should be approved by the Agency before implementation.

/S/

Patrick J Marroum Ph.D. 8/26/1998

RD/FT initialed by M. Mehta Ph.D_ /S/ 8/26/98

cc: NDA 20-401, HFD 110, HFD 860 (Marroum), Chron, Drug, HFD 19 (FOI), CDER Central Document room (attention: Mrs Barbara Murphy).

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JUN 2 2 1998

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA:20-401 (SCF-013).
Diltiazem Capsules.
Tiazac[R] Capsules
Biovail Corporation.

Submission Date: February 27, 1998..

Reviewer: Patrick J Marroum.

Type of submission: Request for a biowaiver for a new dosage strength.

Background:

Tiazac is a once a day diltiazem product approved for the treatment of hypertension.
Currently the approved strengths are the 120, 180, 240, 300 and 360 mg. The sponsor is planning to introduce a new higher strength of 420 mg.
Since the sponsor has developed a level A correlation of acceptable quality, an in vivo bioavailability waiver for this new strength based on comparability of dissolution profiles in the approved media using the approved dissolution method is requested by the firm.

Results:

Figures 1 to 5 show the comparative dissolution profiles of the 420 mg new strengths vs the existing 120m 180, 240 300 and 360 mg. Tables 1 to 5 show the data corresponding to Figures 1 to 5.
The results show that the 420 mg new capsule strength has the same in vitro dissolution profile as the existing strengths and thus is expected to exhibit the same behavior in vivo.

Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics recommends granting an in vivo bioavailability waiver for the new 420 mg strength of Tiazac capsules.

/S/
Patrick J Marroum Ph.D. 6/22/1998.

RD/FT initialed by A Parekh Ph.D__ /S/ 6/22/98

cc: NDA 20-401, HFD 110, HFD 860 (Marroum), Chron, Drug, HFD 19 (FOI), CDER Central Document room (attention: Mrs Barbara Murphy).

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-401/S-013

Chemistry Review(s)

AUG 28 1998

CHEMIST'S REVIEW	1. ORGANIZATION HFD-110	2. NDA Number 20-401
3.**Name and Address of Applicant (City & State)** Biovail Laboratories Incorporated #34 Iturregui Avenue, SABANA ABJAJO, Carolina, Puerto Rico 00983		4.**Supplement(s) Number(s)Date(s)** SCF-013 2-Feb-98
5. **Drug Name** Tiazac™	6.**Nonproprietary Name** Diltiazem Hydrochloride	7.**Amendments&Other (reports, etc) - Dates** S-013 amendment 04-Jun-98;15-Jun-98 24-Jun-98; 26-Jun-98 16-Jul-98; 19-Aug-98 21-Aug-98
8. **Supplement Provides For:** A new dosage strength a 420 mg capsule.		
9. **Pharmacological Category** Antihypertensive Agent	10.**How Dispensed: RX**	11. **Related DMF(s)**
12. **Dosage Form(s)** Capsules extended release	13.**Potency(ies)** mg 120, 180, 240, 300, 360	
14. **Chemical Name and Structure** 1,5-Benzothiazepin-'4(5H)-one, 3-(aceyloxyl)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-monhydrochloride, (+)-cis-		15.**Record/Report CurrentlyReviewed** [X] Yes [ ] No
16. Comments: See page 2.		

17. Conclusions and Recommendations: Recommend an approvable letter be issued for S-013 pending the receipt of final printed labeling and applicant should:

1- Revise the commercial stability commitment as follows:

The first three commercial production lots will be placed on stability at and with testing performed at months on all package presentations (30, 90, and 1000 capsules.)
After the initial year, at least one production batch will be added to the stability program at on all packaging presentations (30, 90, and 1000 capsules.)

1- Revise the certificate of analysis for the drug product to be identical to the quality standard specifications and test methods e.g. the dissolution specification should include the range at each test interval.

2- Use the same dissolution method and specifications for the 420 mg strength as approved in the NDA 20-401 for the other strengths.

Reviewer: Kathleen Jongedyk	**Signature** /S/	**Completed: 26-Aug-98**

Distribution : [ ] Original Jacket [ ] Reviewer [ ] Div. File [ ] CSO

/S/ 26-98

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OCT 16 1998

CHEMIST'S REVIEW	1. ORGANIZATION HFD-110	2. NDA Number 20-401
3.Name and Address of Applicant (City & State) Biovail Laboratories Incorporated #34 Iturregui Avenue SABANA ABJAJO, Carolina, Puerto Rico, U.S.A. 00983		4.Supplement(s) Number(s)Date(s) S-013 Feb. 27, 1998
5. Drug Name Tiazac™	6.Nonproprietary Name Diltiazem Hydrochloride	7.Amendments&Other (reports, etc) - Dates S-013 Suppl. Amendments S-013(AC) Sept. 15, 1998 S-013/FPL Sept. 15, 1998
8. Supplement Provides For: A new dosage strength a 420 mg capsule.		
9. Pharmacological Category Antihypertensive Agent	10.How Dispensed [X] Rx [ ] OTC	11.RelatedIND(s)/NDA(s) /DMF(s)
12. Dosage Form(s) Capsules extended release	13. Potency(ies) mg 120, 180, 240, 300, 360	
14. Chemical Name and Structure 1,5-Benzothiazepin-'4(5H)-one, 3-(aceyloxyl)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-thoxyphenyl)-monhydrochloride, (+)-cis-		Record/Report CurrentlyReviewed [X] Yes [ ] No
16. Comments: September 15, 1998 Final printed labeling submitted is acceptable from the standpoint of CMC information. See page 2		
17. Conclusions and Recommendations: Recommend an approval letter be issued upon concurrence of the medical reviewer for the package insert changes		
18. REVIEWER		
Name Kathleen Jongedyk	Signature /S/	Completed October 1, 1998
Distribution : [ ] Original Jacket [ ] Reviewer [ ] Div. File [ ] CSO		

/S/
10-1-98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-401/S-013

Administrative Documents

OCT 16 1998

RHPM Review of Final Printed Labeling

Application:	NDA 20-401/S-013 Tiazac (diltiazem HCl) Capsules
Applicant:	Biovail Laboratories Incorporated
Letter Date:	September 15, 1998
Receipt Date:	September 21, 1998

Review

NDA 20-401/S-013 provides for a new dosage strength, 420 mg capsules. Although this is a higher strength than what is currently available, it does not change the maximum recommended dose, which is 540 mg. An approvable letter was issued on August 28 1998. The sponsor submitted final printed labeling in a submission dated September 15, 1998.

The labeling has been revised as follows:

- Under **DESCRIPTION**, "420" has been added to the list of available strengths.
- Under **HOW SUPPLIED**, information about the new dosage strength has been added.
- An editorial change was made under **ADVERSE REACTIONS**. The footnote, "*Adverse events occurring in treated patients at 2% or more than placebo-treated patients" had originally followed each of the two tables. In this supplement, the footnote following the first table was deleted so that the footnote following the second table would refer to both tables.

The final printed labeling is identical in content to the draft labeling. Provided that the Chemist is satisfied with the firm's response to other deficiencies outlined in the approvable letter, the supplement should be approved.

/S/

David Roeder
Regulatory Health Project Manager

dr/9-28-98

cc: NDA 20-401
HFD-110
HFD-110/DRoeder/SBenton