CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20401/S19

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-401/S-019

MAR 24 2000

Biovail Laboratories Incorporated
Attention: Mr. John Dubeck
1001 G Street, N.W.
Washington, D.C. 20001

Dear Mr. Dubeck:

Please refer to your supplemental new drug application dated November 16, 1999, received November 17, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tiazac (diltiazem hydrochloride) Capsules.

We acknowledge receipt of your submission dated January 4, 2000.

This supplement provides for draft labeling revised under **Dosage and Administration** to include the following:

> **Sprinkling the Capsule Contents on Food**
>
> Tiazac Extended Release Capsules may also be administered by carefully opening the capsules and sprinkling the capsule contents on a spoonful of applesauce. The applesauce should be swallowed immediately without chewing, and followed with a glass of cool water to ensure complete swallowing of the capsule contents. The applesauce should not be hot and it should be soft enough to be swallowed without chewing. Any capsule contents/applesauce mixture should be used immediately and not stored for future use. Subdividing the contents of a Tiazac Extended Release Capsule is not recommended.

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 agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted November 17, 1999).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-401/S-015." Approval of this submission by FDA is not required before the labeling is used.

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 call:

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

Sincerely,

/S/ 3/24/00

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

APPLICATION NUMBER: NDA 20401/S19

FINAL PRINTED LABELING

APPROVED

MAR 24 2000

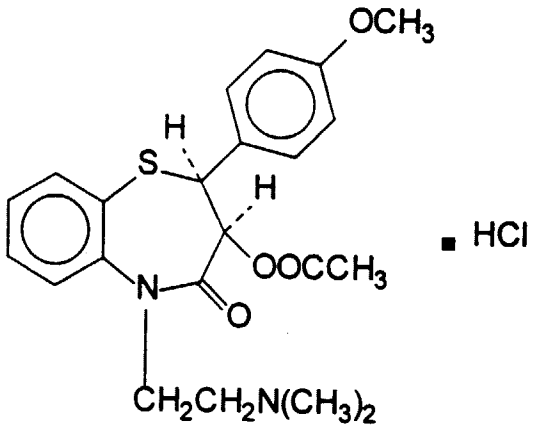
Tiazac®

(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 and 360 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

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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 betablockers 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

Tiazac®

(diltiazem hydrochloride)

Extended Release Capsules

Manufactured by: Biovail Corporation International
Mississauga, Ontario CANADA
L5L 1J9

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

Rev: 10/99

LB-0001-06

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 is both a substrate and an inhibitor of the cytochrome P-450 3A4 enzyme system. Other drugs that are specific substrates, inhibitors, or inducers of the enzyme system may have a significant impact on the efficacy and side effect profile of diltiazem. Patients taking other drugs that are substrates of CYP450 3A4, especially patients

with renal and/or hepatic impairment, may require dosage adjustment when starting or stopping concomitantly administered diltiazem in order 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.

Benzodiazepines. Studies showed that diltiazem increased the AUC of midazolam and triazolam by 3-4 fold and the C_{max} by 2-fold, compared to placebo. The elimination half life of midazolam and triazolam also increased (1.5-2.5 fold) during coadministration with diltiazem. These pharmacokinetic effects seen during diltiazem coadministration can result in incresed clinical effects (e.g., prolonged sodation) of both midazolam and triazolam.

Lovastatin. In a ten-subject study, coadministration of diltiazem (120 mg bid) with lovastatin

resulted in a 304 times increase in mean lovastatin AUC and C_{max} was observed during diltiazem coadministration. Diltiazem plasma levls were not significantly affected by lovastatin or pravastatin.

Rifampin. Coadministration of rifampin with diltiazem lowered thediltiazem plasma concentrations to undetectable levels. Coadministration of diltiazem with rifampin or any known CYP3A4 inducer should be avoided when possible, and alternative therapy considered.

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.

Geriatric Use. Clinical studies of diltiazem did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

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.

Tiazac®

(diltiazem hydrochloride)

Extended Release Capsules

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

Adverse Events (COSTART Term)	Placebo n=57 # pts (%)	Tiazac® Up to 360 mg n=149 # pts (%)	Tiazac® 480 - 540 mg 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*

Adverse Events (COSTART Term)	Placebo n=50 # pts (%)	Tiazac® Up to 360 mg n=158 # pts (%)	Tiazac® 540 mg 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)
A-V Block	0 (0)	0 (0)	2 (4)
infection	0 (0)	2 (1)	1 (2)
flu sundrome	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 ofoverdosage.

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

Tiazac®

(diltiazem hydrochloride)

Extended Release Capsules

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.

3. Beta-blockers. (See WARNINGS and PRECAUTIONS.)

4. Antihypertensives — Diltiazem hydrochloride has an additive antihypertensive effect when used with other antihypertensive agents. Therefore, the dosage of diltiazem hydrochloride or the concomitant antihypertensives may need to be adjusted when adding one to the other.

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.

Sprinkling the Capsule Contents on Food

Tiazac® (diltiazem hydrochloride) Extended-release Capsules may also be administered by carefully opening the capsule and sprinkling the capsule contents on a spoonful of applesauce. The applesauce should be swallowed immediately without chewing and followed with a glass of cool water to ensure complete swallowing of the capsule contents. The applesauce should not be hot, and it should be soft enough to be swallowed without chewing. Any capsule contents/applesauce mixture should be used immediately and not stored for future use. Subdividing the contents of a Tiazac® (diltiazem hydrochloride) Extended-release Capsule is not recommended.

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

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

Avoid excessive humidity.

Rx Only.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20401/S19

MEDICAL REVIEW(S)

JAN - 5 2000

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA Number: 20-401

Name of Drug: Tiazac[R] (diltiazem hydrochloride) Extended Release Capsules

Sponsor: Biovail Laboratories Incorporated

Indications: Hypertension and Chronic Stable Angina

Type of Submission: Supplemental NDA for Labeling Change

Date of Submission: November 16, 1999

Date Review Completed: January 5, 2000

Reviewer: Cristobal G. Duarte, MD

Title of Study: " A Two-way, Single Dose, Open Label, Fasting Bioequivalence Study Comparing Tiazac[R] 420 mg Extended Release Capsules Administered Intact Versus Administration of Capsule Content Sprinkled with Applesauce to Normal Healthy Non-smoking Volunteers".

Principal Investigator and Site of Investigation.	Dr. Paul Y. Tam Biovail Contract Research Toronto, Canada

Objective. The purpose of this study was to compare the rate and extent of absorption of Tiazac[R] (diltiazem hydrochloride) 420 mg extended release capsule when the capsule are administered intact versus when the capsule contents are sprinkled over applesauce under fasting conditions.

Number of Patients. Forty patients entered the study, 3 patients withdrew from the study and 37 patients completed the study.

Period of Study: The period of study was from April 23, 1999 to May 3, 1999.

Informed Consent Form. An informed consent form is included with the submission.

Institutional Review Board. The protocol was reviewed and approved by the Institutional Review Board.

Inclusion Criteria. Healthy, non-smoking, healthy male volunteers between 18 and 45 years of age were selected for the study. Body weight was to be no more than 10% of the

ideal weight for the subject's height and frame. The subject had to be available for the entire study period and willing to adhere to the protocol as evidence by a signed informed consent form. Physical examination had to be normal with a blood pressure between 100-140 mmHg/60-90 mmHg and heart rate between 55-99 bpm and normal electrocardiogram. Tests had to be negative for drugs of abuse, hepatitis B-surface antigen, hepatitis C and HIV. Laboratory results had to be within the normal range.

Exclusion Criteria. The subjects with the following conditions were excluded from the study: known history of hypersensitivity to calcium channel blockers; known history of any organic disease; any clinical significant clinical illness during the last four weeks prior to entry into the study; any physical or organic abnormality; history of drug or alcohol abuse; use of prescription medication, participation in a clinical trial with an investigational drug or blood donation within 30 days preceding the study; use of over-the counter medication within 14 days preceding the study.

Results. Forty subjects were initially enrolled in the study and 37 patients completed the study.

Demographic Characteristics. All subjects were male non-smoking healthy volunteers, mean age was 31±7.6 years (range 18 to 45 years), twenty-four were white, 5 were black, 2 were hispanic, 3 were asian and 1 was a native. Body weights were no more than ±10% of the ideal weight for the subject height and frame.

Study Design. This was a randomized, single dose, open-label, two-way, crossover design. The study consisted of a run-in period and a study period.

Run-in Period. All subjects were assessed to be normal and healthy by physical examination, clinical chemistry, hematology and urinalysis results, hepatitis B-surface antigen and hepatitis C screens, HIV screen, drug of abuse screen and electrocardiogram.

Study Periods. Following a fast of at least 10 hours beginning the evening before the dosing the subjects were institutionalized in the clinic by 9.00 pm. until 48 hr post-drug blood draw for each period.

Subjects on Regimen A received one 420 mg Tiazac^{R} capsule with 240 mg water on day 1 of each study period. Subjects following Regime B received one 420 mg Tiazac^{R} capsule the contents of which were sprinkled over 5 ml of applesauce in a spoon. The applesauce should be swallowed immediately without chewing followed with a 240 ml of cold water on day 1 of each study period. The applesauce should not be hot and it should be soft enough to be swallowed without chewing. Any capsule contents/applesauce mixture should be used immediately and not stored for future use. Each formulation was administered starting at 7 am following an overnight fast. Subjects were observed for the first four hours following drug administration by attending physician and then by the company professional Staff. The study physician was available by pager throughout the study.

Vital signs were monitored upon entry and throughout the study. Electrocardiogram monitoring was also done. Health monitoring was done periodically and at each point subjects were questioned on their overall health status and about adverse events. During each study period twenty-three blood samples (10 ml each) were collected at periodic and approximately hourly intervals from an antecubital vein.

Pharmacokinetic Results. Pharmacokinetic analysis consisted in the analytic determination of diltiazem and its active metabolites, desacetyl diltiazem and desmethyldiltiazem. The results are summarized in the following Table:

Summary of Results

Mean Pharmacokinetic Parameters for Plasma Diltiazem

(N=36)

Parameter	Biovail (A) 1 X 420 mg Arithmetic Mean (±SD)	Tiazac^{R} (B) 1 X 420 mg Arithmetic Mean (±SD)
AUC (0-t)(ng.hr/ml)	4361.38±1931.71	4396.87±1813.27
AUC (0-inf)(ng.hr/ml)	4475.74±1982.83	4510.34±1838.81
C_{max} (ng/ml)	255.34±110.88	265.09±113.64
T_{max} (hours)	7.19±2.10	7.25±2.19
$T_{1/2}$ (hours)	7.91±1.38	7.78±1.38
K_{el} ($hour^{-1}$)	0.090±0.015	0.092±0.016

Mean Pharmacokinetic Parameters for Plasma Desacetyldiltiazem

(N=36)

AUC (0-t)(ng.hr/ml)	470.76±235.22	494.70±233.29
AUC (0-inf)(ng.hr/ml)	531.44±280.89	555.18±277.36
C_{max} (ng/ml)	19.83±8.46	20.93±9.13
T_{max} (hours)	12.93±1.43	12.64±1.98
$T_{1/2}$ (hours)	12.33±2.68	12.13±3.49
K_{el} ($hour^{-1}$)	0.059±0.013	0.061±0.014

Summary of Results (Continued)

Mean Pharmacokinetic Parameters for Plasma Desmethyldiltiazem

(N=36)

Parameter	Biovail (A) 1 X 420 mg Arithmetic Mean (±SD)	Tiazac^R (B) 1 X 420 mg Arithmetic Mean (±SD)
AUC (0-t)(ng.hr/ml)	1581.84±412.92	1597.41±406.56
AUC (0-inf)(ng.hr/ml)	1715.36±458.69	1726.64±442.44
Cmax (ng/ml)	67.93±15.86	69.20±16.64
T_{max} (hours)	10.18±2.47	10.63±2.96
$T_{1/2}$ (hours)	11.23±1.78	10.99±1.85
K_{el} (hour^{-1})	0.063±0.010	0.065±0.012

Comment. Based on the Biovail (A)-t-Tiazac^R (B) comparison of diltiazem and its active metabolites desacetyl diltiazem and desmethyldiltiazem, the 90% geometric confidence intervals for AUC (0-t hours), AUC (0-infinity) and C_{max} were found to be within the 80%-125% range.

Adverse Events. Throughout the study thirty-two subjects experienced a total of one hundred and four adverse events. There were 38 episodes of headache, 21 episodes of sinus bradycardia. 16 episodes of borderline 1° AV block, 8 episodes of SR with borderline 1° AV block, 6 episodes of 1° AV block, 3 episodes of dizziness and SR with 1° AV block, 2 episodes each of nausea and vomiting, and 1 episode each of 2° AV block, cold, epistaxis, flu syndrome and junctional rhythm.

Pharmacodynamic and Laboratory Results. Pharmacodynamics were shown only individually for each patient and the sponsor did not present laboratory results in this submission that was related predominantly with pharmacokinetics. There were no significant pharmacodynamic or laboratory abnormalities in the course of the study.

Label Amendment: The sponsor submits a side by sides labeling of current and proposed supplement for Tiazac^R. The amendment consists in instructions on administration of Tiazac^R by sprinkling the capsule contents on applesauce.

Assessment. The results demonstrate that there is bioequivalence of Tiazac^R 420 mg capsules when administered intact or when the capsule contents are taken after sprinkled in applesauce.

There are no safety concerns that may preclude the enactment of this amendment

Recommendation. The labeling amendment should be approved as requested.

/S/

Cristobal G. Duarte, MD – HFD-110

CC.
ORIG. NDA 20-401
HFD-110
HFD-110/CSO/Mr. Roeder
HFD-110/Dr. Karkowsky
HFD-860/Dr. Marroum
HFD-110/CGD/05Janury00

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20401/S19

CHEMISTRY REVIEW(S)

JAN 20 2000

CHEMIST REVIEW	1. ORGANIZATION HFD-110	2. NDA Number 20-401
3.Name and Address of Applicant (City & State) Biovail Corporation International 2488 Dunwin Drive, Mississauga, Ontario , Canada L5L I.J9		4.Supplements Numbers/Dates SLR-019 16-Nov-99
5. Drug Name Tiazac	6. Nonproprietary Name Diltiazem Hydrochloride	7 Amendments & Other (Reports, etc) Date
8.Supplement Provides For A proposed package insert with the "Dosage and Administration" section revised to include directions for use of the contents of the capsules when opened and sprinkled on a spoonful of applesauce.		
9. Pharmacological Category Hypertension and Angina Pectoris	10.How Dispensed X Rx OTC	11.RelatedIND(s)/ NDA(s)/ DMF(s)
12. Dosage Form(s) Capsules Extended Release	13. Potency(ies) 120, 180, 240, 360, 420 mg	
14. Chemical Name and Structure 1,5-Benzothizepin-4(5H) one, 3-(acetyloxyl)-5-[2-(dimethylamino)ethyl] –2, 3-dihydro-2-(4-methoxyphenyl)- monhydrochloride		15Records/Currently Reviewed X Yes X Yes

16. **Comments:**

Biovail provides a side by side comparison of the approved and proposed package inserts.

Biovail did not change the "Description" and "How Supplied" sections and the prescription legend "Rx Only".
Acceptable The "Description" and "How Supplied" sections and the prescription legend "Rx Only".

Biovail changed the name and address for the "Manufactured by:" statement.
From Manufactured by: To Manufactured by: Biovail Corporation International
Mississauga, Ontario, CANADA
L5L 1J9

Acceptable The corporate address is used by most of the larger pharmaceutical companies in the "Manufacture for or by" labeling statement. Biovail does not have to provide both the "manufactured by:" and "manufactured for" statements on the labeling.

Biovail did not change the "Manufacture for: statement.
Manufactured for: Forest Pharmaceuticals, Inc.
Subsidiary of Forest Laboratories, Inc.
St. Louis, MO 63045
Draft package insert carries the Rev.10/99 LB-0001-06
Biovail did not change the storage statement. Storage conditions: Store at controlled room temperature
20°-25°C (68°- 77°F)
Avoid excessive humidity

Remarks: There are not objections to approving S-019 from the standpoint of CMC information.
Request the designation
in the labeling be revised to "Extended Release Capsules" the USP nomenclature.

18. REVIEWER

Name Kathleen E. Jongedyk	Signature /S/	Completed 19-Jan-2000

Distribution: Original Reviewer Division File CSO 20401s19.100

/S/
1-20-00

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20401/S19

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

FEB 1 2000

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Submission Dates: 11/16/99, 1/4/2000

NDA:	20-401/019
Name of Drug:	Tiazac® (Diltiazem HCL) ER Capsules, 120mg, 180mg, 240mg, 300mg, 360mg and 420mg
Indication of Drug:	Hypertension and Angina Pectoris
Sponsor:	Biovail Laboratories, Inc., Ontario, Canada
Type of Submission:	Labeling Supplement
Reviewer:	Hong Zhao, Ph.D.

Introduction

In this supplement, the sponsor proposes to add the following statement in the **Dosage and Administration** section of the Tiazac® ER Capsules (NDA 20-401) package insert:

"***Sprinkling the Capsule Contents on Food***
Tiazac® Extended Release Capsules may also be administered by carefully opening the capsules and sprinkling the capsule contents on a spoonful of applesauce. The applesauce should be swallowed immediately without chewing, and followed with a glass of cool water to ensure complete swallowing of the capsule contents. The applesauce should not be hot and it should be soft enough to be swallowed without chewing. Any capsule contents/applesauce mixture should be used immediately and not stored for future use. Subdividing the contents of a Tiazac Extended Release Capsule is not recommended."

To support this labeling statement the sponsor submitted a bioequivalence study report (Study # 2175, B99-384PK-DILG01) comparing Tiazac® 420 mg capsules (highest strength) administered in two formats: by sprinkling the capsule contents over a spoonful of applesauce or taking the capsule intact.

Bioequivalence Study Review

What is the study design?

This was a randomized, open label, two-way, crossover single dose study to compare the rate and extent of absorption of Tiazac® 420 mg ER capsules, when the capsules were administered intact versus when the capsule contents were sprinkled over applesauce, both treatments under fasting condition. There was a one-week washout period between study periods. Forty (40) healthy male volunteers participated and 36 subjects completed the study. Following each drug administration, blood samples were collected at 0 (pre-dosing), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, 14, 16, 24, 36 and 48 hours post dosing for determination of plasma concentrations of diltiazem and its active metabolites, desacetyldiltiazem and desmethyldiltiazem.

What are the study results?

See Appendix for study results. The major pharmacokinetic parameters are listed in the following tables:

Diltiazem	C_{max} (ng/mL)	AUC_{0-t} (ng.hr/mL)	$AUC_{0-\infty}$ (ng.hr/mL)	T_{max} (h)	$T_{1/2}$ (h)
Regimen A	255±111	4361±1932	4476±1983	7.2±2.1	7.9±1.4
Regimen B	265±114	4397±1813	4510±1839	7.3±2.2	7.8±1.4
Ratio of Mean*(B/A)	1.03	1.01	1.01		
90% CI	95-112	95-106	96-106		

* Geometric mean. Regimen A- subjects received one 420 mg Tiazac® ER intact capsule with 240 mL water (reference); Regimen B- subjects received one 420 mg Tiazac® ER capsule, the contents of which were sprinkled over 5 mL of applesauce in a spoon, with 240 mL water (test).

Desacetyl-diltiazem	C_{max} (ng/mL)	AUC_{0-t} (ng.hr/mL)	$AUC_{0-\infty}$ (ng.hr/mL)	T_{max} (h)	$T_{1/2}$ (h)
Regimen A	19.8±8.5	471±235	531±281	12.9±1.4	12.3±2.7
Regimen B	20.9±9.1	495±233	555±277	12.6±2.0	12.1±3.5
Ratio of Mean*(B/A)	1.05	1.05	1.05		
90% CI	99-111	99-111	100-110		

Desmethyl-diltiazem	C_{max} (ng/mL)	AUC_{0-t} (ng.hr/mL)	$AUC_{0-\infty}$ (ng.hr/mL)	T_{max} (h)	$T_{1/2}$ (h)
Regimen A	67.9±15.9	1582±413	1715±459	10.2±2.5	11.2±1.8
Regimen B	69.2±16.6	1597±407	1727±442	10.6±3.0	11.0±1.9
Ratio of Mean*(B/A)	1.02	1.01	1.01		
90% CI	98-106	98-104	98-104		

What conclusion can be drawn from this BE study?

The study results demonstrate that the test product, Tiazac® 420 mg ER capsules, when administered with the capsule contents sprinkled over applesauce is bioequivalent to administration of the capsule intact.

Comment 1

The results of this bioequivalence study demonstrate that the test product, Tiazac® 420 mg ER capsules, when administered with the capsule contents sprinkled over applesauce is bioequivalent to administration of the capsule intact.

Comment 2

The proposed statement shown below is factually correct and acceptable and can be added in the **Dosage and Administration** section of the Tiazac® ER Capsules (NDA 20-401) labeling.

"***Sprinkling the Capsule Contents on Food***

Tiazac® Extended Release Capsules may also be administered by carefully opening the capsules and sprinkling the capsule contents on a spoonful of applesauce. The applesauce should be swallowed immediately without chewing, and followed with a glass of cool water to ensure complete swallowing of the capsule contents. The applesauce should not be hot and it should be soft enough to be swallowed without chewing. Any capsule contents/applesauce mixture should be used immediately and not stored for future use. Subdividing the contents of a Tiazac Extended Release Capsule is not recommended."

Recommendation

The proposed statement mentioned above in the Comment 2 can be added in the **Dosage and Administration** section of the Tiazac® ER Capsules (NDA 20-401) labeling regarding ***Sprinkling the Capsule Contents on Food.***

Please convey this Recommendation and Comments 1 and 2 to the sponsor.

Hong Zhao, Ph.D.____ /S/ 2/1/2000

RD/FT Initialed by Raman Baweja, Ph.D.____ /S/ 2/1/2000.

cc: NDA 20-401/019 (Tiazac®, diltiazem HCL ER Capsule), HFD-110, HFD-860 (Zhao, Baweja, Mehta), Central Documents Room (CDR-Biopharm)

SUMMARY OF RESULTS

SECTION 1.0: PLASMA DILTIAZEM

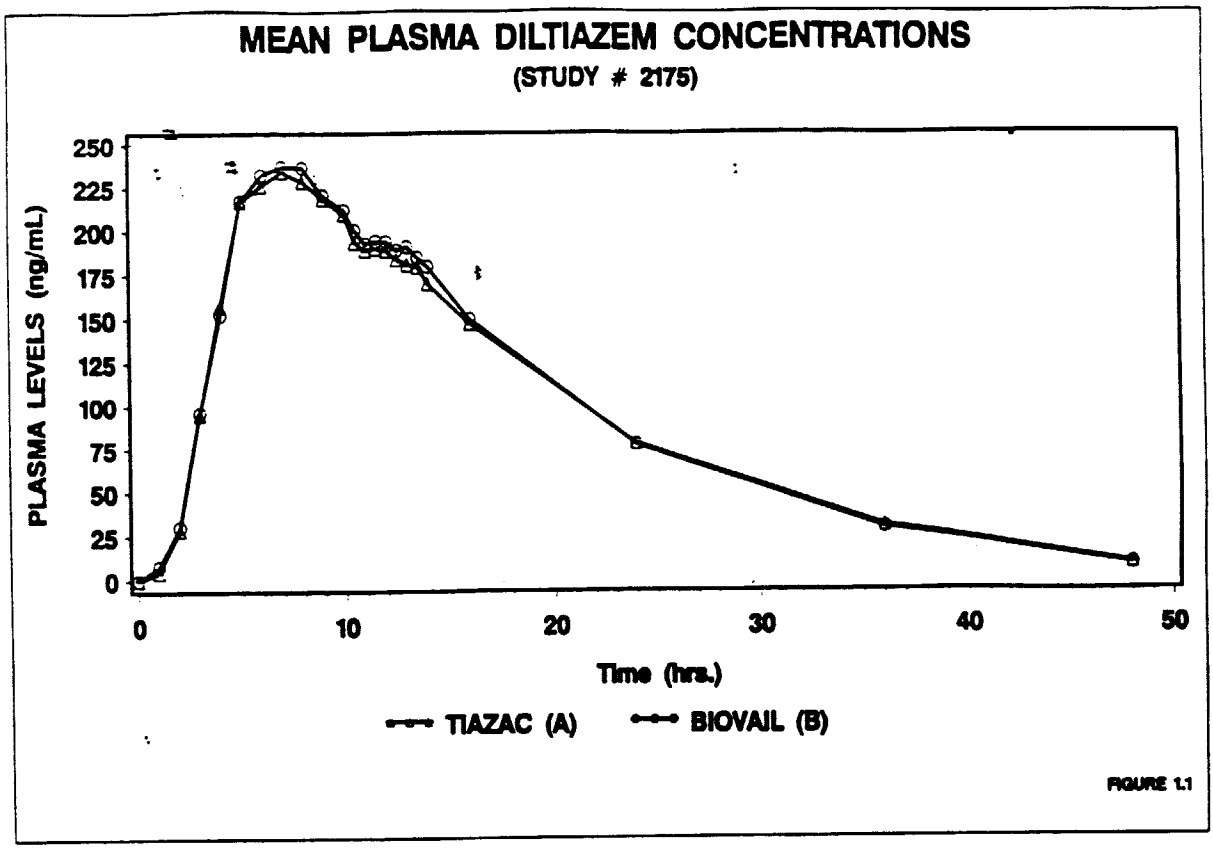
Mean Pharmacokinetic Parameters for Plasma Diltiazem (n = 36)

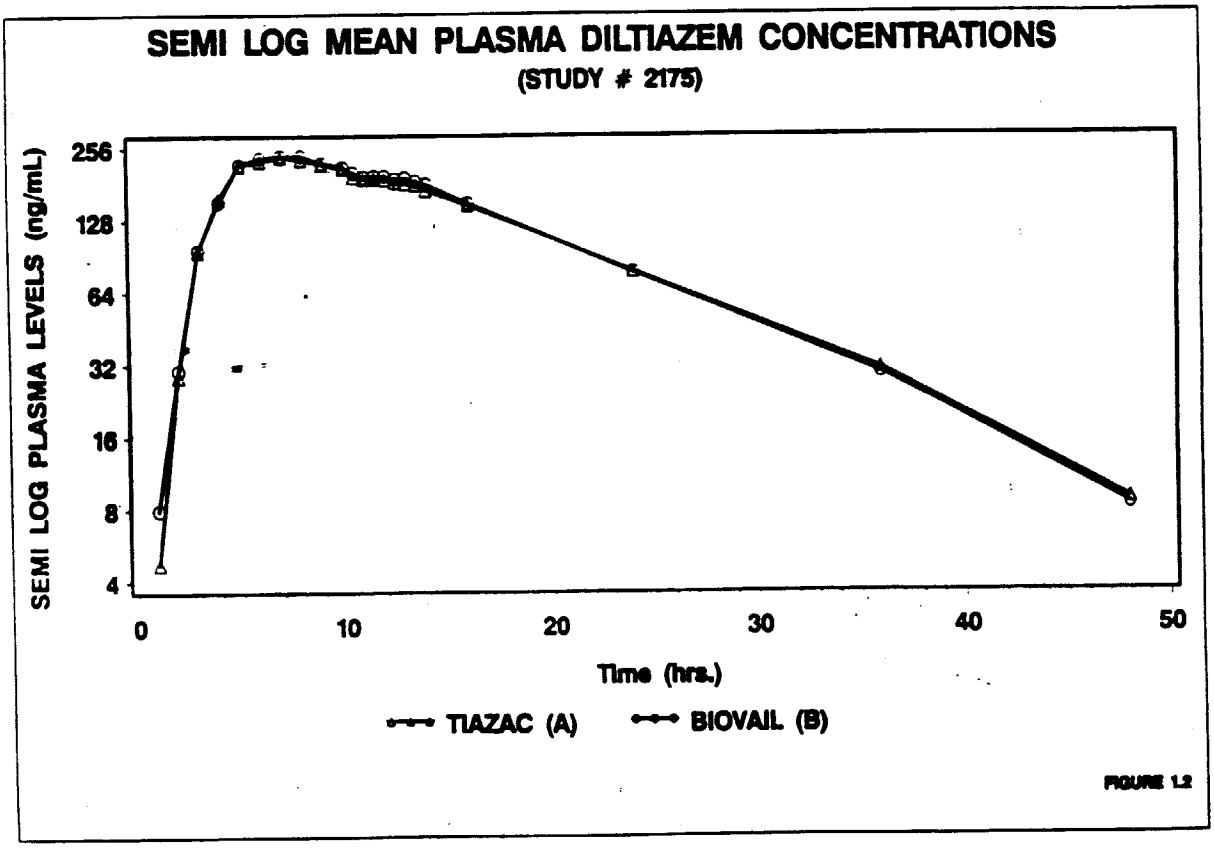
Parameter	Tiazac® (A) 1 x 420 mg Arithmetic Mean (±SD)	Biovail (B) 1 x 420 mg Arithmetic Mean (±SD)
AUC (0 - t)(ng·hr/mL)	4361.38 ± 1931.71	4396.87 ± 1813.27
AUC (0 - inf)(ng·hr/mL)	4475.74 ± 1982.83	4510.34 ± 1838.81
C_{max} (ng/mL)	255.34 ± 110.88	265.09 ± 113.64
T_{max} (hours)	7.19 ± 2.10	7.25 ± 2.19
$t_{1/2}$ (hours)	7.91 ± 1.38	7.78 ± 1.38
K_{el} ($hour^{-1}$)	0.090 ± 0.015	0.092 ± 0.016

Biovail (B) vs. Tiazac® (A)

	AUC (0 - t)	AUC (0 - infinity)	C_{max}
90% Geometric C.I.[1]	95% - 106%	96% - 106%	95% - 112%
Ratio of Means[2]	101%	101%	103%
Intra-Subject C.V.[3]	13.44%	13.18%	20.20%

[1] 90% Geometric Confidence Interval using log-transformed data and Tiazac® (A) as reference
[2] Calculated using geometric means according to the formula: $e^{(\text{Biovail (B)} - \text{Tiazac® (A)})} \times 100\%$
[3] Intra-subject coefficient of variation (C.V.)


MEAN PLASMA DILTIAZEM CONCENTRATIONS
(STUDY # 2175)
PLASMA LEVELS (ng/mL)
250
225
200
175
150
125
100
75
50
25
0
0
10
20
30
40
50
Time (hrs.)
TIAZAC (A)
BIOVAIL (B)
FIGURE 1.1


SEMI LOG MEAN PLASMA DILTIAZEM CONCENTRATIONS
(STUDY # 2175)
SEMI LOG PLASMA LEVELS (ng/mL)
256
128
64
32
16
8
4
0
10
20
30
40
50
Time (hrs.)
TIAZAC (A)
BIOVAIL (B)
FIGURE 1.2

SUMMARY OF RESULTS

SECTION 2.0: PLASMA DESACETYLDILTIAZEM

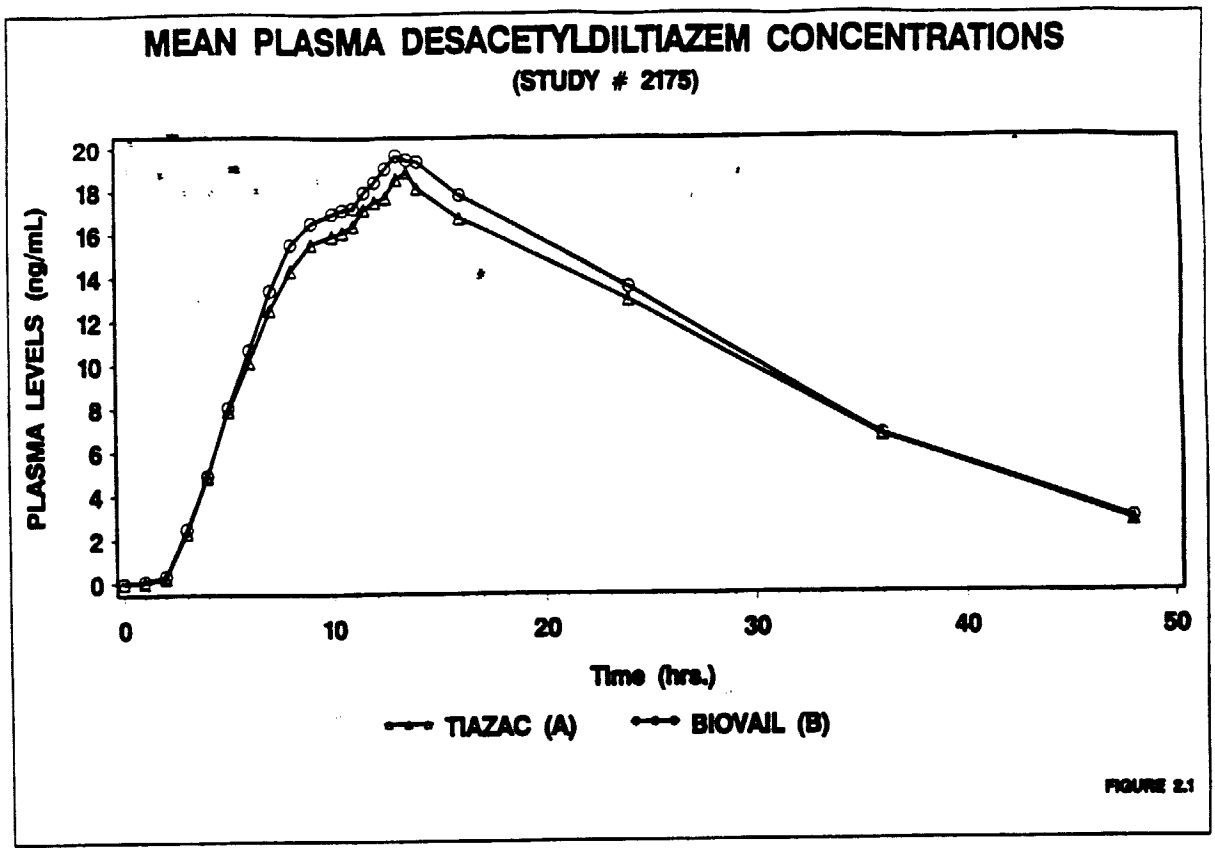
Mean Pharmacokinetic Parameters for Plasma Desacetyldiltiazem (n = 36)

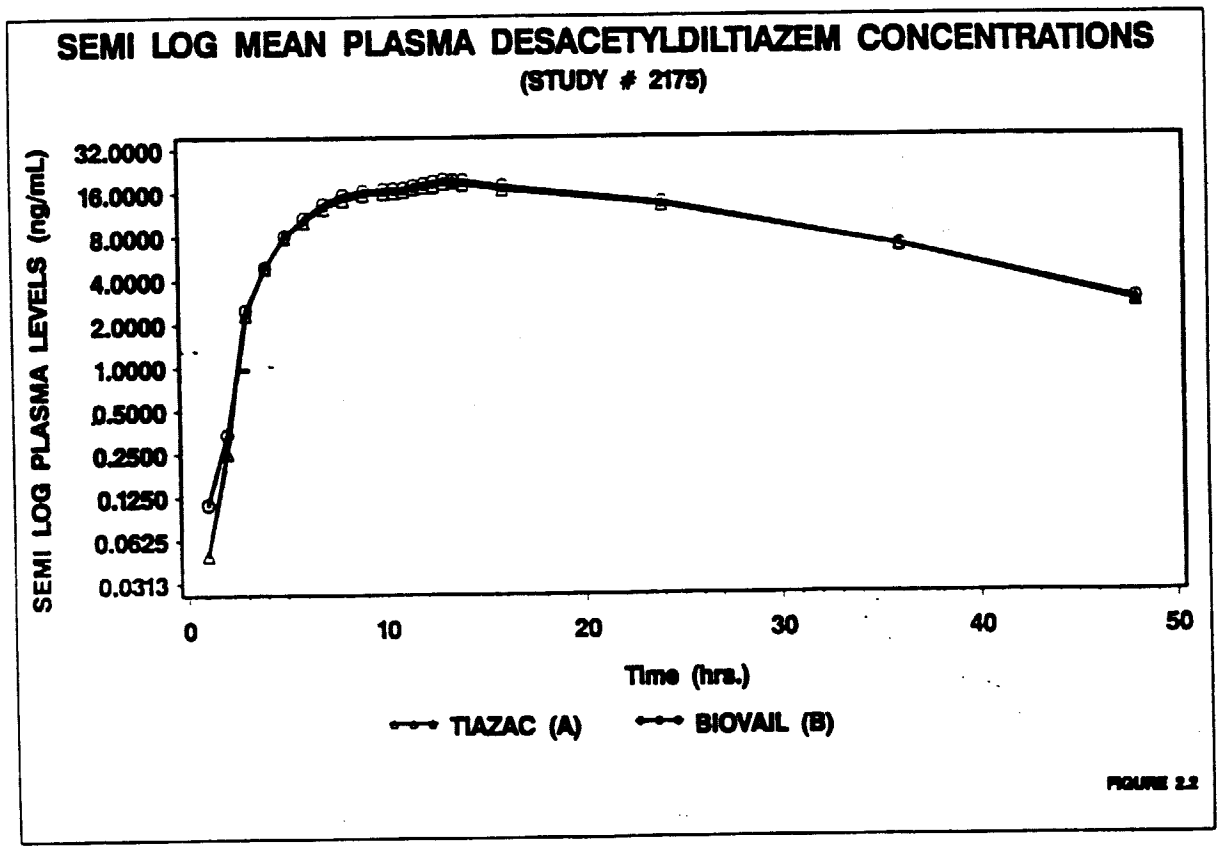
Parameter	Tiazac® (A) 1 x 420 mg Arithmetic Mean (±SD)	Biovail (B) 1 x 420 mg Arithmetic Mean (±SD)
AUC (0 - t)(ng·hr/mL)	470.76 ± 235.22	494.70 ± 233.29
AUC (0 - inf)(ng·hr/mL)	531.44 ± 280.89	555.18 ± 277.36
C_{max} (ng/mL)	19.83 ± 8.46	20.93 ± 9.13
T_{max} (hours)	12.93 ± 1.43	12.64 ± 1.98
$t_{1/2}$ (hours)	12.33 ± 2.68	12.13 ± 3.49
K_{el} (hour^{-1})	0.059 ± 0.013	0.061 ± 0.014

Biovail (B) vs. Tiazac® (A)

	AUC (0 - t)	AUC (0 - infinity)	C_{max}
90% Geometric C.I.[1]	99% - 111%	100% - 110%	99% - 111%
Ratio of Means[2]	105%	105%	105%
Intra-Subject C.V.[3]	13.97%	12.40%	14.56%

[1] 90% Geometric Confidence Interval using log-transformed data and Tiazac® (A) as reference
[2] Calculated using geometric means according to the formula: e (Biovail (B) - Tiazac® (A)) x 100%
[3] Intra-subject coefficient of variation (C.V.)


MEAN PLASMA DESACETYLDILTIAZEM CONCENTRATIONS
(STUDY # 2175)
PLASMA LEVELS (ng/mL)
20
18
16
14
12
10
8
6
4
2
0
0
10
20
30
40
50
Time (hrs.)
TIAZAC (A)
BIOVAIL (B)
FIGURE 2.1


SEMI LOG MEAN PLASMA DESACETYLDILTIAZEM CONCENTRATIONS
(STUDY # 2175)
SEMI LOG PLASMA LEVELS (ng/mL)
32.0000
16.0000
8.0000
4.0000
2.0000
1.0000
0.5000
0.2500
0.1250
0.0625
0.0313
0
10
20
30
40
50
Time (hrs.)
TIAZAC (A)
BIOVAIL (B)
FIGURE 2.2

Appendix

SUMMARY OF RESULTS

SECTION 3.0: PLASMA DESMETHYLDILTIAZEM

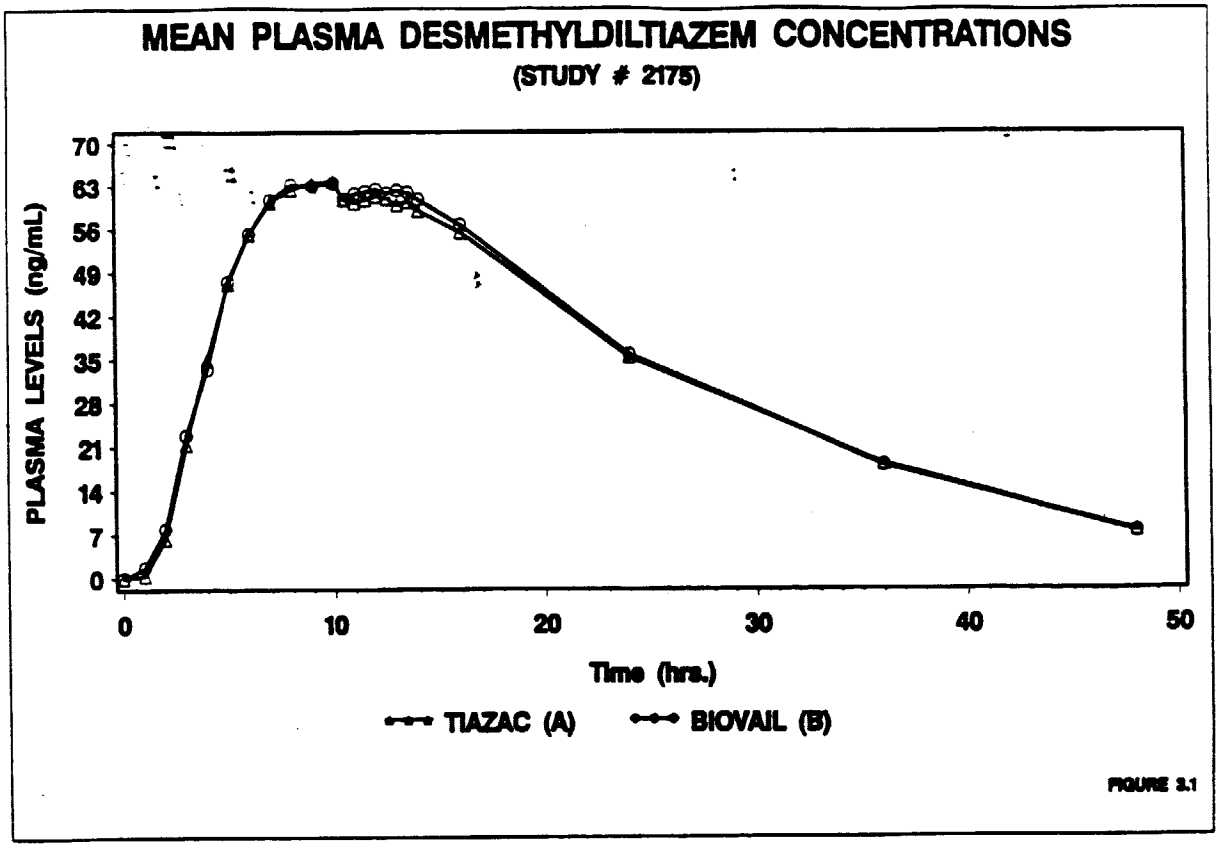
Mean Pharmacokinetic Parameters for Plasma Desmethyldiltiazem (n = 36)

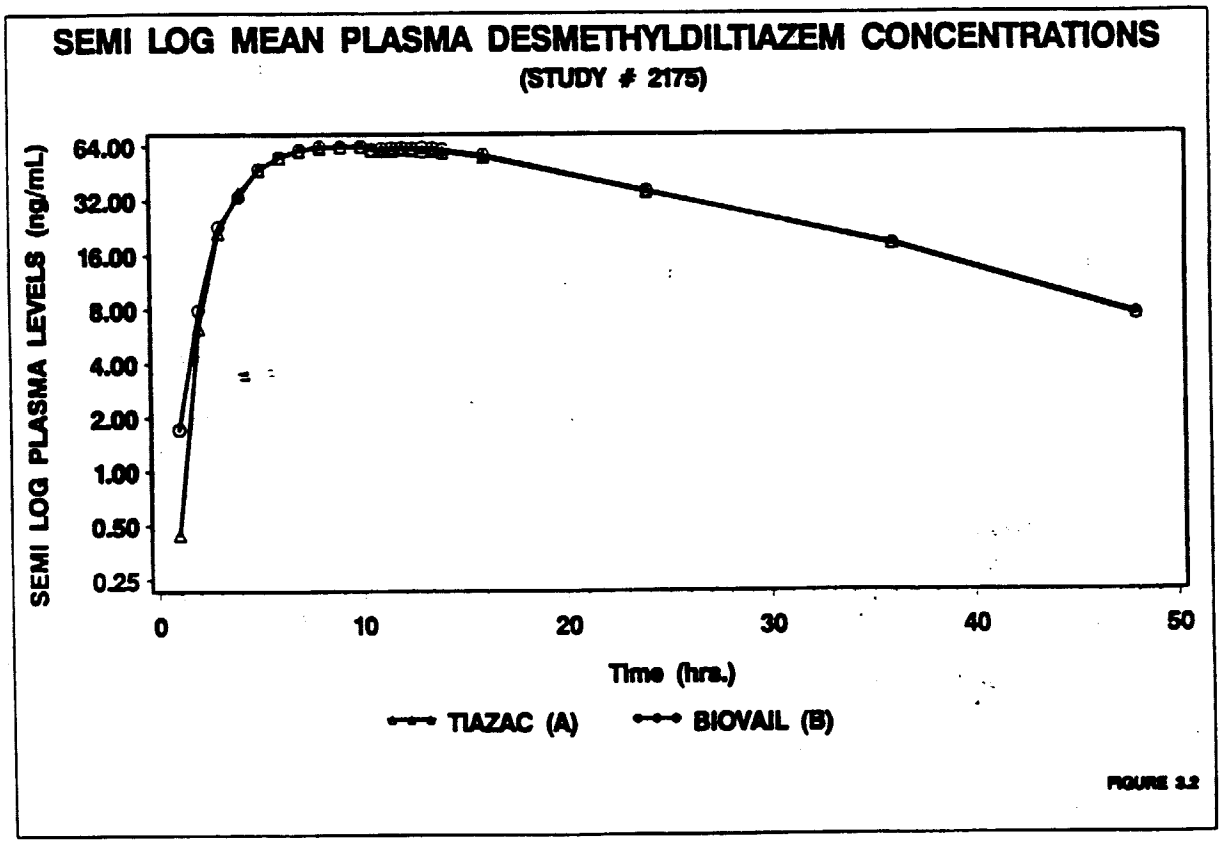
Parameter	Tiazac® (A) 1 x 420 mg Arithmetic Mean (±SD)	Biovail (B) 1 x 420 mg Arithmetic Mean (±SD)
AUC (0 - t)(ng·hr/mL)	1581.84 ± 412.92	1597.41 ± 406.56
AUC (0 - inf)(ng·hr/mL)	1715.36 ± 458.69	1726.64 ± 442.44
C_{max} (ng/mL)	67.93 ± 15.86	69.20 ± 16.64
T_{max} (hours)	10.18 ± 2.47	10.63 ± 2.96
$t_{1/2}$ (hours)	11.23 ± 1.78	10.99 ± 1.85
K_{el} ($hour^{-1}$)	0.063 ± 0.010	0.065 ± 0.012

Biovail (B) vs. Tiazac® (A)

	AUC (0 - t)	AUC (0 - infinity)	C_{max}
90% Geometric C.I.[1]	98% - 104%	98% - 104%	98% - 106%
Ratio of Means[2]	101%	101%	102%
Intra-Subject C.V.[3]	7.78%	7.74%	10.44%

[1] 90% Geometric Confidence Interval using log-transformed data and Tiazac® (A) as reference
[2] Calculated using geometric means according to the formula: $e^{(\text{Biovail (B)} - \text{Tiazac® (A)})} \times 100\%$
[3] Intra-subject coefficient of variation (C.V.)


MEAN PLASMA DESMETHYLDILTIAZEM CONCENTRATIONS
(STUDY # 2175)
PLASMA LEVELS (ng/mL)
70
63
56
49
42
35
28
21
14
7
0
0
10
20
30
40
50
Time (hrs.)
TIAZAC (A)
BIOVAIL (B)
FIGURE 3.1


SEMI LOG MEAN PLASMA DESMETHYLDILTIAZEM CONCENTRATIONS
(STUDY # 2175)
SEMI LOG PLASMA LEVELS (ng/mL)
64.00
32.00
16.00
8.00
4.00
2.00
1.00
0.50
0.25
0
10
20
30
40
50
Time (hrs.)
TIAZAC (A)
BIOVAIL (B)
FIGURE 3.2

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20401/S19

ADMINISTRATIVE DOCUMENTS

RHPM Review of Draft Labeling

Application: NDA 20-401/S-019
Tiazac (diltiazem hydrochloride) Capsules

Applicant: Biovail Laboratories Incorporated

Date of Supplement: November 16, 1999

Type of Supplement: Labeling

Review

NDA 20-401 provides for draft labeling revised under **Dosage and Administration** to include the following:

> **Sprinkling the Capsule Contents on Food**
>
> Tiazac Extended Release Capsules may also be administered by carefully opening the capsules and sprinkling the capsule contents on a spoonful of applesauce. The applesauce should be swallowed immediately without chewing, and followed with a glass of cool water to ensure complete swallowing of the capsule contents. The applesauce should not be hot and it should be soft enough to be swallowed without chewing. Any capsule contents/applesauce mixture should be used immediately and not stored for future use. Subdividing the contents of a Tiazac Extended Release Capsule is not recommended.

In addition, they revised the first part of the **Manufacturing Statement** from:

(

to:

Manufactured by:
Biovail Corporation International
Mississauga, Ontario CANADA
L5L 1J9

The reviews are complete, and the Medical Officer, Biopharmaceutist/Clinical Pharmacologist, and Chemist recommend approval with the proposed labeling.

An approvable letter will be drafted for Dr. Lipicky's signature.

/S/

David Roeder
Regulatory Health Project Manager

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