CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 20401/S-007

Trade Name: TIAZAC

Generic Name: DILTIAZEM HYDROCHLORIDE

Sponsor: BIOVAIL CORPORATION INTERNATIONAL

Approval Date: JANUARY 30, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: NDA 20401/S-007

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tentative Approval Letter			X	
Approvable Letter			X	
Final Printed Labeling		X		
Medical Review(s)				X
Chemistry Review(s)	X			
EA/FONSI	X			
Pharmacology Review(s)				X
Statistical Review(s)				X
Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)				X
Bioequivalence Review(s)				X
Administrative Document(s)	X			
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20401/S-007

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

D. Rue dec

Food and Drug Administration
Rockville MD 20857

NDA 20-401/S-007

JAN 30 1998

Biovail Corporation International
Attention: Ms. Mimi Brennan
2488 Dunwin Drive
Mississauga, Ontario
Canada L5L 1J9

Dear Ms. Brennan:

Please refer to your January 27, 1997 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tiazac (diltiazem HCl) Capsules, 120, 180, 240, 300 and 360 mg.

We acknowledge receipt of your submissions dated March 7 and 27 and July 3 and 25, 1997 and January 28, 1998.

The user fee goal date is January 30, 1998.

The supplemental application provides for the use of Tiazac for the treatment of chronic stable angina.

We have completed the review of this supplemental application including the submitted draft labeling 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 enclosed draft. (Please note that, for your convenience, we have struck-out deletions and underscored our additions.) Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed draft.

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 "FINAL PRINTED LABELING" for approved supplemental NDA 20-401/S-007. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising
and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

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,

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

Enclosure

cc:
Original NDA
HFD-110
HF-2/MedWatch (with draft/final labeling)
HFD-002/ORM (efficacy supplements only)
HFD-92/DDM-DIAB (with draft/final labeling)
HFD-101 (with draft/final labeling, efficacy supplements only)
HFD-101/L.Carter (efficacy supplements only)
HFD-40/DDMAC (with draft/final labeling)
HFD-613/OGD (with draft/final labeling)
HFD-735/DPE (with draft/final labeling)
DISTRICT OFFICE
HFD-810/ONDC Division Director
HFI-20/Press Office (with draft/final labeling)
HFD-110/DRoeder
sb/1/27/98;1/30/98
R/D: JShort/1/27/98
CResnick/1/27/98
KU/1/27/98
NMorgenstern/1/30/98

Approval Date: 18-Sep-95

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20401/S-007

CHEMISTRY REVIEW(S)

SEP 12 1997

CHEMIST'S 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 1J9		4.Supplement Number/Date) SE1-07--1/27/97
5. Drug Name Tiazac™	6.Nonproprietary Name Diltiazem Hydrochloride	7.Amendments/Other(reports etc) - Dates
8. Supplement Provides For: SE1 provides for a new indication stable angina pectoris and supportive clinical data.		
9. Pharmacological Category Antihypertensive Agent	10How Dispensed [X] Rx [ ] OTC	11.Related IND/NDA/DMF(s
12. Dosage Form(s) Capsules extended release	13 Potency(ies) 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) monohydrochloride, (+)-cis-		Records&Reports/ Currently/Reviewed [X] Yes [ ] No

6. Comments: SE1-007 is submitted in accordance with 21 CFR 315.70. SE1-007 provides for a new indication stable angina pectoris and supportive data from clinical studies whose design was agreed upon in the September 22, 1993 meeting with the applicant and HFD-110. The original NDA 20-410 was approved for the indication of essential hypertension on September 11, 1995.

The same batch of beads used for the pivotal hypertension clinical trials that were the basis of approval of Tiazac™ were also used for the angina study.

Batch numbers of the beads used in the SE-007 studies are as follows:

Placebo	94C013
120 mg	94C011
180 mg	93M006
240 mg	93M007
360 mg	93M008

Dissolution or stability data are not provided for the above lots in this submission. Biovail extended the original expiration date 31-Dec-95 to 31-Mar-96 following additional stability tests because the study took longer than anticipated to complete.

17. Conclusions and Recommendations: Action on SE1-007 requires a review by the medical officer. No action is indicated from the standard point of manufacturing and controls.

8. REVIEWER

Name Kathleen Jongedyk	Signature Kathleen Z Jongedyk	Completed 10-Sept- 97

Distribution: [ ] Orig.Jack [ ] Rev. [ ] Div. File [ ] CSO [ ] District

9/12/97

Biovail Corporation International owner of NDA 20-401 acquired the manufacturing site for coated beads in Tiazac™, Galephar PR, Inc., Carolina, Puerto Rico on September 19, 1995 . The name Galephar PR, Inc was changed to Biovail Laboratories Incorporated.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20401/S-007

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

D. Roeder

MAR 17 1997

CONFIDENTIAL ENVIRONMENTAL ASSESSMENT -- NDA 20-401 S-007

Tiazac (diltiazem hydrochloride) Capsules
Biovail Corporation International
Efficacy Supplement (Angina)

Submission Type	Doc Date	CDER Date	Assigned Date	Completed
Supplement S-007	Mar 7, 97	Mar 10, 97	Mar 13, 97	Mar 14, 97

Brief History:
The preparation of an Environmental Assessment (EA) is required for an efficacy supplement to an existing NDA. Biovail Corp. states that the only change described in the supplement is the new indication namely, angina. The indication approved in the original NDA was hypertension.

The applicant refers to the FONSI for the same active moiety, diltiazem hydrochloride, prepared by Florian Zielinski on August 28, 1995 and approved on September 6, 1995. The first three (3) pages of the FONSI are attached.

The only change in the original EA is due to an increase in the production and use of the drug substance for the additional indication. The original estimate (Aug 4, 1995) of the total annual market volume in the fifth year after NDA approval (MV_5) was stated to be The revised MV_5 estimate provided on March 7, 1997 increases to for all indications.

Evaluation:
It is well known that diltiazem is extensively metabolized; less than 4% of the administered drug is excreted unchanged in the urine. In this case, approx. will be excreted into the aquatic environment resulting in an Expected Environmental Concentration (EEC) of part per billion.

Diltiazem undergoes hydrolysis to desacetyl diltiazem in aqueous solutions (pH 1-7). Maximum stability is at pH 5 (half life 42 days at room temperature). Hydrolysis prevents the build up of diltiazem in the aqueous environment.

Summary: No significant impact expected due to approval of the supplement.

Florian Zielinski 3/14/97

Florian Zielinski
Review Chemist
March 14, 1997

Distribution:
Original NDA file 20-401 S-007
HFD 110 Division File
HFD 110 Florian Zielinski
HFD 110 CSO, Dave Roeder
Initialed by RJ Wolters

3/17/97

CONFIDENTIAL

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

TIAZAC CAPSULES

Diltiazem Hydrochloride Once Daily Extended-release Capsules

NDA 20-401

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF CARDIORENAL DRUG PRODUCTS
(HFD-110)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-401

TIAZAC CAPSULES
(Diltiazem Hydrochloride Once Daily Extended-release Capsules)

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research carefully considered the potential environmental impact of this action and concluded that it will not have a significant effect on the quality of the human environment and that an environmental impact statement will not be prepared.

In support of their new drug application for Tiazac Capsules, Biovail Corporation International (Toronto, Ontario, Canada) prepared an environmental assessment (attached) in accordance with 21 CFR 25.31a-Format 1.(a) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Diltiazem hydrochloride is a synthetic drug administered in a Once Daily Extended-release Capsule for treating angina and hypertension. The drug substance is manufactured at sites described in Drug Master Files referenced in the Environmental Assessment. Drug product manufacturing operations are conducted at Biovail facilities in Steinbach, Manitoba, Canada and Gelephar PR facilities in Carolina, Puerto Rico. Unit dose packaging is done at a site identified in the Environmental Assessment.

The finished drug product, Tiazac Capsules (Diltiazem hydrochloride Once Daily Extended-release Capsules) will be used by patients in hospitals, clinics and their homes. Patients will excrete the drug and its metabolites in urine into the sewer system (POTW). Chemical and physical data indicate the drug and its metabolites are restricted to the aquatic environment and are degraded by hydrolysis.

Significant environmental effects are not expected because the Maximum Expected Emitted Concentration (MEEC) of diltiazem hydrochloride is many times smaller than concentrations associated with effects in the aquatic environment. Hydrolysis in the aquatic environment results in a much lower Expected Environmental Concentration (EEC).

Production waste and non-usable product is incinerated at licensed facilities. Empty and partially empty packages resulting from hospital and clinic use will be disposed according to their policies and regulations. Empty and partially empty containers resulting from home use will be disposed in the municipal solid waste management system which includes landfill and incineration; insignificant quantities of unused drug may be disposed in the sewer system.

The Center for Drug Evaluation and Research concluded that the product can be manufactured, used and disposed without any significant adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

August 28, 1995 Florian Zielinski
DATE Prepared by Florian Zielinski, PhD, Review Chemist
Division of Cardiorenal Drug Products (HFD-110)

8-30-95 Robert J Wolters
DATE Division Concurrence by Robert J Wolters, PhD
Supervisory Chemist, (HFD-110)

9-5-95 Nancy B Sager
DATE Approved by Environmental Scientist
Center for Drug Evaluation and Research

9/6/95 Robert A Jerussi
DATE Concurred by Robert A Jerussi, PhD
Associate Director for Chemistry
Center for Drug Evaluation and Research

Attachment: Environmental Assessment
(FOI version provided by FAX August 25, 1995)

Original: NDA 20-401
cc: HFD-110 Division File
HFD-110 FW Zielinski
HFD-110 CSO, Dave Roeder
HFD-004 FONSI File NDA # 20-401
HFD-004 Docket File
HFD-019 FOI COPY

File Name FWZ C:\...\wp60\...\curntwrk\fonsi401.V2 August 28, 1995

ROEDER

OCT 28 1997

(Confidential)

(CDER/ ODE I/ DCRDP - HFD 110)

MEDICAL OFFICER REVIEW

NDA #: **20-401**

DRUG NAME: **Tiazac™ (Diltiazem HCl) Extended Release Capsules**

SPONSOR: **Biovail Corporation International**

MEDICAL OFFICER: **Khin Maung U, M.D.**

Submission Date:	*27-Jan-1997*
Receipt Date:	*30-Jan-1997*
Date Assigned:	*24-Feb-1997*
Review Completed:	*14-May-1997*

(Confidential)

CONTENTS

Material Reviewed

The following is a list of the volume numbers which served as the basis for this review:
M15.1 to M15.12

Efficacy review was based primarily on data submitted in the following volumes:
1, 2, 3, 4, 5, 6, 7

Safety review was based primarily on the safety data submitted in the following volumes:
1, 3, 4, 5, 8, 9, 10, 11, 12

CRF tabulations were not submitted. The sponsor submitted that there was agreement between FDA and sponsor that (i) CRF tabulations would not be required as virtually all data on the CRFs are appended to the study report in well-formatted computer generated listings and (ii) a database search would not be necessary for the safety update report, an integrated summary of the safety of two previous pivotal trials on hypertension plus the current angina trial being considered an adequate basis for the safety update.

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER REVIEW

NDA #:	20-401		
NDA Volume:	M15.1-15.23	Document ID #: SE1-007	
DRUG NAME:	Tiazac™ (Diltiazem HCl) Extended-release Capsules		
SPONSOR:	Biovail Laboratories, Inc.		
TYPE OF DOCUMENT:	Supplemental NDA		
DATE OF CORRESPONDENCE:	*27-Jan-1997*	DATE ASSIGNED:	*24-Feb-1997*
DATE RECEIVED:	*30-Jan-1997*	DATE COMPLETED	*14-May-1997*
MEDICAL OFFICER:	Khin Maung U, M.D.		

Sponsor's Requested Labeling:

For this NDA Supplement, the sponsor proposed to add the following in the labeling of Tiazac™:-

(1) Under *Pharmacodynamics*:

Angina: *In a double-blind parallel group placebo controlled trial, Tiazac™ increased exercise tolerance times in patients with chronic stable angina. At trough, 24 hours after dosing, exercise tolerance times using a Bruce exercise protocol, increased by 186%, 293%, 236% and 228% compared to placebo for 120 mg, 240 mg, 360 mg and 540 mg/day treated patient groups respectively. At peak, 8 hours after dosing, exercise tolerance times were statistically significantly increased by 288%, 487%, 414% and 314% compared to placebo for 120 mg, 240 mg, 360 mg and 540 mg/day treated groups respectively. Compared to baseline, Tiazac™ treated patients experienced statistically significant reductions in anginal attacks of 46% to 62% while the number of attacks increased by 72% in placebo treated patients. Similarly, Tiazac™ treated patients used 57% to 86% less nitroglycerin compared to baseline while nitroglycerin use was increased by 50% in placebo treated patients.*

(2) Under *Dosage and Administration*:

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..

Angina: *Doses 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.*

Resume

The study was a 6 week multicenter, double-blind, randomized, placebo-controlled, parallel-group, dose-response trial. Following a 2 to 3 week single-blind placebo washout phase, 257 subjects were enrolled by 32 centers into the double-blind treatment phase. Subjects were randomly assigned to receive either placebo or one of the Diltiazem OD ER dose groups: 120 mg, 240 mg, 360 mg or 540 mg. Subjects assigned to the higher dose groups were forcibly titrated over a 7 day period. All subjects then received their target dose of drug for the 2 week maintenance phase. Thus, subjects were on double-blind treatment (placebo or active drug) for a total of 3 weeks, their dose being stable for the last 2 weeks of that period (either placebo, 120 mg, 240 mg, 360 mg or 540 mg daily). Following the 2-week, multiple-dose, maintenance phase, there was a one-week follow-up placebo phase.

The Primary Efficacy Variable was the total duration of exercise (sec). The Secondary Efficacy Variables were:- duration of exercise (sec) until the onset of angina, duration of exercise (sec) until the onset of ≥1 mm ST segment depression persisting ≥0.08 second beyond the J-point, angina attack rate (a diary of total number of anginal attacks/day was kept by patients), and nitroglycerine consumption (a diary of total nitroglycerine tablet consumption/day was kept by patients).

Using an intent-to-treat analysis, endpoint analysis showed that the time subjects walked on the treadmill increased relative to the baseline total duration of exercise on ETT by 14 seconds (4.1%), 26 seconds (8.0%), 41 seconds (12.7%), 33 seconds (9.9%) and 32 seconds (9.4%), respectively, with placebo and with Tiazac™ at trough at the doses of 120 mg (P = 0.332, not significant), 240 mg (P = 0.002), 360 mg (P = 0.030) and 540 mg (P = 0.051, not significant). This finding was supported by time point analyses at Visits 5 and 6 with the 240 mg group that showed significantly increased exercise duration on ETT at both visits (P = 0.011 and P = 0.002, respectively) and the 360 mg group being significant at Visit 5 (P = 0.002) compared to placebo. The dose response was rather flat, with improvement increasing from 120 mg to 240 mg dose after which there was no further increase in effect at 360 mg and 540 mg. At peak, all four doses of Tiazac™ showed statistically significant improvement in the mean walking times compared to placebo. Tiazac™ 120 mg, 240 mg, 360 mg and 540 mg treatment groups reduced the mean number of anginal attacks significantly (P = 0.001 overall) by 55%, 53%, 46% and 62%, respectively, whereas placebo increased the mean number of attacks by 72%. Diltiazem 240 mg, 360 mg and 540 mg treatment groups showed statistically significant (P = 0.018, P = 0.023 and P = 0.026, respectively) reductions in nitroglycerine tablet consumption relative to baseline nitroglycerine tablet consumption (by 55%, 70% and 60%, respectively) compared to the placebo group which showed an increase (by 50%). There were no statistically significant differences in the improvements in time to angina and time of onset of 1 mm ST-segment depression between placebo and the four diltiazem treatment groups at endpoint. While the submission contained only one pivotal clinical trial, the efficacy findings may be considered adequate to meet the regulatory requirements for approvability because there were: (1) a positive effect of Tiazac™ on the primary efficacy variable that was demonstrated at an alpha level of 0.002 {for: (i) 240 mg Tiazac™ at endpoint, (ii) for 240 mg at Visit 6, and (iii) for 360 mg at Visit 5}; (2) a dose-related response (albeit only at 120 mg and 240 mg), and (3) the secondary variables that showed significant improvements compared to placebo (P = 0.001 for reduction in number of anginal attacks overall, and P = 0.026 - 0.018 for reductions in nitroglycerine tablet consumption).

A total of 83 subjects reported at least one adverse event in the double-blind phase of the study. Overall, the two highest doses of Tiazac™ - 360 mg and 540 mg - had a statistically significantly larger number of subjects reporting an adverse event compared to placebo. The incidence of adverse events increases with dose, peripheral edema and dizziness bearing the strongest relationship to dose. The type and frequency of adverse events reported in this study were not different from those reported in the literature for other currently marketed formulations of diltiazem and were similar to those seen in previous studies in hypertensive patients with this formulation. One randomized subject who had a serious adverse event (worsening of ischemia while on 240 mg Tiazac™ daily) required early withdrawal from the study; he recovered completely from the event. No death was reported in the study.

The results of the current clinical trial (efficacy and safety) were found to be consistent with the known efficacy and safety results reported in the literature for other once/day sustained-release preparations of diltiazem. Overall, diltiazem OD ER (Tiazac™) provided statistically significant improvement in exercise tolerance time with an adverse event profile similar to that reported for other currently marketed formulations of sustained-release diltiazem.

The proposed indication/labeling change is **approvable** with more detailed information added in the labeling to provide more complete and accurate information.

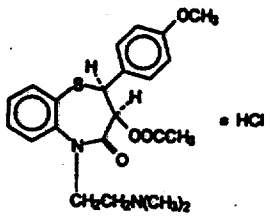
1. GENERAL INFORMATION

Name of Drug: Tiazac™ Extended-release Capsules
Generic: Diltiazem HCL Extended-release Capsules

Tiazac™ (diltiazem hydrochloride) is a calcium ion cellular influx inhibitor (slow channel blocker) available for oral administration. 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.

2. CHEMISTRY

Diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)-one,3-(acetyloxy)-5-[2-(dimethylamino) ethyl] -2,3-dihydro-2-(4-methoxyphenyl)-,monohydrochloride,(+)-cis. It has a molecular weight of 450.98. Molecular formula is: $C_{22}H_{26}N_2O_4S.HCl$. The structural formula of diltiazem hydrochloride is:



Diltiazem hydrochloride is a white to off-white powder with a bitter taste; it is soluble in water, methanol and chloroform.

3. PHARMACOLOGY

3.1 Pharmacological Category

Tiazac™ (diltiazem hydrochloride) is a calcium ion cellular influx inhibitor (slow channel blocker). 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.

3.2 Proposed Indication

It is proposed that Tiazac™ be approved for the treatment of angina pectoris.

3.3 Important Related Drugs

Three classes of medications are used in the treatment of angina pectoris. Their pharmacologic effects are directed toward altering the myocardial oxygen supply and demand relationship.

Nitrates are systemic as well as coronary arterial vasodilators. They reduce preload and afterload of the heart, produce coronary vasodilatation, relieve vasospasm and decrease the left-ventricular end-diastolic pressure and subendocardial wall tension[1]. The net effects of these actions are to increase coronary arterial flow and to shift the distribution of flow back toward subendocardial regions. Nitrates are the exogenous equivalent of the endothelium-derived relaxing factor and act by increasing intracellular levels of cyclic guanosine monophosphate (cGMP)[2]. The development of tolerance is a major disadvantage to chronic nitrate therapy, decreased effectiveness being encountered whenever a nitrate compound is regularly given without a 10- to 12-hr nitrate-free period[3,4] (e.g., 9 p.m. to 7 a.m.); during the nitrate-free period the patient should be on other anti-anginal therapy such as a beta blocker or calcium antagonist[1].

ß-adrenoceptor blocking agents decrease the myocardial and arterial responses to circulating and neuronally released catecholamines. They act primarily by reducing exercise-induced increases in heart rate and decreasing myocardial contractility, thus lowering the myocardial oxygen demand[1]. They are most useful in a patient with high sympathetic tone manifested by sinus tachycardia and elevated blood pressure. They also block reflex tachycardia that may be induced by nitroglycerine or arterial vasodilators[5]. In general, all ß-blockers are effective in the management of patients with stable angina pectoris; cardioselective ($ß_1$-receptor) blockers are preferred in patients with a history of bronchospastic disease, diabetes mellitus or peripheral vascular disease. In a specific subset of patients with chest pain suggestive of myocardial infarction, the risk of developing myocardial infarction was reduced by 13%[6,7]. Adverse effects of ß-blockers include excess bradycardia, hypotension, ventricular dysfunction, bronchospasm, inhibition of metabolic and circulatory response to hypoglycemia and cold extremities, and effects unrelated to ß-blockade such as impotence, lethargy, depression, confusion, hallucination and constipation.

Calcium channel antagonists decrease the entry of calcium through the slow, voltage-sensitive calcium channels of vascular smooth muscle cells. This action decreases resting tone in vascular, including coronary, smooth muscle. Diminished resting tone in coronary vessels increases flow through them. In general, they decrease myocardial oxygen requirements by producing arterial dilatation and reducing arterial blood pressure and afterload, and by reducing myocardial contractility[1]. There are five classes of calcium channel blockers:

(i) Dihydropyridines: these include isradipine, nifedipine, nicardipine, amlodipine, felodipine, nimodipine, nisoldipine, and nitrendipine;
(ii) Phenylalkylamines: e.g., verapamil, gallopamil and tiapamil;
(iii) Benzothiazepines: e.g., diltiazem and clentiazem;
(iv) Diarylaminopropylamines: e.g., bepridil (mixed calcium and sodium channel blocker; and
(v) Diphenylpiperazines.

The dihydropyridines have greater vascular selectivity whereas the non-dihydropyridines have greater myocardial selectivity and clinically evident inhibitory effect on the SA and AV nodes with beta-blocker like activity.

All classes of calcium antagonists are effective in the management of patients with stable angina pectoris. In general, calcium antagonists are as effective as ß-blockers with which they are frequently used concurrently. Calcium antagonists are of special value in patients who have conditions that may be made worse by ß-blockers such as asthma, chronic obstructive pulmonary disease or peripheral vascular disease. Elderly patients often tolerate calcium antagonists better than ß-blockers. Verapamil, which has a stronger negative inotropic effect, is useful in the management of patients with angina pectoris due to hypertrophic obstructive cardiomyopathy[1].

In unstable angina, many trials[8-11] have shown that verapamil, nifedipine and diltiazem can efficiently control chest pain with striking results in Prinzmetal's variant angina, but no reduction in the rate of myocardial infarction, death or severe refractory angina has been documented. In some studies using nifedipine as a single therapy, an unfavorable trend was found[8,9].

Adverse effects of calcium antagonists include ankle edema, headache, palpitations, flushing, hypotension and aggravation of angina due to coronary steal, especially with dihydropyridine derivatives (nifedipine, nicardipine, etc.). Atrioventricular nodal delay may occur with verapamil and diltiazem; rarely, higher degrees of heart block occur, particularly when these agents are used concurrently with a ß-blocker. Other side effects include constipation, particularly with verapamil. All calcium antagonists can have a negative inotropic effect, particularly verapamil.

Combination Drug Therapy for Stable Angina Pectoris: Patients with infrequent angina can be maintained effectively with short-acting nitrates. In patients with more frequent angina, the use of a long-acting ß-blocker or a calcium antagonist is advisable during the nitrate-free period to prevent the development of nitrate tolerance[1]. The use of a ß-blocker or either diltiazem or verapamil tends to block the reflex tachycardia produced by nitrates in some patients[1].

The combination of ß-blockers and calcium antagonists is widely used in the management of patients with stable angina pectoris. The combination of a ß-blocker with verapamil is particularly likely to worsen heart failure or cause heart block and should be used with caution in patients with left ventricular dysfunction or the elderly[1]. The combination of a ß-blocker and diltiazem is usually well-tolerated although it too can produce heart failure and heart block[1].

In severe stable angina pectoris, triple therapy is frequently used although it is often no more effective than double therapy and is associated with increased likelihood of adverse effects. The selection of ß-blocker and calcium antagonist should be individualized, and the determination of the optimal combination often requires a series of therapeutic trials with various combinations[1].

3.4 Chemistry, Manufacturing and Controls

The sponsor submitted that no significant changes have been made to the manufacturing process or formulation that was described in NDA 20-401. The same batch of beads used for the pivotal hypertension trials that were the basis of approval of Tiazac™ were also used for the angina study.

The batch numbers used were:

Placebo:	94C013
Diltiazem 120 mg	94C011
Diltiazem 180 mg	93M006
Diltiazem 240 mg	93M007
Diltiazem 360 mg	93M008

The expiry date was originally 31-Dec-1995, but this was extended (following additional stability tests) to 31-March-1996 because the study took longer than anticipated to complete.

3.5 Dosage form, route and dose regimens of administration

Trade Name:	Diltiazem OD ER
INN:	Diltiazem Hydrochloride
Substance No.	HR 1321A
Dosage form:	capsule
Frequency	2 capsules q.d.

The number of diltiazem or placebo (Pbo) capsules to be taken by each patient for each treatment in the double-blind phase of the study is given in the table below:

	Treatment Group												
	Placebo	120 mg		240 mg			360 mg			540 mg			
DAY	Pbo	120	Pbo	120	240	Pbo	240	360	Pbo	180	240	360	Pbo
1 to 3	2	1	1	1	0	1	1	0	1	0	1	0	1
4 to 7	2	1	1	0	1	1	0	1	1	0	0	1	1
8 to 14	2	1	1	0	1	1	0	1	1	1	0	1	0
15 to 21	2	1	1	0	1	1	0	1	1	1	0	1	0

3.6 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, 90 mg, 180 mg, 360 mg and 540 mg were -5.4, -6.3, -6.2, -8.2 and -11.8 mmHg, 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 measured following two week intervals of treatment was reduced by -3.7 mmHg with 120 mg/day versus -2.0 mmHg with placebo, by -7.6 mmHg after escalation to 240 mg/day versus -2.3 mmHg with placebo, by -8.1 mmHg after escalation to 360 mg/day versus -0.9 mmHg with placebo, and by -10.8 mmHg after escalation to 480/540 mg/day versus -2.2 mmHg with placebo.

Angina: Findings from the current study will be added.

3.7 Pharmacokinetics

Diltiazem is well absorbed from the gastrointestinal tract but undergoes substantial hepatic first-pass effect. The absolute availability 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 to 4.5 hr. 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 desmethyldiltiatem. 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 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 those 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 co-administered 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.

4. CLINICAL BACKGROUND

4.1 Effects of Calcium channel antagonists

Calcium ions play a role in mediating a number of vital cardiovascular functions[12,13]: regulation of the inotropic state of the myocardium, generation of impulses in the sinus and the atrioventricular nodes, and regulation of the tone of vascular smooth muscle including coronary arteries and peripheral resistance arterioles. Calcium channel blocking drugs inhibit the slow channels of the cell membrane which permit the entry of some sodium in addition to calcium and are activated much more slowly than the fast channels through which sodium predominantly enters to cause the initial rapid rise in the action potential. In addition to their effects on the slow channels, calcium channel antagonists can inhibit the availability of calcium ions for excitation coupling at intracellular sites, such as at the inner surface of the sarcolemma, sarcoplasmic reticulum or mitochondria or at any site where calcium may be made available as an excitation-response messenger[14].

Three distinct receptor sites for nifedipine, verapamil and diltiazem, respectively called N, V and D, have been identified on the calcium channel protein[15,16]. The greater overlap between V and D sites than between N and D or N and V sites explains in part the common pharmacologic properties of verapamil and diltiazem.

Four mechanisms have been proposed to explain the antianginal effects of calcium antagonists[17]: (1) coronary vaodilation; (2) decreased myocardial oxygen demand mediated by decreased

afterload, decreased heart rate and negative inotropic effect; (3) redistribution of blood flow to ischemic areas; and (4) direct cellular anti-ischemic effect.

4.1.1 Effects of calcium antagonists on vascular tissue

Depolarization of vascular smooth muscle cells is primarily dependent on the slow inward calcium movement through the calcium channel. Contraction of vascular smooth muscle is regulated by the cytoplasmic concentration of free Ca^{2+}. Three mechanisms are responsible for contraction of vascular smooth muscle cells[18]. The first is mediated by voltage-sensitive calcium channels that open in response to membrane depolarization. The second mechanism involves receptor-mediated hydrolysis of membrane phosphatidylinositol with the formation of inositol triphosphates which result in the release of intracellular calcium from sarcoplasmic reticulum. The third mechanism involves poorly defined receptor-operated calcium channels. In addition, vascular smooth-muscle cells have significantly less intracellular calcium stores than do myocardial cells and so rely more heavily on the influx of extracellular calcium[18] for contraction whereas cardiac and skeletal muscle rely on a recirculating internal pool of calcium. Because calcium-entry blockers are membrane-active drugs, they reduce the entry of calcium into cells and therefore exert a much larger effect on vascular wall contraction[19,20]. This preferential effects allows calcium-channel blockers to dilate coronary and peripheral arteries in doses that do not severely affect myocardial contractility or have little, if any, effect on skeletal muscle[20].

The calcium channel blockers are less active in veins than in arteries, and are ineffective at therapeutic doses (in contrast to nitrates) for increasing venous capacitance[21].

4.1.2 Effects of calcium antagonists on myocardial contractility

In contrast to vascular smooth muscle, in the myocardium there are only voltage-sensitive calcium channels. The voltage-sensitive calcium channel is subdivided into three subtypes: L (long lasting), N (nervous) and T (transient) based on their conductances and sensitivities to voltage[13]. Only L-type calcium channels are sensitive to calcium channel antagonists.

Force generation during cardiac muscle contraction depends, in part, on calcium influx during membrane depolarization. All calcium channel antagonists have been demonstrated to exert potent negative inotropic effects[22] in the following order of potency for depressing force development during constant pacing at similar concentrations[23]: nifedipine > verapamil > diltiazem. The negative inotropic effects of the calcium channel antagonists are dose-dependent. The excitation-concentration coupling of vascular smooth muscle is 3 to 10 times more sensitive to the action of calcium channel antagonists than is that of myocardial fibers[23]. Hence, the relatively low doses of these drugs used *in vivo* to produce vasodilatation or beneficial antiarrhythmic effects may not produce significant negative inotropic effects[24]. Furthermore, in intact animals and human beings, the intrinsic negative inotropic properties of these compounds are greatly modified by a baroceptor-mediated reflex augmentation of ß-adrenergic tone consequent to vasodilatation and a decrease in blood pressure[25,26]. While this mechanism plays an important role in patients with normal or nearly normal left ventricular function, it is unlikely to play a similar role in patients with severe congestive heart failure, in whom the baroceptor sensitivity is markedly attenuated[27].

4.1.3 Electrophysiologic effects

While verapamil, diltiazem, nifedipine and bepridil depress myocardial contractility, their electrophysiologic effects on the heart are different qualitatively[17]. Nifedipine and other dihydropyridines have a more selective action at the slow channels. Verapamil and diltiazem at higher doses inhibit currents in the fast channels similar to local anesthetics. Bepridil has known but poorly characterized type I antiarrhythmic properties.

Verapamil and diltiazem prolong the conduction and refractoriness of the AV node; the AH interval is lengthened more than is HV interval. The rate of discharge of the sinus

node, which depends on the calcium ion current, is depressed by all calcium channel blockers. In vivo, this effect can be compensated or overcompensated for by activation of baroceptor reflexes which increase sympathetic nervous activity[25,26].

In sinoatrial (SA) and AV nodal cells, verapamil and diltiazem modify slow-channel potentials in three ways[17]: (1) first there is a decrease in the rate of rise and slope of diastolic slow depolarization and an increase in the membrane threshold potential which reduces the rate of firing in the cell[28]; (2) second, the action potential upstroke is decreased in amplitude which slows conduction[29]; and (3) third, the duration of the action potential is increased[28]. These electrophysiological effects are dose related, and above the clinical range, electrical standstill may occur in SA and AV nodal cells[30]. Verapamil and diltiazem also exert a depressant effect on the AV node and in low concentrations directly prolong the effective AV nodal refractory period[31]. Verapamil may have additional vagomimetic effects[32].

4.1.4 Hemodynamic Effects of Calcium Antagonists

Calcium antagonists decrease coronary vascular resistance and increase coronary blood flow, nifedipine being the most potent. The decrease in blood pressure results in reflex tachycardia and positive inotropy mediated by sympathetic stimulation which outweighs the direct negative inotropic effect. The net result is a reduction of blood pressure, an improvement in myocardial contractility and a modest increase in heart rate and cardiac output. Verapamil induces a selective dilatation of arterial resistance vessels with little effect on venous resistance vessels, and had more direct negative chronotropic, chromotropic and inotropic effects than dihydropyridines. The directive negative inotropic effect of verapamil is partially offset by a decrease in afterload and the reflex increase in sympathetic tone, so that in patients without congestive heart failure, ventricular performance may improve. However, in patients with congestive heart failure, verapamil can cause a marked decrease in contractility and left ventricular function and is relatively contraindicated. Diltiazem also induces a selective dilatation of arterial resistance vessels. But it decreases heart rate and has a modest overall inhibitory effect on myocardial contractility. The negative inotropic and chronotropic effect of diltiazem is more modest than that of verapamil.

4.2 Relevant Human Experience with Calcium antagonists in treatment of ischemic heart disease

Over the last 20 years, multiple double-blind placebo-controlled clinical studies involving thousands of patients with stable effort angina have confirmed the efficacy of diltiazem and other calcium channel blocking agents[17,18]; patients show a reduction in chest pain attacks and nitroglycerine consumption, and improved exercise tolerance. Calcium-channel antagonists appear to be as safe and effective as ß-blockers and nitrates when used as monotherapies in patients with angina. There is no rebound symptoms upon abrupt withdrawal with verapamil, nifedipine or diltiazem[33,34].

4.2.1 Diltiazem in Stable Effort Angina

4.2.1.1 Diltiazem versus Placebo

Table Lit-1 shows the studies in which the efficacy of diltiazem in chronic stable effort angina was evaluated. In three studies[35-37], diltiazem (90 and 120 mg) prolonged exercise time before onset of angina by 29-57% and time to ischemic ST-segment depression by 75%, suppressed exercise induced angina by 47% and increased the workload to 1 mm ST-segment depression by 48% one to three hours after a single oral dose. One study of 14 patients with effort angina using atrial pacing to control heart rate[38] showed that the previously demonstrated antianginal effect of intravenous diltiazem was no longer apparent when the heart rate was kept constant. This suggests that the anti-ischemic effect of diltiazem in effort angina is primarily mediated by a reduction in

myocardial oxygen demand rather than improved myocardial oxygen delivery, a mechanism similar to that of ß-blockers. In 7 placebo-controlled blinded clinical trials, diltiazem (120-360 mg) prolonged exercise duration and time to 1 mm ST-segment depression and decreased the frequency of spontaneous anginal attacks[39-45]. The antianginal effect of diltiazem was dose dependent in a daily dose range of 120-360 mg[42] with progressive improvement in exercise duration to 1 mm ST-segment depression, total exercise time and time to angina in all patients.

Table Lit-1 Efficacy of diltiazem as an anti-ischemic agent in chronic stable angina: Diltiazem versus Placebo

Study	Design	Patients (n)	Treatment period (wks.)	Daily dose of Diltiazem (mg)	Endpoint
Koiwaya et al, 1981[35]	P	9	2h	90	TMT
Hossack et al, 1982[36]	No P	15	1h	120	TMT, CV HD
Wagniart et al, 1982[37]	DB, P	12	3 h	120	TMT
Joyal et al, 1986[38]	No P	14	15 min	1.4 µg/k/min i.v.	CV HD
Hossack et al, 1982[39]	SB, P, CO	57	2	120 - 240	TMT
Hossack and Bruce, 1981[40]	DB, P	10	2	120 - 240	TMT
Pool et al, 1980[41]	DB, P, CO	15	2	120 - 240	TMT
Go and Hollenberg, 1984[42]	DB, P, CO	11	2	360	TMT
Khurmi et al, 1984[43]	DB, P	17	52	360	TMT
Weiner et al, 1986[44]	DB, P, CO	18	3	240 & 360	D, TMT
Theroux et al, 1991[45]	P, DB, CO	60	2	360	TMT, HM

DB = double-blind; SB = single-blind; P = placebo-controlled; "No P" = nonplacebo-controlled; CO = cross-over; TMT = treadmill exercise time (total time or time to 1 mm ST-segment depression) and/or exercise workload; HM = Holter monitor evidence of myocardial ischemia; D = frequency of anginal attacks reported in a diary; CV HD = cardiovascular hemodynamic measurements before and during atrial pacing.

4.2.1.2 Diltiazem compared to or combined with a ß-blocker

Table Lit-2 Efficacy of diltiazem as an anti-ischemic agent in chronic stable angina: Diltiazem compared to ß-blockers

Study	Design	Patients (n)	Treatment period (wks.)	Daily dose of Diltiazem (mg)	Daily dose of Propranolol (mg)	Endpoint
Anderson et al, 1984[46]	DB, P, CO	12	3 h	120	100	TMT, RVG
Chaitman et al, 1984[47]	DB, P	15	1, 3, 8 h	120	80	TMT
Strauss and Parisi, 1985[48]	DB, P, CO	24	2	360	80 - 320	D, TMT
Johnston et al, 1985[49]	DB, P, CO	19	4	240	160	D, NT, TMT
Subramanian, 1983[50]	DB, P, CO	29	2	180 - 360	240	TMT, HM
El-Tamimi et al, 1989[51]	No P	11	1	120, 360	100 (atenolol)	TMT
Humen et al, 1986[52]	DB, No P	24	2	240 - 360	170 (mean)	TMT, RVG
Hung et al, 1983[53]	DB, P	12	2	360	240	TMT, RVG

DB = double-blind; P = placebo-controlled; "No P" = nonplacebo-controlled; CO = cross-over; TMT = treadmill exercise time (total time or time to 1 mm ST-segment depression) and/or exercise workload; RVG = Radionuclide ventriculography at rest and during exercise; HM = Holter monitor evidence of myocardial ischemia; D = frequency of anginal attacks reported in a diary; NT = sublingual nitroglycerine consumption

In two placebo-controlled double-blind clinical studies (Table Lit-2) comparing the acute effects of single oral doses of diltiazem (120 mg) and propranolol (80 and 100 mg) on exercise performance in 27 patients with stable effort angina[46,47], exercise time was prolonged significantly, being greater with diltiazem than with propranolol in one study[46]. In six chronic studies (Table Lit-2) comparing diltiazem (120-360 mg daily) to propranolol (80-320 mg

daily) or to propranolol (100 mg daily) in 119 patients with effort angina[48-53] the frequency of spontaneous anginal attacks and exercise-induced ischemia were equally suppressed by diltiazem and propranolol in all studies except one[53] in which high-dose diltiazem (360 mg daily) is more effective than propranolol (240 mg daily). The combination of diltiazem and propranolol or atenolol was well tolerated[53] and resulted in the same[51] or greater[48] improvement in exercise time and relief from angina.

4.2.1.3 Diltiazem versus Nifedipine

Diltiazem (180-360 mg daily) is more effective than nifedipine (30-120 mg daily) whether used as monotherapy or in combination with propranolol in reducing spontaneous or exercise-induced ischemia in patients with stable effort angina. Seven placebo-controlled trials[47,54-59] compared the anti-ischemic effects of diltiazem 120-360 mg daily with nifedipine 30-120 mg daily in 295 patients with stable effort angina (Table Lit-3). In the acute study[47], 20 mg nifedipine and 120 mg diltiazem were equally effective in improving total exercise time and time to 1 mm ST-segment depression 3 hours after oral administration, but the improvement in exercise time continued up to 8 hours after treatment with diltiazem but not nifedipine. In 3 placebo-controlled, comparative double-blind studies[54-56], diltiazem (180-360 mg daily) was more effective than nifedipine (30-120 mg) daily in reducing anginal frequency[54,55], improving total exercise time and time to 1 mm ST-segment depression[54,57], and decreasing ambulatory ischemia[54,55]. In two studies[54,55], nifedipine failed to affect any measure of ambulatory ischemia and was accompanied by no change[55] or an increase in mean hourly heart rates[54] unlike diltiazem[54,55] or propranolol[54] both of which effectively reduced ambulatory ischemia, the frequency of anginal episodes and exercise time to 1 mm ST-segment depression[54]. In two prospective placebo-controlled, blinded trials[56,58] of propranolol-nifedipine and propranolol-diltiazem combinations in 38 patients with stable effort angina, both combinations were found to be equally effective in reducing anginal frequency, nitroglycerine consumption and exercise-induced ischemia.

Table Lit-3 Efficacy of diltiazem as an anti-ischemic agent in chronic stable angina: Diltiazem compared to Nifedipine

Study	Design	Patients (n)	Treatment period (wks)	Daily dose of Diltiazem (mg)	Daily dose of Nifedipine (mg)	Endpoint
Stone et al, 1990[54]	P, DB, CO	56	2	360	79	D, NT, TMT, HM
Frishman et al, 1988[55]	P, DB, CO	20	2	180 - 360	30 - 120	D, NT, TMT, HM
Khurmi et al, 1987[56]	P	146	2-4	360	60	D, NT, TMT
Morse 1988[57]	P, SB, CO	19	4	120 - 360	30 - 90	D, NT, TMT
Johnston et al, 1985[58]	P, DB, CO	19	4	240	60	D, TMT, RVG
Schurtz et al, 1982[59]	DB, P, CO	20	2	180	30	TMT
Chaitman et al, 1984[47]	DB, P	15	1, 3, 8 h	120	20	TMT

DB = double-blind; SB = single-blind; P = placebo-controlled; CO = cross-over; TMT = treadmill exercise time (total time or time to 1 mm ST-segment depression) and/or exercise workload; RVG = Radionuclide ventriculography at rest and during exercise; HM = Holter monitor evidence of myocardial ischemia; D = frequency of anginal attacks reported in a diary; NT = sublingual nitroglycerine consumption

4.2.1.4 Diltiazem versus verapamil

Of three studies (Table Lit-4) comparing the anti-ischemic effects of diltiazem and verapamil in 237 patients with stable effort angina[56,60,61] the one double-blind cross over study showed that diltiazem (360 mg daily) was as effective as high dose verapamil (480 mg daily) at 6 and 37 weeks after starting therapy in reducing the frequency of spontaneous angina and exercise-induced angina[60].

Table Lit-4 Efficacy of diltiazem as an anti-ischemic agent in chronic stable angina: Diltiazem compared to Verapamil

Study	Design	Patients (n)	Treatment period (wks)	Daily dose of Diltiazem (mg)	Daily dose of Nifedipine (mg)	Endpoint
Khurmi et al, 1987[59]	P	146	2-4	360	60	D, NT, TMT
Weiner et al, 1985[60]	DB, CO	46	6, 37	360	480	D, NT
Khurmi et al, 1987[61]	P	45	16	360	360	TMT

DB = double-blind; P = placebo-controlled; CO = cross-over; TMT = treadmill exercise time (total time or time to 1 mm ST-segment depression) and/or exercise workload; D = frequency of anginal attacks reported in a diary; NT = sublingual nitroglycerine consumption

4.2.2 Efficacy of long acting (twice-a-day) diltiazem in chronic stable angina pectoris

In two studies of 268 patients[62,63] comparing sustained release diltiazem 90-180 mg bid versus placebo, the treadmill exercise time was increased significantly with diltiazem, and time to ST segment depression and time to angina were also increased significantly (Table Lit-5). Comparison of controlled-release diltiazem bid with standard diltiazem given t.i.d or q.i.d (Table Lit-5) showed that both formulations are equally effective[64-66] in reducing the number of anginal attacks. In 4 studies (Table Lit-5), controlled release diltiazem was compared to ß-blockers, namely, metoprolol[65,67], atenolol[68] and propranolol[69]. Exercise duration was longer and maximal workload was higher in patients on controlled release diltiazem than metoprolol[67] whereas with atenolol, the time to onset of 1-mm ST-segment depression was longer and the number of ischemic episodes during ambulatory monitoring lower with atenolol and combination therapy than with diltiazem[68].

Table Lit-5 Efficacy of long acting (twice-a-day) diltiazem as an anti-ischemic agent in chronic stable angina

Study	Design	Patients (n)	Treatment period (wks)	Dose of b.i.d Diltiazem (mg)	Daily dose of other drugs (mg)	Endpoint
Theroux et al, 1991[62]	P, DB, CO	60	2	180 mg bid	Placebo	TMT
Weiss et al, 1993[63]	P, DB	208	3, 12 hr	60, 90, 180,240 bid	Placebo	TMT
Vliegren et al, 1993[64]	DB, CO	49	7	90-180 mg bid	Std. diltiazem 60 - 120 mg tid	D, NT, TMT
Brorson et al, 1994[65]	DB, CO	13 + 23	1	120 mg bid 120 mg bid + metoprolol	Std diltiazem 60 mg qid Std + metoprolol	D, NT, MWL
Bowman et al, 1995[66]	DB, CO	41	1	90-180 mg bid	30-90 mg qid	D, NT, MWL
Vliegren et al, 1991[67]	DB	56	8-32	120 mg bid	Metoprolol 100 mg bid	TMT, MWL
Stefessen et al 1993[68]	DB, CO	25	3	120 mg bid	Atenolol 100 mg qd / combination	TMT, HM
Borzak et al, 1993[69]	DB, P	63	2	Mean = 350 mg in 2 doses	Mean = 293 mg propranolol in 2 doses or 79 mg nifedipine/3doses	TMT, D, NT, HM

DB = double-blind; P = placebo-controlled; CO = cross-over; TMT = treadmill exercise time (total time or time to 1 mm ST-segment depression) and/or exercise workload; MWL = maximal work load; HM = Holter monitor evidence of myocardial ischemia; D = frequency of anginal attacks reported in a diary; NT = sublingual nitroglycerine consumption

4.2.3 Efficacy of long acting (once-a-day) diltiazem in chronic stable angina pectoris

Recently, 8 clinical trials (Table Lit-6) compared the efficacy of diltiazem once/day preparations with placebo[70,71,78], standard diltiazem given tid[72-74], sustained-released diltiazem given bid[75], with atenolol once/day[76] and with sustained-released isosorbide dinitrate[77]. In 666 patients with chronic stable angina, diltiazem once/day significantly decreased angina episodes, decreased nitroglycerin consumption, and increased time to ischemic threshold and time to angina threshold compared to placebo[70-72,78]. Diltiazem once/day was as effective and safe for chronic stable angina as immediate-release diltiazem given tid[72-74] or sustained-released diltiazem given twice/day[75]. Both diltiazem-R once/day and atenolol significantly prolonged the exercise time and time to onset of 1-mm ST-segment depression, with atenolol decreasing heart rate at maximal work levels while diltiazem did not[76]. Significantly more marked and sustained therapeutic effects were observed with sustained-release isosorbide dinitrate than with sustained-release diltiazem; combined therapy increased the therapeutic effects (ST depression at 2, 6, 12 hours) significantly over that of the individual drugs[77].

Table Lit-6 Efficacy of long acting (once-a-day) diltiazem as an anti-ischemic agent in chronic stable angina:

Study	Design	Patients (n)	Treatment period (wks)	Dose of q.d Diltiazem (mg)	Daily dose of other drugs (mg)	Endpoint
Cutler et al, 1995[70]	P, DB	189	2	120, 240 or 480 mg qd	Placebo	TMT, D, NT, HM
Frances et al, 1995[71]	DB	182	1	200, 300 mg qd	Placebo	TMT, D, NT
Klinke et al, 1995[72]	DB, P	68	1	180, 360 mg qd	Std. diltiazem 60 - 120 mg tid or placebo	D, NT, TMT
Pool et al, 1994[73]	CO	195	8	120 - 360 mg qd	Std. diltiazem 30 - 120 mg tid	D, NT, TMT
Trimarco et al, 1995[74]	DB	144	4	200 - 300 mg qd	60 mg tid - qid	TMT
Savard et al, 1995[75]	DB	35	18 days	180, 240 or 360 mg qd	diltiazem SR 90, 120, 180 mg bid	D, NT, TMT
Kaku et al, 1994[76]	CO	7	2	100 mg qd	Atenolol 50 mg qd	TMT
Lehmann et al 1991[77]	DB, P, CO	14	5 days	120 mg	ISD 120 mg or ISD + diltiazem or placebo	TMT, MWL
Thadani et al, 1994[78]	DB, P	227	2	60, 120, 240, 360, 480 mg qd	Placebo	TMT, D,NT

DB = double-blind; P = placebo-controlled; CO = cross-over; TMT = treadmill exercise time (total time or time to 1 mm ST-segment depression) and/or exercise workload; MWL = maximal work load; HM = Holter monitor evidence of myocardial ischemia; D = frequency of anginal attacks reported in a diary; NT = sublingual nitroglycerine consumption

5. CLINICAL STUDIES

Foreign Marketing History

Tiazac™ has been approved under the name Viazem SR in the UK by the Medicines Control Agency on February 19, 1996. Marketing is planned for the end of the first quarter of 1997.

5.1 Proposed Indication

The sponsor requested approval of a new indication: stable angina pectoris.

5.2 Objective/Rationale

The objective of this trial is to evaluate the effect of multiple doses of Diltiazem OD ER (120 mg, 240 mg, 360 mg and 540 mg) taken once daily on exercise-induced angina pectoris and exercise-induced myocardial ischemia compared to placebo in subjects with chronic stable angina.

5.3 Design

The phases of the clinical trial included:

i) Single blind, Placebo, Washout Phase (2-3 weeks) -- Visit 0, 1
ii) Multiple dose, double blind, titration phase (1 week) – Visits 2 (or 2a), 3 and 4
iii) Multiple dose, double blind, maintenance phase (2 weeks) -- Visits 5 and 6
iv) Single blind, Placebo, Follow up phase (1 week) -- Visit 7.

Visits were as follows:
Visit 0: entry visit
Visit 1: after one week on placebo
Visit 2: after 2 weeks on placebo. Patient eligible for randomization at this visit.
Visit 2a: after 3 weeks on placebo. (This visit was only necessary if the subject did not qualify for randomization at Visit 2.)
Visit 3: 3 days after randomization (Visit 2 or 2a).
Visit 4: 7 days after randomization. End of titration phase.
Visit 5: 14 days after randomization.
Visit 6: 21 days after randomization. End of maintenance phase and start of final week on placebo.
Visit 7: after final week on placebo. End of study.

The study was a 6 week multicenter, double-blind, randomized, placebo-controlled, parallel-group, dose-response trial. Following a 2 to 3 week single-blind placebo washout phase, all eligible subjects were enrolled into the double-blind treatment phase.

Double blinding was ensured by having all active (120 mg, 180 mg, 240 mg, 360 mg) and placebo medications contained in size zero (0) opaque white capsules. All patients took two capsules (one from each of two bottles) of study medication once daily for every day they are in the study. These two capsules accommodated all randomized dose levels for the study. The number of Diltiazem or placebo (Pbo) capsules taken by each patient for each treatment in the double-blind phase of the study is given in the table below:

	Treatment Group												
	Placebo	120 mg		240 mg			360 mg			540 mg			
DAY	Pbo	120	Pbo	120	240	Pbo	240	360	Pbo	180	240	360	Pbo
1 to 3	2	1	1	1	0	1	1	0	1	0	1	0	1
4 to 7	2	1	1	0	1	1	0	1	1	0	0	1	1
8 to 14	2	1	1	0	1	1	0	1	1	1	0	1	0
15 to 21	2	1	1	0	1	1	0	1	1	1	0	1	0

Subjects were stratified according to the duration of their treadmill exercise test at Visit 2 (or 2a) as assessed by the Bruce Protocol:

Stratum 1: 3 to < 5 minutes
Stratum 2: 5 to 7 minutes

The Exercise Stress Test (Bruce Protocol) is described in the Table Pro-1 below.

Table Pro-1 Exercise Stress Test (Bruce Protocol)

EXERCISE STRESS TEST
BRUCE PROTOCOL

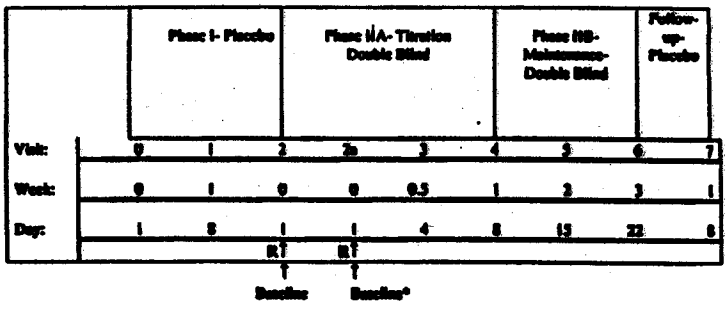
Stabilization Phase (Prior to Start of Actual Exercise)	Stage 0	The subject will NOT be walking on the treadmill belt. This time (Stage 0) will NOT be included in actual exercise duration			
	Stage	Speed (MPH)	Grade (%)	Duration (min.)	Cumulative Time Elapsed (min.)
During Actual Exercise	1	1.7	10	3	3
	2	2.5	12	3	6
	3	3.4	14	3	9
	4	4.2	16	3	12
	5	5.0	18	3	15
Post-Exercise Cooling-Down Phase	Although the subject may be walking on the treadmill belt as the machine gradually comes to a halt, this time will NOT be included in the actual exercise duration				

Within each stratum, subjects were randomly assigned to receive either placebo or one of the Diltiazem OD ER dose groups: 120 mg, 240 mg, 360 mg or 540 mg. Subjects assigned to the higher dose groups were forcibly titrated over a 7 day period. All subjects then received their target dose of drug for the 2 week maintenance phase. Thus, subjects were on double-blind treatment (placebo or active drug) for a total of 3 weeks, their dose being stable for the last 2 weeks of that period (either placebo, 120 mg, 240 mg, 360 mg or 540 mg daily). Following the 2-week, multiple-dose, maintenance phase, there was a one-week follow-up placebo phase.

The phases of the study are given in Table Pro-2 below:

Table Pro-2. Study Design Schematic

Study Schematic



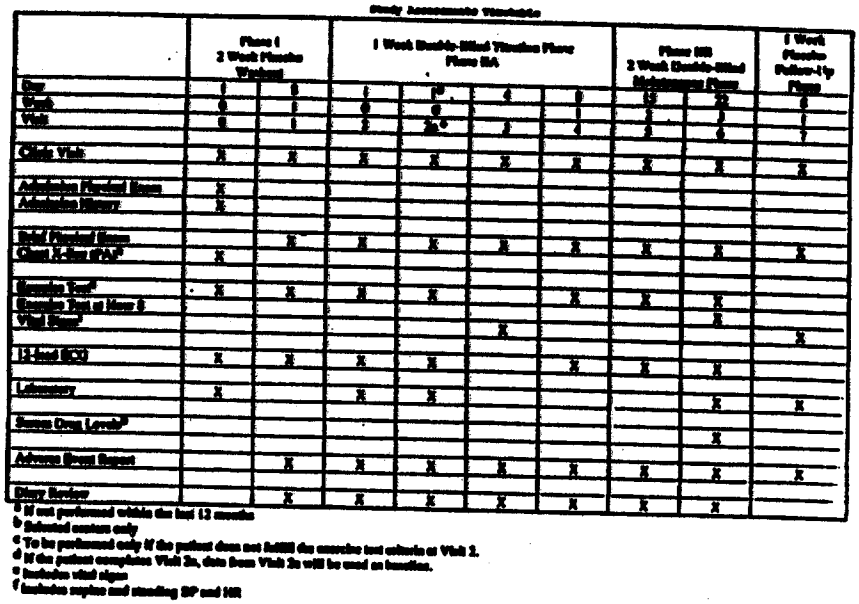
* If the patient completes Visit 2a, the data obtained from Visit 2a will be used as baseline.

Sublingual nitroglycerine prn was the only treatment for angina other than the study drug that was allowed throughout the trial. Vasoactive medications including ACE inhibitors, calcium channel blockers, ß-blockers, and long acting nitrates were discontinued prior to the washout phase or at admission (Visit 0). Subjects receiving a ß-blocker had the dose of their ß-blocker gradually reduced, but these subjects must be off their ß-blocker prior to being given the first bottle of placebo.

Later, the protocol was amended (on 02-May-1995) to allow up to 25 mg daily of hydrochlorthiazide (to control hypertension).

An outline of the procedures performed at each visit is given in the Table Pro-3 below.

Table Pro-3 Study procedures



5.4 Protocol

Title: *A dose response study of the safety and efficacy of diltiazem once-daily extended release in the treatment of chronic stable exercise-induced angina pectoris* (Protocol HR 1321A/8/USA/301/AP)

5.4.1 Population and Procedures

5.4.1.1 Definition of Disease: Chronic stable angina pectoris that is exercise limiting and caused by documented coronary disease (see below)

5.4.1.2 Inclusion Criteria

Subjects who

A. have chronic stable angina that
   1. is triggered by physical effort, and
   2. is relieved by rest and/or sublingual nitroglycerine, and
   3. has been experienced for the past 3 months or longer with no change in pattern or frequency.

   AND

   have coronary artery disease documented by one or more of the following:
   - angiography showing >60% obstruction in at least 1 major coronary artery, or
   - a positive thallium stress myocardial perfusion scintigram, or
   - a positive stress radionuclide cineangiogram showing regional dysfunction with failure of the normal rise in left ventricular ejection fraction with exercise, or
   - a history (> 3 months) of myocardial infarction (documented by ECG and elevated cardiac enzymes) or

- coronary by-pass graft or percutaneous transluminal coronary angioplasty (performed more than 6 months prior to subject admission).

B. at visits 1, 2 (or 2a) are able to exercise on a treadmill following the Bruce protocol between 3 and 7 minutes and develop angina pectoris PLUS ≥ 1 mm ST-segment depression (this ST depression is an addition to any minor ST depression (up to 0.5 min) that may be present at the pre-exercise resting ECG at each visit) persisting ≥ 0.08 seconds beyond the J-point during the exercise test.
AND
The total duration of exercise on treadmill between Visit 1 and Visit 2 (or 2A) must vary by ≤15%. {The variability is calculated from the equation: (L-S)/L where L= duration of exercise from the longer of the two tests and S = duration of exercise from the shorter of the two tests.}
[N.B. All exercise tolerance tests were made at "trough" levels, i.e., 24 hours after the last dose of study medication. In addition, at visit 6 (after 3 weeks of double blind treatment), a second exercise tolerance test was performed at 8 hours post-dose to measure peak effect.]

C. are least 18 years of age, of any sex, and any race.
If female, the patient must:

1. be post-menopausal for least one year, or
2. have had a hysterectomy, or
3. had had a tubal ligation, or
4. have taken (received) a contraceptive (oral, parenteral or implanted) for at least one month prior to study entry and agreed to continue use during the study, or
5. have an intrauterine device (IUD) in place at least 28 days prior to study entry and throughout the study, or
6. agree to use a spermicide and barrier methods, and
7. is non-nursing.

If female and pre-menopausal, the patient must have:

1. had normal menstrual flow within one month prior to study entry, and
2. a negative pregnancy test (serum B-subunit HCG RIA) at Visits 0 and 2 (or 2a).

5.4.1.3 Exclusion Criteria

Subjects who have

A. cardiac abnormalities (except exertional angina resulting from coronary artery disease) including arrhythmia requiring medication and/or artificial pacemaker, heart block (second degree, complete, left bundle branch), frequent and symptomatic PVCs, Wolff-Parkinson-White syndrome, basal changes of ST segment on ECG other than minor ST-T wave changes (up to 0.5 mm ST depression), left ventricular hypertrophy identified by ECG, congestive heart failure, clinically significant and uncorrected valvular heart disease, myocarditis, pericarditis, unstable angina pectoris, or known or suspected and uncorrected high grade left main coronary artery stenosis;

B. experienced a myocardial infarction within the last 3 months or undergone coronary artery bypass graft or PTCA within the past 6 months;

C. terminated the treadmill exercise testing at Visit 1 or Visit 2 (or Visit 2a) for a reason other than moderate angina (defined as the severity of pain that would ordinarily cause a subject to stop exercise during normal, everyday activity;

D. at Visit 2 (or 2a), a supine systolic blood pressure <90 or > 180 mmHg, or supine diastolic blood pressure > 104 mmHg; have a history of vasovagal syncope;

E. uncontrolled chronic illness other than coronary artery disease including a history of stroke, evidence of anemia, hyperthyroidism, renal impairment, hepatic impairment, active gastrointestinal ulcers, locomotion problems including those resulting from peripheral vascular disease or arthritis.

F. a requirement for medication (other than sublingual nitroglycerine prn) that is known to either influence angina pectoris/myocardial ischemia or the ischemic ECG response (such as ß-blockers, long acting nitrates, digoxin or psychotropic drugs);

G*. a requirement for antihypertensive medication (including diuretics);

H. kidney, liver, and/or hematological disease as evidenced by BUN > 50 mg/dl, serum creatinine > 2.0 mg/dl, total bilirubin > 2 mg/dl, SGOT or SGPT > 2 times upper limit of normal, WBC < 3.0/L, hemoglobin < 10.0 g/dl;

I. subjects who have received an experimental drug within 30 days prior to Visit 0;

J. a hypersensitivity to diltiazem;

K. any GI disorder affecting drug absorption;

L. body weight exceeding the Metropolitan Life Insurance upper limits by 50%;

M. planned elective surgery within the next 2 months.

[N.B. *On 02-May-1995, the protocol was amended to allow a maximum of 25 mg hydrochlorothiazide q.d. to control hypertension. The dose of hydrochlorothiazide was not to be changed during the period the patient was in the study. No other diuretics or any other anti-hypertensive medication was allowed. Any hypokalemia that occurred was to be controlled by diet alone without potassium supplements. The reason for this protocol change was poor recruitment rate of patients requiring medication for hypertension which would make it easier to find appropriate patients. The addition of hydrochlorothiazide was not expected to effect the assessment of angina as described in the protocol.]

5.4.2 Efficacy Endpoints

The following treadmill exercise testing variables were evaluated:

5.4.2.1 Primary Efficacy Variable

Total duration of exercise (sec)

This was defined as the total time the subject is able to exercise on the treadmill until he had to stop because of moderate angina (defined as the severity of pain that would ordinarily cause a subject to stop exercising during normal everyday activity), extreme fatigue, shortness of breath or the investigator believed that stopping the test was in the subject's best interests (e.g., >3 mm ST depression, arrhythmia, severe hypotension, etc.). Moderate angina must be the only reason the treadmill was stopped at Visits 1 and 2 (or 2a) or the patient was not eligible to participate in the double-blind phase of the study.

[N.B. All exercise tolerance tests were made at "trough" levels, i.e., 24 hours after the last dose of study medication. In addition, at visit 6 (after 3 weeks of double blind treatment), a second exercise tolerance test was performed at 8 hours post-dose to measure peak effect.]

5.4.2.2 Secondary Efficacy Variables

1. duration of exercise (sec) until the onset of angina
2. duration of exercise (sec) until the onset of ≥1 mm ST segment depression persisting ≥0.08 second beyond the J-point
3. angina attack rate (a diary of total number of anginal attacks/day was kept by patients)
4. nitroglycerine consumption (a diary of total nitroglycerine tablet consumption/day was kept by patients)

Patients' Diaries: Each patient documented the total number of angina attacks and total nitroglycerine tablet consumed on a daily basis in a diary. This information was reviewed by a study staff member at each clinic visit and the information transcribed onto the case report form.

5.4.3 Safety Variables

5.4.3.1 Clinical parameters

All reported or observed clinical adverse events were recorded.

5.4.3.2 Abnormalities in 12-lead ECG

Resting, supine ECG (resting stage ETT) was performed at Visits 0, 1, 2 (or 2a), 4, 5, and 6.

5.4.3.3 Laboratory Tests

The following laboratory tests were obtained before the exercise tests at Visits 0, 2 (or 2a), 6 and 7. Sample collection, sample transport and analysis were conducted by SmithKline Beecham Chemical Laboratories.

Hematology: Hemoglobin, hematocrit, WBC and differential counts, RBC and Platelet counts

Serum pregnancy: Serum B-subunit HCG RIA (not at visit 7)

Blood Chemistry: Glucose, BUN, serum creatinine, cholesterol, triglycerides, total bilirubin, alkaline phosphatase, LDH, SGOT, SGPT, sodium, potassium, chloride, calcium, CO_2, inorganic phosphorus

Urinalysis: specific gravity, pH, protein, glucose, cells

Diltiazem levels: A subset of 100 patients will have blood samples (10 ml) taken for plasma diltiazem levels from selected centers at the following time intervals:

Sample #1. after trough ETT and prior to dose
Sample #2. between 1 hour post-dose and 8 hour ETT
Sample #3. anytime after the final ETT & prior to discharge.

5.4.4 Statistical considerations

Baseline demographic and background variables were summarized by treatment group to assess comparability of each group at the beginning of the randomization phase. Descriptive statistics including means were compared for between-group homogeneity using either ANOVA or Mantel-Haenszel tests.

The primary analysis to evaluate treatment effect was based on each subject's last treatment evaluation (Endpoint analysis). The Endpoint analysis included all subjects with baseline and post-baseline data. An intent to treat analysis was done where the last known results for subjects dropping out prior to completing 3 weeks of double blind treatment were carried forward to the Endpoint analysis. In addition to the Endpoint analysis, results were analyzed at 1, 2 and 3 weeks of double-blind treatment (visits 4, 5 and 6 respectively) for subjects having data for that visit (time point analysis).

Comparisons of baseline and change from baseline data were made at each evaluation and at Endpoint using ANOVA model with treatment group, investigator, and stratification considered as fixed effects. Treatment by investigator and treatment by stratification interactions were considered as additional terms in the model. If the assumptions of normality and homogenous error variances were not satisfied, alternative analysis, e.g., Mantel-Haenszel tests, were used to assess efficacy. Where appropriate, time to event analysis were also performed. No adjustment in alpha-level was made for multiple comparisons.

At the Endpoint of the study, graphs of the mean (or median) total duration of exercise were used to facilitate a visual assessment of the dose-response relationship, and appropriate models applied to quantitatively describe the relationship between dose and response. Also, trough/peak percentages for total duration of exercise were calculated for each treatment group to summarize the percent of the peak effect remaining at trough, i.e., at approximately 24 hours post-dose.

The pharmacokinetic data were to be analyzed using non-linear mixed effect modeling techniques (NOMMEM). Information collected in the trial relative to different experiment variables (gender, weight, age, co-administration of drugs) were used to reduce the unexplained variability in the plasma concentrations and in the response to the drug.

5.4.4.1 Sample size:

The sample sizes required to demonstrate that Diltiazem OD ER increased total exercise time significantly more than placebo were calculated using change from baseline data. Two-tailed t-tests with alpha = 0.05 were used. The standard deviation was estimated as being 70 seconds (Reference: Thadani, U et al. Dose-response evaluation of once-daily therapy with a new formulation of diltiazem for stable angina pectoris. Presented as an abstract.) Power was calculated to detect a difference from placebo of 30, 45 and 60 seconds.

Based on these calculations, a total sample size of 250 subjects (50 placebo and 50 each in the four dose ranges of Diltiazem OD ER) is required to obtain adequate power (> 0.80) to detect an increase of ≥ 45 seconds in total exercise time for Diltiazem than for placebo based on a linear dose-response relationship.

5.4.4.2 Safety:

Safety data including laboratory assessments, vital signs, ECG and adverse events were tabulated and displayed by treatment group. Important changes from baseline in laboratory values were summarized. Adverse events were tabulated according to the affected body system.

5.4.4.3 Withdrawals:

Subjects withdrawing from the study for whatever reason and at any time were analyzed for between-group differences using a Mantel-Haenszel test.

5.4.4.4 Interim Analysis:

An interim analysis was intended when approximately one-half of the subjects had completed the study, for the purpose of evaluating efficacy, to design a further study, or to terminate a negative study. Total exercise time at Endpoint was to be analyzed using a very small alpha-level (0.0001) so that no alpha-level adjustment was necessary for the final analysis. These results were not to be used to modify the design or stop a positive study. Individuals directly involved with the conduct of the study were not able to identify treatment assignment for individual subjects or aware of the results of this analysis.

5.5 Protocol Amendment

One amendment was made on 02-May-1995.

The reasons for the protocol amendment were given as follows:

1) Impending transfer of sponsorship from Hoechst-Roussel Pharmaceutical Inc (HRPI) to Biovail Corporation International (BCI)
2) Adding a concomitant anti-hypertensive therapy (hydrochlorthiazide)
3) Change in Biovail personnel.

The changes made to the protocol in this amendment were as follows:

1) Change "HRPI" to "BCI"
2) Allow 25 mg daily of hydrochlorthiazide as treatment for concomitant hypertension
3) Change in Medical Monitor
4) Correction of minor mistakes in protocol (not affecting drug packaging, labeling, Case Report Forms or any study criteria).

5.6 Ethical Requirements

The sponsor submitted that the study complied with FDA guidelines relating to good clinical practice in clinical research and also with the ethical concepts described in the declaration of Helsinki.

5.6.1 Institutional Review Board

At each study site, an Institutional Review Board (IRB) reviewed and approved this protocol and the informed consent form prior to initiation of the study. The amendment to the protocol was also reviewed and approved by the same IRB before implementation of the amendment.

For sites that had no internal requirement to submit to a local IRB, a central IRB was chosen by BCI as follows:

The central IRB also reviewed and approved the protocol, informed consent form and the amendment to protocol. The central IRB also reviewed and approved any advertisements that were used by sites approved by them.

5.6.2 Informed Consent

Investigators using local IRBs designed their own consent forms. The central IRB designed consent forms for all sites approved by them. All consent forms were reviewed and approved by the sponsor (HRPI or BCI).

Subjects were enrolled in this study only after the investigator and his/her associate had obtained legally effective informed consent. All subjects were required to sign the IRB approved consent form prior to any study related procedure including tapering off any current medication.

5.6.3 Confidentiality

Subjects were identified in the CRFs by screening # (the investigator's 2 letter code/2 figure number), initials, date of birth, sex, and randomization number. If the subject's name appeared in any copies of reports, e.g., Chest X-ray, ECG, it was blacked out and replaced with initials.

5.6.4 Record Retention

Investigators were informed to keep all study documents, correspondence and pink copies of the CRFs for at least 2 years after the FDA approval date for the angina indication or until BCI informs them that the investigations have been discontinued and the NDA canceled.

7 Study Time Table

The first subject entered this study on 03-Oct-1994 and the last subject completed the study on 25-Mar-1996.

5.8 Investigators

The investigators (center numbers) are listed in the table below.

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6 RESULTS

6.1 Population enrolled/analyzed

388 subjects were considered for the study and signed consent forms. 12 dropped out or were withdrawn before they came for Visit 0 assessment and therefore had CRFs completed. The remaining 376 entered the placebo washout phase.

The sponsor attributed the strict entry criteria to the relatively high screen failure rate (119 patients failing to meet the criteria for randomization. The reasons for the 119 screening failures are as follows:

Did not meet Inclusion/Exclusion criteria:	71
Adverse events:	4
Investigator deemed withdrawal necessary for the patient's best interests:	8
Subject withdrew because they believed it was in their best interests:	5
Other reasons*:	31*

(* 15 of the 31 were withdrawn because of their exercise tolerance test results at Visit 0 which suggested to the investigators that they were unlikely to qualify at visit 1.)

Table Com-1 lists the patient disposition for the study.

There were 257 subjects were randomized into 5 treatment groups. 12 of these 257 subjects dropped-out prior to Visit 6 and one more dropped-out immediately after Visit 6. Thus, 244 subjects completed the study.

Table Com-1 Patient disposition

		Diltiazem QD LR				
	N	Placebo	120 mg	240 mg	360 mg	480 mg
Screened	376					
Randomized	257	50	52	54	52	49
* Patients in "high" stratum	170	36	33	32	35	32
* Patients in "low" stratum	87	13	18	22	17	16
Completed Study	244	47 (94.0%)	51 (98.1%)	50 (92.6%)	51 (98.1%)	45 (91.8%)
Premature Discontinuation	13	3 (6.0%)	1 (1.9%)	4 (7.4%)	1 (1.9%)	4 (8.2%)
Premature Discontinuations						
Adverse events	5	0	0	3	0	2
Lack of Efficacy	3	2	0	0	0	1
Others	5	1	1†	1	1	1‡
Time when discontinuations occurred						
Patient withdrew after Visit 3	3	1	1†	0	0	1
Patient withdrew after Visit 4	4	0	0	2	0	2
Patient withdrew after Visit 5	5	2	0	2	1	0
Patient withdrew after Visit 6	1	0	0	0	0	1‡
Summary of Patient Count at each Visit (Week)						
Placebo Washout: Visit 0 (Week -2)	257	50 (100%)	52 (100%)	54 (100%)	52 (100%)	49 (100%)
Visit 1 (Week -1)	257	50 (100%)	52 (100%)	54 (100%)	52 (100%)	49 (100%)
Randomization: Visit 2* (Week 0)	257	50 (100%)	52 (100%)	54 (100%)	52 (100%)	49 (100%)
End of Titration: Visit 4 (Week 1)	254	49 (98.0%)	51 (98.1%)	54 (100%)	52 (100%)	48 (98.0%)
Visit 5 (Week 2)	250	49 (98.0%)	51 (98.1%)	52 (96.3%)	52 (100%)	46 (93.9%)
Visit 6 (Week 3)	245	47 (94.0%)	51 (98.1%)	50 (92.6%)	51 (98.1%)	46 (93.9%)
Placebo Follow-up Visit 7 (Week 4)	244	47 (94.0%)	51 (98.1%)	50 (92.6%)	51 (98.1%)	45 (91.8%)

†: did not meet inclusion/exclusion criteria (walked > 7 min at ETT).
‡: withdrawal was associated with adverse event though it was not recorded as such.
*: patients stratified as "high" or "low" stratum in these rows do not add up.

6.2 Withdrawals

The causes of withdrawal of the 13 subjects are given in Table Com-2. The data on all 13 subjects are included in the safety analysis.

Of the 13 who dropped-out, 3 subjects withdrew prior to undergoing the ETT at Visit 4 (one week after randomization) and therefore data on these 3 subjects are not available for efficacy evaluation as defined by the protocol. They are #2204 (Placebo group - center/investigator = SM; reason: unable to keep clinic appointments), #1451 (Diltiazem 120 mg group - center/investigator = HY; reason: found not to meet inclusion/exclusion criteria) and #1003 (Diltiazem 540 mg group - center/investigator = GA; reason: unsatisfactory therapeutic response). Their data, however, are included in the safety analysis.

Table Com-2 Causes of Premature Withdrawals from the Study

ID #	Treatment Group	Last Visit completed	Reason for Withdrawal	Details of Reason for Withdrawal
2204	Placebo	3	Other	Unable to keep clinic appointment within study timeline.
2402	Placebo	5	Unsatisfactory therapeutic response	Experienced increased angina, EKG showed supraventricular tachycardia
6905	Placebo	5	Unsatisfactory therapeutic response	Angina worsened with episodes of angina at rest
1451	120 mg	3	Did not meet criteria for inclusion/exclusion	
5201	240 mg	4	Adverse Event	Headache, rash, constipation; patient discontinued 4 days prior to notifying investigator
5903	240 mg	4	Other	Missed several appointments for personal reasons; unable to return for visits within time window
7154	240	5	Adverse Event	Worsening ischemia. Hospitalized at Visit 5; had angiogram with angioplasty and stenting of Proximal LAD, and angioplasty of Diagonal and Ramus
7253	240 mg	5	Adverse Event	Injured right knee; unable to complete Visit 6.
5854	360 mg	5	Other	Unable to do Visit 6 due to equipment malfunction; subject dropped from study by investigator
1003	540 mg	3	Unsatisfactory therapeutic response	
2551	540 mg	6	Investigator deems necessary	Ankle edema; investigator thought patient should go back on standard therapy rather than stay on placebo another week
6102	540 mg	4	Adverse Event	Pruritic rash on buttock which spread to chest and forearm. Study medication stopped.
6401	540 mg	4	Adverse Event	Patient experienced abdominal bloating, shortness of breath, ankle edema and headaches

6.3 Demographic distribution:

The demographic distribution among treatment groups are similar with regard to age, sex and race (Table Com-3).

6.3.1 Centers:

36 of the 41 participating centers entered subjects. 32 of these 36 centers managed to randomize at least one subject. The number of randomized subjects per center varied between 1 and 24, and are given in Table Com-4, and the number of evaluable patients per center are given in Table Com-5. There was no center where a disproportionate number of patients was withdrawn.

Table Com-3 Demographic distribution

			Diltiazem CD LR				
		Placebo	120 mg	240 mg	360 mg	540 mg	P-value
Number of patients		50	52	54	52	49	
Age (years)	Mean (SE)	63.3 (1.4)	62.8 (1.4)	64.2 (1.2)	64.7 (1.3)	64.2 (1.3)	0.867
	Range	41-83	42-84	42-80	42-82	41-80	
Sex	Male (%)	40 (80.0%)	38 (73.1%)	43 (79.6%)	42 (80.8%)	36 (73.5%)	0.795
	Female (%)	10 (20.0%)	14 (26.9%)	11 (20.4%)	10 (19.2%)	13 (26.5%)	
Race	White (%)	45 (90.0%)	45 (86.5%)	45 (83.3%)	46 (88.5%)	43 (87.8%)	0.878
	Black (%)	4 (8.0%)	6 (11.5%)	7 (13.0%)	3 (5.8%)	5 (10.2%)	
	Other (%)	1 (2.0%)	1 (1.9%)	2 (3.7%)	3 (5.8%)	1 (2.0%)	
Height (in)	Mean (SE)	67.6 (0.6)	67.3 (0.5)	67.5 (0.5)	68.0 (0.5)	68.2 (0.5)	0.758
	Range	54-74	58-76	57-74	59-75	62-76	
Weight (lb)	Mean (SE)	187.3(4.5)	181.1(4.0)	186.3(4.1)	185.3(4.5)	185.2(5.5)	0.895
	Range	139-271	116-269	128-254	124-247	89-288	

Table Com-4 Randomized subjects per center

		Diltiazem CD LR				
Investigator	Placebo	120 mg	240 mg	360 mg	540 mg	Total
AB	1	0	0	0	0	1
BI	3	3	4	3	2	15
BL	1	0	0	0	1	2
CA	1	2	2	1	1	7
CH	1	1	1	1	2	6
CO	1	1	2	1	2	7
CT	4	5	5	5	5	24
DE	3	3	3	3	3	15
DH	0	1	2	2	0	5
FL	2	2	1	2	1	8
FM	2	1	0	1	1	5
GA	2	3	3	2	2	12
GL	2	2	3	2	3	12
GR	1	2	0	1	1	5
HY	0	1	0	0	0	1
JN	3	3	3	4	3	16
KA	2	1	2	2	2	9
KI	2	1	1	2	2	8
KN	1	1	0	0	0	2
LA	0	0	0	1	0	1
LE	2	3	3	3	3	14
LO	0	0	1	1	0	2
NA	0	1	2	0	1	4
PE	2	2	1	2	2	9
PO	0	1	1	2	1	5
RE	2	1	3	1	3	10
SM	4	5	4	3	4	20
SO	2	2	2	2	0	8
TO	1	1	1	1	1	5
WA	3	2	2	3	2	12
WE	0	1	1	0	0	2
WR	2	0	1	1	1	5
Totals	**50**	**52**	**54**	**52**	**49**	**257**

Table Com-5 Evaluable subjects per center

Investigator	Placebo	Diltiazem CD LR 120 mg	240 mg	360 mg	540 mg	Total
AB	1	0	0	0	0	1
BI	3	3	4	3	2	15
BL	1	0	0	0	1	2
CA	1	2	2	1	1	7
CH	1	1	1	1	2	6
CO	1	1	2	1	2	7
CT	4	5	5	5	5	24
DE	3	3	3	3	3	15
DH	0	1	2	2	0	5
FL	2	2	1	2	1	8
FM	2	1	0	1	1	5
GA	2	3	3	2	1	11
GL	2	2	3	2	3	12
GR	1	2	0	1	1	5
JN	3	3	3	4	3	16
KA	2	1	2	2	2	9
KI	2	1	1	2	2	8
KN	1	1	0	0	0	2
LA	0	0	0	1	0	1
LE	2	3	3	3	3	14
LO	0	0	1	1	0	2
NA	0	1	2	0	1	4
PE	2	2	1	2	2	9
PO	0	1	1	2	1	5
RE	2	1	3	1	3	10
SM	3	5	4	3	4	19
SO	2	2	2	2	0	8
TO	1	1	1	1	1	5
WA	3	2	2	3	2	12
WE	0	1	1	0	0	2
WR	2	0	1	1	1	5
Totals	**49**	**51**	**54**	**52**	**48**	**254**

6.4 Adherence to protocol

6.4.1 Randomization: 9 subjects were not randomized at visit 2 and went on to have a visit 2a. Of these, 4 subjects should have been randomized at visit 2 but were incorrectly continued for another week in the placebo run-in.

6.4.2 Visit interval: The target visit interval for the period from randomization to Visit 6 was 21 days, the objective being to have all subjects on their final dose level for at least 14 days. The actual visit intervals range from 17 to 24 days (given in Table Com-6), with the majority (173 subjects or 70.6%) having a visit interval of 21 days. Only 6 subjects were on their final dose level for less than 14 days (#1202, #2252, #5353, #5853, #5952 for 13 days, and # 7204 for 12 days, all in the 540 mg group).

6.4.3 Chest X-ray: The protocol required Chest X-ray to be done at visit 0 if the results were not available from a Chest X-ray done in the year prior to visit 0. Of 47 subjects who did not have a Chest X-ray done in the previous year, 39 had their Chest X-rays done 1-35 days late (attributed to scheduling difficulties) and 8 subjects erroneously said that they had a Chest X-ray done recently but was not documented in hospital records.

Table Com-6 Visit interval (days)

Visit interval	Diltiazem CD LR					
Visit interval	Placebo	120 mg	240 mg	360 mg	480 mg	Total
17	0	1	0	0	0	1
19	0	0	0	0	1	1
20	6	3	7	6	3	25
21	33	37	32	40	31	173
22	5	9	8	4	9	35
23	3	1	3	1	1	9
24	0	0	0	0	1	1
Totals	47	51	50	51	46	245

6.4.4 Trough BP and ETT: The protocol required BP measurement and ETT to be done at "trough" levels (i.e., 24 hours after the previous dose of medication). At visit 6, 32 subjects had their BP measured < 23 hours (including 2 subjects who had BP measured 4 and 8 minutes < 22 hours).

6.4.5 Peak ETT: 8 subjects had their "8-hour" ("peak" level) ETT done <7 1/2 hours (including subject #6051 at 5 hr 50 min, and subject #7151 at 5 hr 56 min post-dose).

6.4.6 Blood pressure range: At visit 2, a systolic BP >180 mmHg was cause for withdrawal. One subject (#7354) had a systolic BP of 188 mmHg, but was not withdrawn by investigator, completed the study in the placebo treatment group without adverse events.

6.4.7 Protocol violations and inclusion/exclusion criteria violations: The sponsor submitted that the following subjects are associated with various types of deviations from protocol:

#1703, #1704, #1705:	ST depression was measured from baseline, not isoelectric line.
#2352, #2451, #6351, and #6702:	At Visit 6, capsule count indicates that dosing on the day of Visit was from bottles labeled "Visit 6" (which contained placebo) rather than from Visit 5 bottles. The 8-hour post dose data reflects the effect of a placebo rather than an active dose in these subjects.
#5752:	Subject remained on 50 mg hydrochlorothiazide rather than the 25 mg allowed by the protocol amendment.
#5851:	The subject's thallium tests was technically negative because, although it showed a perfusion defect, it did not show reperfusion. No other documented evidence of coronary artery disease was available but the ETT showed significant ST depression. This subject was allowed to enter the study.
#5852:	The subject had stable angina but no documented proof of coronary artery disease. Cardiac catheterization showed no one artery blocked >60% but there was extensive diffuse blockage. This subject was allowed to enter the study.
#6701:	Took Lotensin throughout the study.
#6801:	Took Lasix throughout the study.
#6802:	Subject had PTCA only 5 months ago, but subject was allowed to enter the study.
#7154:	Took Prozac and Deseryl throughout the study.
#7252:	Subject had 50% obstruction in one vessel and less obstruction later in the same vessel. This was allowed to count as a 60% blockage and the subject was allowed to enter the study.

6.4.8 Subject compliance (capsule count)
Subject compliance was measured by capsule counts and subject diaries according to protocol for all trough measurements (24-hour post-dose).

For medication taken on the day of Visit 6, there were 4 cases of mis-compliance noted in the CRFs. For subjects #2351, #2451, #6351 and # 6702, the capsule count at Visit 6 indicated that dosing on the day of Visit 6 was from the bottles labeled "Visit 6" (which contained placebo) rather than from the Visit 5 bottles. Their 8-hour post-dose data thus reflects the effect of a placebo rather than an active dose in these subjects.

For subjects #6004, #6505, #7251 and #7353, it was discovered after the database was locked that these subjects did, indeed, take the assigned drug correctly, but the investigators had entered data incorrectly in the CRFs, making it appear as if the patients had not been compliant.

6.5 Baseline data comparability between the treatment groups

No statistically significant differences were found between the treatment groups with regard to the following variables (Table Com-7): Chest X-ray, Duration of angina, Normal duration of anginal attacks at entry, Normal frequency of anginal attacks, History of myocardial infarcts, History of angioplasty surgery, History of coronary artery bypass graft (CABG) surgery, Baseline 12-lead resting ECG abnormalities, Baseline blood pressure (supine and standing), Baseline heart rate (supine and standing).

Table Com-7 Comparability of baseline data

			Diltiazem OD ER				
		Placebo	120 mg	240 mg	360 mg	540 mg	P value
Number of patients		50	52	54	52	49	
Duration of angina (yr)	Mean (SE)	7.9 (0.9)	8.1 (0.9)	6.6 (0.7)	6.7 (0.7)	8.7 (1.1)	0.353
	Range	0-35	0-29	0-25	0-24	0-33	
Duration of attacks (min)	Mean (SE)	3.8 (0.6)	3.6 (0.5)	3.9 (0.5)	2.8 (0.3)	3.5 (0.5)	0.576
	Range	1-30	0-20	1-20	1-15	1-20	
Freq. of attacks (week)	Mean (SE)	3.4 (1.4)	2.6 (0.4)	2.2 (0.3)	2.4 (0.4)	2.5 (0.6)	0.841
	Range	0-70	0-14	0-7	0-15	0-28	
History of MI	N (%)	24 (48.0)	24 (46.2)	28 (51.9)	19 (36.5)	23 (46.9)	0.606
History of Angioplasty	N (%)	13 (26.0)	12 (23.1)	16 (29.6)	11 (21.2)	15 (30.6)	0.777
History of CABG	N (%)	16 (32.0)	15 (28.8)	15 (27.8)	11 (21.2)	10 (20.4)	0.615
Chest X-ray (Normal)	N (%)	30 (60.0)	32 (61.5)	40 (74.1)	32 (61.5)	30 (61.2)	0.585
(Abnormal)	N (%)	20 (40.0)	19 (36.5)	13 (24.1)	20 (38.5)	19 (38.3)	
(Not done)	N (%)	0	1 (1.9)	1 (1.9)	0	0	
Resting supine 12-lead EKG (Normal)	N (%)	13 (26.0)	16 (30.8)	24 (44.4)	11 (21.2)	11 (22.4)	0.059
(Abnormal)	N (%)	37 (74.0)	36 (69.2)	30 (55.6)	41 (78.8)	38 (77.6)	
Supine Systolic BP (mmHg)	Mean (SE)	144.4 (2.5)	142.3 (2.3)	138.9 (2.4)	136.5 (2.4)	137.4 (2.8)	0.159
	Range	108-188	110-177	110-180	90-168	92-178	
Supine Diastolic BP (mmHg)	Mean (SE)	81.8 (1.4)	83.6 (1.2)	80.9 (1.2)	81.7 (1.2)	81.1 (1.3)	0.589
	Range	56-103	65-98	57-100	60-102	62-100	
Supine Heart Rate (bpm)	Mean (SE)	73.0 (1.7)	68.3 (1.1)	71.8 (1.4)	68.9 (1.5)	71.3 (1.5)	0.121
	Range	49-108	53-91	46-95	45-92	54-94	
Standing Systolic BP (mmHg)	Mean (SE)	142.1 (2.6)	141.5 (2.5)	137.9 (2.6)	137.6 (2.4)	136.9 (2.5)	0.457
	Range	108-186	106-180	90-194	100-193	110-180	
Standing Diastolic BP (mmHg)	Mean (SE)	84.6 (1.3)	85.5 (1.3)	81.8 (1.4)	83.7 (1.4)	83.4 (1.4)	0.381
	Range	64-108	67-108	56-102	62-104	50-100	
Standing Heart Rate (bpm)	Mean (SE)	77.7 (1.7)	75.6 (1.3)	78.9 (1.4)	75.3 (1.8)	78.1 (1.7)	0.425
	Range	54-110	54-105	57-103	46-107	56-102	

There were no statistically significant differences between the treatment groups in medical history and findings at physical examination (Table Com-8) All but 3 subjects (#1054, #7451, %7501) were taking anti-anginal medication prior to entering the study, including short-acting nitrates, ß-blockers, calcium channel blockers and ACE inhibitors. 63 subjects were maintained on some form of diltiazem prior to entering the study.

Table Com-8 Comparability of medical history/previous illnesses and physical findings

		Diltiazem QD LR				
Clinical Features		Placebo	120 mg	240 mg	360 mg	540 mg
Number of Subjects		50	52	54	52	49
Arrhythmias		9	5	13	11	6
Congestive Heart Failure		2	3	3	0	0
Hypertension		30	22	27	26	26
Other cardiovascular dis.		14	16	11	12	14
EENT diseases		19	20	28	24	23
Respiratory diseases		15	9	9	5	17
Gastrointestinal diseases		19	20	29	20	18
Genitourinary diseases		14	19	21	22	15
Skin diseases		8	12	10	13	13
Musculoskeletal diseases		24	32	30	29	23
Neurological diseases		9	9	11	12	6
Endocrine dis. (general)		26	27	30	26	29
Diabetes mellitus		14	13	14	8	17
Major surgery		23	27	26	28	28
Allergies		16	21	17	19	21
Other		15	13	15	21	15
General appearance	(Normal)	48	48	51	49	47
	(Abnormal)	2	4	3	3	2
Head & Neck	(Normal)	39	39	42	42	35
	(Abnormal)	11	12	11	10	14
	(Not done)	0	1	1	0	0
Chest	(Normal)	42	42	43	41	39
	(Abnormal)	8	10	11	11	10
Abdomen	(Normal)	45	50	49	50	47
	(Abnormal)	5	1	4	2	2
	(Not done)	0	1	1	0	0
Extremities	(Normal)	43	44	48	42	42
	(Abnormal)	7	7	6	9	7
	(Not done)	0	1	0	1	0
Urogenital	(Normal)	23	20	23	21	21
	(Abnormal)	0	1	1	0	0
	(Not done)	27	31	30	31	28
Musculoskeletal	(Normal)	50	51	51	46	47
	(Abnormal)	0	0	2	6	2
	(Not done)	0	1	1	0	0
Skin	(Normal)	30	24	39	32	31
	(Abnormal)	20	28	15	20	17
	(Not done)	0	0	0	0	1
Neurological	(Normal)	49	51	53	49	49
	(Abnormal)	1	0	0	1	0
	(Not done)	0	1	1	2	0
Other	(Normal)	26	24	31	29	24
	(Abnormal)	1	1	2	0	2
	(Not done)	23	27	21	23	23
Resting supine 12-lead EKG	(Normal)	13	13	20	12	15
	(Abnormal)	37	39	34	40	34

6.5.1 Comparability of Exercise Tolerance Tests:

Subjects in the 5 treatments groups were comparable at baseline for total duration of exercise, time to onset of angina and time to onset of 1-mm ST-segment depression (Table Com-9). The extreme duration of exercise duration (8 min 24 sec) belonged to Subject #1451 who was dropped from the study prior to the next ETT at Visit 4, and was therefore excluded from efficacy analyses (being one of the 3 randomized but non-evaluable subjects).

Table Com-9 Comparability of Baseline* Exercise Tolerance Test data

		Diltiazem OD ER					
		Placebo	120 mg	240 mg	360 mg	540 mg	P value
Number of patients		50	52	54	52	49	
Total Duration of Exercise (sec)	Mean (SE)	340.1 (9.5)	330.7 (10.8)	323.1 (9.3)	334.0 (9.7)	336.0 (9.6)	0.785
	Range	189-420	184-504	189-418	187-420	185-417	
Time to Onset of Angina (sec)	Mean (SE)	248.8 (10.4)	245.1 (11.8)	231.6 (10.0)	242.4 (11.0)	253.2 (11.0)	0.684
	Range	120-377	59-420	80-410	96-414	112-400	
Onset of ST-segment depression† (sec)	Mean (SE)	262.6 (12.7)	263.0 (13.9)	265.8 (12.2)	262.6 (12.2)	259.3 (14.0)	0.998
	Range	40-418	30-420	30-400	100-400	80-416	

*: Baseline is defined at the evaluation at Visit 2 or Visit 2a.
†: onset of ≥1 mm ST-segment depression persisting ≥ 0.08 seconds beyond the J-point

6.6 **Efficacy considerations**

The following considerations were employed in the analysis of efficacy results:-

1. **Baseline** was the visit at which the subject was randomized (Visit 2 or 2a). The 3-week double blind treatment period began upon randomization.
2. **Endpoint** was considered Visit 6 (after 3 weeks of double blind study medication) for those who completed Visit 6 (n=245). For those subjects who completed Visit 4 or 5, but dropped out before Visit 6 (n=9), Endpoint was considered as Visit 4 or 5.
3. A **time point analysis** (for Visits 4, 5 and 6) was also performed for each variable. This analysis did not carry forward the last visit data for the drop-outs, and used data only from subjects who had values at these visits.
4. The outcome variable in the efficacy analysis was the *change* from a subject's baseline value to his or her endpoint. This is defined as *visit data minus baseline data*.
5. The **primary efficacy endpoint** was the **change in total duration of exercise for the exercise tolerance test (ETT).**
6. The **secondary efficacy endpoints** include **change in duration of exercise until onset of angina and change in duration of exercise until onset of ≥ 1 mm ST-segment depression persisting ≥ 0.08 seconds beyond the J-point.**
7. The secondary efficacy variables also included **changes in angina attack rate and in sub-lingual nitroglycerine use between baseline and endpoint.** For this analysis, the baseline is the mean of the week prior to randomization and the endpoint is the mean of the week prior to subject's last valid visit (Visit 4 or 5 or 6).
8. Treatment by center interaction was not statistically significant (P>0.10) for all efficacy variables.
9. No statistically significant interaction was observed between treatment effect and stratum.
10. For each variable, "trough" data is presented (i.e., data collected 24 hours after the last dose of study medication was taken).
11. For the primary variable, "peak" data was also presented (i.e., data from the ETT carried out 8 hours after the last dose of study medication was given at Visit 6).

6.7 The Primary Efficacy Variable - Total duration of exercise on ETT

In Table Eff-1, the endpoint analysis showed that there was a significant increase (P = 0.024 overall) in the time subjects walked on the treadmill relative to their baseline total duration of exercise on ETT at trough (24 hours after dosing) by 14 seconds (4.1%), 26 seconds (8.0%), 41 minutes (12.7%), 33 seconds (9.9%) and 32 seconds (9.4%), respectively, with placebo and with Tiazac™ at the doses of 120 mg (P = 0.332, not significant), 240 mg (P = 0.002), 360 mg (P = 0.030) and 540 mg (P = 0.051, not significant).

Table Eff-1 Mean improvement (seconds) in total duration of exercise at Endpoint

		Diltiazem OD ER				Overall
	Placebo	120 mg	240 mg	360 mg	540 mg	P value
Number of Subjects	49	51	54	52	48	
Baseline (seconds): Mean (SE)	343 (9.18)	327 (10.41)	323 (9.29)	334 (9.69)	339 (9.26)	0.565
Range						
Improvement (seconds) Mean (SE)	14 (8.15)	26 (6.40)	41 (7.19)	33 (7.51)	32 (6.43)	0.024
Range						
P-value†	-	0.332	0.002	0.030	0.051	

†: comparisons of diltiazem doses against placebo by two-way ANOVA model without interaction
(N.B. ANOVA for center by dose interaction: P = 0.974)

12 27 19 18

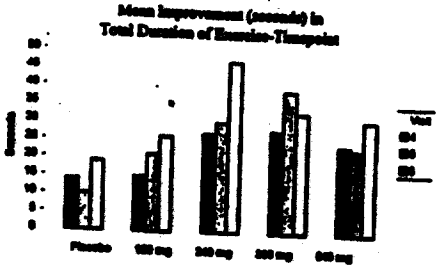
This finding was supported by time point analyses at Visits 5 and 6 (Table Eff-2 and Figure Eff-1), with the 240 mg group that showed significantly increased duration of exercise on ETT at both visits (P = 0.011 and P = 0.002, respectively) and the 360 mg group being significant at Visit 5 (P = 0.002) compared to placebo.

Table Eff-2 Time point analysis of Mean improvement (seconds) in total duration of exercise

				Diltiazem OD ER				Overall
			Placebo	120 mg	240 mg	360 mg	540 mg	P value
Visit 4	Baseline	N	49	52	54	52	48	
		Mean (SE)	343 (9.2)	327(10.4)	323 (9.3)	334 (9.7)	339 (9.3)	0.565
		Range						
	Improvement	Mean (SE)	14 (5.0)	15 (6.7)	27 (7.2)	28 (6.4)	24 (6.8)	0.220
		Range						
	P-value‡			0.930	0.119	0.100	0.271	
Visit 5	Baseline	N	49	51	52	51	46	
		Mean (SE)	343 (9.2)	327(10.4)	324 (9.6)	335 (9.8)	338 (9.5)	0.631
		Range						
	Improvement	Mean (SE)	10 (7.2)	21 (5.6)	30 (6.7)	39 (6.6)	23 (7.0)	0.014
		Range						
	P-value‡			0.314	0.011	0.002	0.112	
Visit 6	Baseline	N	47	51	50	51	46	
		Mean (SE)	346 (9.3)	327(10.4)	323 (9.8)	333 (9.8)	338 (9.5)	0.505
		Range						
	Improvement	Mean (SE)	19 (7.7)	26 (6.4)	47 (7.0)	33 (7.6)	31 (6.7)	0.019
		Range						
	P-value‡			0.527	0.002	0.057	0.122	

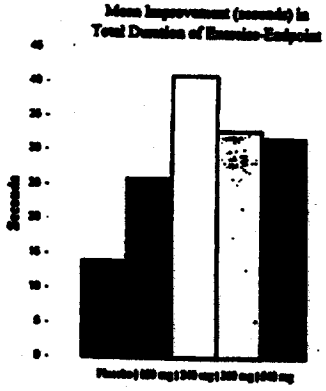
†: Overall treatment effect in the ANOVA model
‡: comparisons of diltiazem doses against placebo by two-way ANOVA model without interaction

Figure Eff-1 Mean improvement (seconds) in total duration of exercise (Time point analysis at Visits 4, 5 and 6)



The dose response curve was fairly flat (Figure Eff-2), the change in walking times increasing by 12 seconds when the dose was doubled from 120 mg (mean improvement = 14 seconds) to 240 mg (mean improvement = 26 seconds). Increasing the dose to 360 mg and 540 mg did not change the mean walking time beyond that seen in the 240 mg group.

Figure Eff-2 Improvement in total duration of exercise in relation to dose of diltiazem



An analysis of the duration of exercise at "peak" levels (i.e., ETT carried out 8 hours post-dose at Visit 6) also showed that all four diltiazem OD ER groups (including the 120 mg group) had statistically significant ($P < 0.001$ overall) increases in duration of exercise relative to the baseline total duration of exercise on ETT by 13 seconds (3.8%), 38 seconds (11.6%), 64 minutes (19.8%), 55 seconds (16.69%) and 42 seconds (12.4%), respectively, with placebo and with Tiazac™ at single oral doses of 120 mg ($P = 0.018$), 240 mg ($P < 0.001$), 360 mg ($P < 0.001$) and 540 mg ($P = 0.004$).

Table Eff-3. Means of Baseline and improvement (seconds) in total duration of exercise at "Peak" (Visit 6, 8 hours post-dose)

		Diltiazem OD ER				
	Placebo	120 mg	240 mg	360 mg	540 mg	Overall‡
Number of Subjects	47	51	50	50	46	
Baseline (seconds): Mean (SE)	346 (9.3)	327 (10.4)	323 (9.8)	331 (9.9)	338 (9.5)	P=0.497
Range						
Improvement (seconds) Mean (SE)	13 (6.7)	38 (7.8)	64 (9.0)	55 (8.6)	42 (9.3)	P<0.001
Range						
P-value†	-	0.018	<0.001	<0.001	0.004	

†: comparisons of diltiazem doses against placebo by two-way ANOVA model without interaction
‡: Overall treatment effect in the ANOVA model

6.8 Secondary Efficacy Variables

6.8.1 Number of anginal attacks per day

The endpoint analysis showed that while there were large variations in the response to diltiazem, the doses of 120 mg, 240 mg, 360 mg and 540 mg changed (reduced) the mean (range) number of anginal attacks statistically significantly (P = 0.001, overall) by -0.23 (-2.1 to -+0.3), -0.23 (-1.8 to 0.7), -0.19 (-2.4 to 1.4) and -0.24 (-1.4 to 0.1) respectively, whereas placebo increased the mean number of attacks by 0.21 (-1.4 to +4.4), (Table Eff-4).

Table Eff-4. Mean improvement in daily rate of anginal attacks at Endpoint

		Diltiazem OD ER				Overall
	Placebo	120 mg	240 mg	360 mg	540 mg	P value
Number of Subjects	49	51	53	49	48	
Baseline / per day: Mean (SE)	0.29 (0.06)	0.42 (0.10)	0.43 (0.08)	0.41 (0.09)	0.39 (0.09)	0.743
Range						
Improvement Mean (SE)	0.21 (0.13)	-0.23 (0.06)	-0.23 (0.06)	-0.19 (0.08)	-0.24 (0.05)	**0.001**
Range						
P-value†	-	**<0.001**	**0.001**	**0.001**	**0.001**	

†: comparisons of diltiazem doses against placebo by two-way ANOVA model without interaction

This finding is also supported by time point analysis, with the diltiazem treatments reducing the number of attacks significantly at Visits 4, 5 and 6, while placebo increased the number of attacks (Table Eff-5).

Table Eff-5. Time point analysis of mean improvement in daily rate of anginal attacks

			Diltiazem OD ER					Overall
			Placebo	120 mg	240 mg	360 mg	540 mg	P value
Visit 4	Baseline	N	49	51	53	49	48	
		Mean (SE)	0.29 (0.06)	0.42 (0.10)	0.43 (0.08)	0.41 (0.09)	0.39 (0.09)	0.743
		Range						
	Improvement	Mean (SE)	0.18 (0.10)	-0.22 (0.06)	-0.18 (0.05)	-0.14 (0.08)	-0.16 (0.07)	**0.019**
		Range						
	P-value‡			**0.002**	**0.008**	**0.015**	**0.008**	
Visit 5	Baseline	N	49	51	53	49	46	
		Mean (SE)	0.29 (0.06)	0.42 (0.10)	0.43 (0.08)	0.41 (0.09)	0.39 (0.09)	0.743
		Range						
	Improvement	Mean (SE)	0.13 (0.09)	-0.21 (0.06)	-0.16 (0.06)	-0.20 (0.07)	-0.15 (0.05)	**0.012**
		Range						
	P-value‡			**0.003**	**0.015**	**0.002**	**0.010**	
Visit 6	Baseline	N	49	51	49	49	46	
		Mean (SE)	0.29 (0.06)	0.42 (0.10)	0.45 (0.09)	0.41 (0.09)	0.33 (0.08)	0.623
		Range						
	Improvement	Mean (SE)	0.21 (0.13)	-0.23 (0.06)	-0.27 (0.06)	-0.19 (0.08)	-0.24 (0.06)	**0.001**
		Range						
	P-value‡			**0.001**	**<0.001**	**0.001**	**<0.001**	

†: Overall treatment effect in the ANOVA model
‡: comparisons of diltiazem doses against placebo by two-way ANOVA model without interaction

However, because the standard errors were large, and the range of anginal attacks at baseline for all doses started with zero, a non-parametric test was thought to be necessary. Reviewing data from patients' diaries for the frequency of anginal attacks showed that a large number of patients (74 (29%) of 255 patients) did not report any angina attack throughout the period of the diary recording. This made the number of patients who had recorded anginal attacks during the reporting period rather small in each group for making valid statistical comparisons.

Patients who had at least one attack of angina reported at any one visit from Visit 2 through Visit 6 were further subdivided into the following three groups (Table Eff 5-1):

(1) Patients in whom the number of anginal attacks reported at Visit 6 or the last visit (endpoint) did not change from that at Visit 2 (baseline);
(2) Patients in whom there was a reduction in the frequency of anginal attacks at Visit 6 or the last visit (endpoint) compared to that at Visit 2 (baseline) - i.e., showed improvement; and
(3) Patients in whom there was an increase in the frequency of anginal attacks at Visit 6 or the last visit (endpoint) compared to that at Visit 2 (baseline) - i.e., showed worsening of disease.

Table Eff 5-1. Frequency of anginal attacks

	Tiazac 540 mg	Tiazac 360 mg	Tiazac 240 mg	Tiazac 120 mg	Placebo	All
Number of patients	49	50	54	52	50	255
Number of patients with incomplete data	1	2	1	1	1	6
∴ Number of patients eligible for analysis	48	48	53	51	49	249
Number (%) of patients who had no angina attacks	18 (36.7)	12 (24.0)	12 (22.2)	15 (28.8)	17 (34.0)	74 (29.0)
∴ Number (%) of patients who had angina attacks	30	36	41	36	32	175
Number (%) without change in frequency of angina attacks	7 (23.3)	3 (8.3)	5 (12.2)	9 (25.0)	6 (18.8)	29 (16.6)
Number (%) who had reduced frequency of angina attacks	21 (70.0)	25 (69.4)	26 (63.4)	24 (66.7)	14 (43.8)	111 (63.4)
Number (%) who had increased frequency of angina attacks	2 (6.7)	8 (22.2)	10 (24.4)	3 (8.3)	12 (37.5)	35 (20.0)

Absence of any change in frequency of anginal attacks was observed in 8.3% to 25% of patients without any dose-response relationship.

There was a trend for dose-response relationship among patients who had reduction (improvement) in the frequency of anginal attacks, being highest (70%) for the highest dose (540 mg) of Tiazac™ and the least (43.8%) for placebo (with the exception of Tiazac™ 120 mg dose group).

Similarly, there was a trend for dose-response relationship among patients who had an increase (i.e., worsening) in the frequency of anginal attacks, being the least (6.7%) for the highest dose (540 mg) of Tiazac™ and the highest (37.5%) for placebo (with the exception of Tiazac™ 120 mg dose group).

However, as mentioned above, while the numbers of patients showing improvement or worsening were all in the right direction, they were too small to be able to make valid statistical comparison or obtain statistically significant differences.

6.8.2 Consumption of sublingual nitroglycerine per day:

The endpoint analysis showed no statistically significant differences overall (P=0.098) between the 5 treatment groups (Table Eff-6), but the 240 mg, 360 mg and 540 mg treatment groups showed reductions in nitroglycerine tablet consumption statistically significant from the placebo group which showed an increase.

Table Eff-6 Mean reduction in rate of nitroglycerine tablets used per day at Endpoint

		Diltiazem OD ER					Overall
	Placebo	120 mg	240 mg	360 mg	540 mg	P-value
Number of Subjects	49	51	53	49	48	
Baseline / per day: Mean (SE)	0.18 (0.05)	0.23 (0.05)	0.31 (0.09)	0.23 (0.08)	0.25 (0.08)	0.775
Range						
Improvement Mean (SE)	0.09 (0.11)	-0.13 (0.05)	-0.17 (0.07)	-0.16 (0.08)	-0.15 (0.07)	0.098
Range						
P-value†	-	0.06	0.018	0.023	0.026	

†: comparisons of diltiazem doses against placebo by two-way ANOVA model without interaction

By time point analysis (Table Eff-7), placebo was found to increase the mean number of nitroglycerine tablets used by 50% or more whereas the diltiazem 120 mg, 240 mg, 360 mg and 540 mg treatments reduced the number of nitroglycerine significantly (compared to placebo group) at visit 4, and the diltiazem 240 mg, 360 mg and 540 mg treatments reduced the number of nitroglycerine significantly (compared to placebo group) at Visits 5 and 6.

Table Eff-7. Time point analysis of mean reduction in rate of nitroglycerine tablets used per day

			Diltiazem OD ER				Overall
		Placebo	120 mg	240 mg	360 mg	540 mg	P-value
Visit 4	Baseline	N	49	51	53	49	48	
		Mean (SE)	0.18 (0.04)	0.23 (0.05)	0.31 (0.09)	0.23 (0.08)	0.25 (0.08)	0.775
		Range						
	Improvement	Mean (SE)	0.14 (0.10)	-0.16 (0.05)	-0.18 (0.06)	-0.13 (0.06)	-0.11 (0.07)	0.071
		Range						
	P-value‡			0.018	0.008	0.035	0.044	
Visit 5	Baseline	N	49	51	53	49	46	
		Mean (SE)	0.18 (0.04)	0.23 (0.05)	0.31 (0.09)	0.23 (0.08)	0.25 (0.08)	0.775
		Range						
	Improvement	Mean (SE)	0.09 (0.09)	-0.11 (0.05)	-0.12 (0.07)	-0.16 (0.08)	-0.10 (0.07)	0.154
		Range						
	P-value‡			0.069	0.049	0.018	0.074	
Visit 6	Baseline	N	49	51	49	49	46	
		Mean (SE)	0.18 (0.04)	0.23 (0.05)	0.32 (0.10)	0.23 (0.08)	0.22 (0.07)	0.742
		Range						
	Improvement	Mean (SE)	0.09 (0.11)	-0.13 (0.05)	-0.21 (0.07)	-0.16 (0.08)	-0.19 (0.06)	0.047
		Range						
	P-value‡			0.052	0.007	0.020	0.011	

†: Overall treatment effect in the ANOVA model

‡: comparisons of diltiazem doses against placebo by two-way ANOVA model without interaction

6.8.3 *Time to onset of angina*:

There are no statistically significant differences (P= 0.144) in the improvement in time to angina between placebo and the four diltiazem treatment groups at endpoint (Table Eff-8).

Table Eff-8. Mean improvement (seconds) from baseline to time to angina at Endpoint

		Diltiazem OD ER				Overall
	Placebo	120 mg	240 mg	360 mg	540 mg	P-value
Number of Subjects	48	50	52	48	45	
Baseline / per day: Mean (SE)	250 (10.6)	241 (11.8)	232 (10.4)	236 (11.3)	250 (10.9)	0.708
Range						
Improvement (seconds) Mean (SE)	28 (11.4)	10 (9.0)	37 (10.5)	22 (9.3)	16 (9.3)	0.144
Range						
P-value†	-	0.140	0.376	0.823	0.364	

†: comparisons of diltiazem doses against placebo by ANOVA model without interaction

Also, there are no statistically significant differences in improvement in time to angina between placebo and the four diltiazem treatment group by time point analysis (Table Eff-9) except for an overall significant difference (P=0.048) observed at Visit 5 which was not supported by the comparison of the improvement seen with each diltiazem dose to that with placebo.

Table Eff-9. Time point analysis of mean improvement (seconds) from baseline to time to angina

			Diltiazem OD ER				Overall
		Placebo	120 mg	240 mg	360 mg	540 mg	P-value
Visit 4	Baseline N	45	46	49	45	40	
	Mean (SE)	245 (10.8)	233 (11.4)	229 (10.7)	234 (11.6)	247 (12.2)	0.747
	Range						
	Improvement Mean (SE)	19 (8.5)	5 (6.6)	25 (9.3)	24 (9.5)	15 (8.9)	0.232
	Range						
	P-value‡	-	0.101	0.886	0.641	0.525	
Visit 5	Baseline N	44	46	46	45	40	
	Mean (SE)	248 (11.1)	241 (11.7)	221 (9.7)	236 (12.1)	244 (11.3)	0.462
	Range						
	Improvement Mean (SE)	21 (9.4)	7 (8.7)	16 (9.6)	40 (8.5)	19 (8.6)	0.048
	Range						
	P-value‡	-	0.138	0.599	0.127	0.917	
Visit 6	Baseline N	42	43	46	44	36	
	Mean (SE)	246 (11.3)	227 (11.6)	226 (10.7)	234 (11.5)	242 (12.3)	0.682
	Range						
	Improvement Mean (SE)	30 (12.6)	14 (9.1)	47 (10.7)	22 (10.0)	5 (9.0)	0.097
	Range						
	P-value‡	-	0.260	0.266	0.854	0.193	

†: Overall treatment effect in the ANOVA model
‡: comparisons of diltiazem doses against placebo by two-way ANOVA model without interaction

6.8.4 *Time to onset of 1 mm ST-segment depression*:
There are no statistically significant differences (P= 0.337) in the improvement in time to onset of 1 mm ST-segment depression between placebo and the diltiazem treatment groups except the 360 mg treatment group at endpoint (Table Eff-10).

Table Eff-10 Mean improvement (seconds) from baseline to time to 1 mm ST-segment depression at Endpoint

		Diltiazem CD LR				Overall
	Placebo	120 mg	240 mg	360 mg	540 mg	P-value
Number of Subjects	45	43	51	48	43	
Baseline / per day: Mean (SE)	262 (12.2)	248 (14.9)	263 (12.6)	260 (12.8)	257 (14.9)	0.943
Range						
Improvement (seconds) Mean (SE)	6 (11.6)	27 (9.7)	20 (9.6)	36 (10.9)	25 (10.2)	0.337
Range						
P-value†	-	0.136	0.148	0.041	0.219	

†: comparisons of diltiazem doses against placebo by ANOVA model without interaction

Also, there are no statistically significant differences in improvement in time to 1 mm ST-segment depression between placebo and the four diltiazem treatment group by time point analysis (Table Eff-11) except for a significant difference (P = 0.011) observed at Visit 5 for diltiazem 540 mg treatment group.

Table Eff-11 Time point analysis of mean improvement (seconds) from baseline to time to 1 mm ST-segment depression

			Diltiazem CD LR				Overall
		Placebo	120 mg	240 mg	360 mg	540 mg	P-value
Visit 4	Baseline N	37	38	46	36	38	
	Mean (SE)	254 (13.1)	239 (15.6)	262 (12.8)	246 (14.5)	250 (16.1)	0.826
	Range						
Improvement	Mean (SE)	4 (10.6)	22 (9.4)	17 (11.1)	16 (12.8)	19 (8.9)	0.326
	Range						
P-value‡			0.055	0.075	0.258	0.129	
Visit 5	Baseline N	43	38	42	38	37	
	Mean (SE)	258 (12.5)	236 (15.6)	253 (14.1)	242 (13.7)	244 (15.6)	0.810
	Range						
Improvement	Mean (SE)	8 (8.6)	16 (12.4)	-1 (11.8)	33 (11.5)	43 (11.0)	0.027
	Range						
P-value‡			0.437	0.822	0.068	0.011	
Visit 6	Baseline N	38	38	40	38	34	
	Mean (SE)	257 (12.6)	231 (14.6)	260 (15.0)	237 (12.9)	234 (15.9)	0.468
	Range						
Improvement	Mean (SE)	10 (13.3)	26 (10.5)	26 (11.7)	35 (12.0)	28 (11.9)	0.455
	Range						
P-value‡			0.478	0.244	0.072	0.591	

†: Overall treatment effect in the ANOVA model
‡: comparisons of diltiazem doses against placebo by two-way ANOVA model without interaction

6.8.5 *ETT Trough/Peak percentages*:

The sponsor presented that the trough/peak percentages for the four diltiazem treatment groups were similar, being 97.6%, 96.1%, 96.8% and 99.4%, respectively, for diltiazem 120 mg, 240 mg, 360 mg and 540 mg treatment groups (Table Eff-12) and not different from placebo (102.3%).

Table Eff-12. Mean ETT Trough/peak percentages at Endpoint

			Diltiazem OD ER			
		Placebo	120 mg	240 mg	360 mg	540 mg
Number of Subjects		47	51	50	50	46
ETT Trough/Peak %	Mean (SE)	102.3 (1.7)	97.6 (1.6)	96.1 (1.8)	96.8 (2.2)	99.4 (2.0)
	Range					

However, using data from Table Eff-1 for trough effect and from Table Eff-3 for peak effect of the placebo and different doses of Dilatiazem OD ER, Table Eff-13 shows that the trough/peak ratios of the mean improvements in total duration of exercise on ETT with Diltiazem OD ER are similar within the active treatment groups (without any dose-response relationship) and quite different from that observed with placebo.

Table Eff-13. Mean Improvement in ETT at Trough/Peak (percentages) at Endpoint

	Diltiazem OD ER				
	Placebo	120 mg	240 mg	360 mg	540 mg
Number of Subjects	47	51	50	50	46
Mean Improvement (sec) at trough†	14	26	41	33	32
Mean Improvement (sec) at peak*	13	38	64	55	42
Improvement at Trough /Improvement at Peak %	107.7	68.4	64.1	60.0	76.2

† From Table Eff-1; * From Table Eff-3

Subtracting the effect of placebo to obtain the effect of Diltiazem OD ER over placebo at trough and peak, Table EFF-14 shows that the improvement in ETT at trough by Diltiazem OD ER over placebo effect was about 45-62% of that observed at peak in the 4 Diltiazem OD ER treatment groups, without any dose-response relationship.

Table Eff-14. Placebo-subtracted Mean Improvement in ETT at Trough/Peak (percentages) at Endpoint

	Diltiazem OD ER			
	120 mg	240 mg	360 mg	540 mg
Number of Subjects	51	50	50	46
Mean Improvement (sec) over placebo at trough†	12	27	19	18
Mean Improvement (sec) over placebo at peak*	25	51	42	29
Improvement over placebo at Trough /Improvement over placeboat Peak %	48.0	52.9	45.2	62.1

† From Table Eff-1; * From Table Eff-3

6.9 Discussion on Efficacy Results

Recently, 8 clinical trials (Table Lit-6) compared the efficacy of diltiazem once/day preparations with placebo[70,71,78], standard diltiazem given tid[72-74], sustained-release diltiazem given bid[75], with atenolol once/day[76] and with sustained-released isosorbide dinitrate[77]. In 439 patients with chronic stable angina, diltiazem once/day significantly decreased angina episodes and nitroglycerin consumption, and increased time to ischemic threshold and time to angina threshold compared to placebo[70,71,72]. These reported results are compared to the results from this submission.

6.9.1 Improvement in total duration of exercise on ETT

The study protocol evaluated efficacy using, as an objective parameter, of the mean improvement in total duration of exercise on ETT at trough which was expected to show the 24 hour anti-ischemic and anti-anginal effects of extended-release diltiazem (Diltiazem OD ER). The mean improvement in the total duration of exercise on ETT at trough was statistically significant for 240 mg (P=0.002) and 360 mg (P=0.03) treatment groups compared to placebo.

Table EffDis-1 compares the mean improvement in total duration of exercise observed in similar studies[70,71,78] using the treadmill exercise time or ergometric parameters. All of these studies and the submission showed that extended-release Diltiazem at doses less than 240 mg (120 mg in the submission and in the study by Cutler et al[70], 200 mg used in the study by Frances et al[71], and 60 and 120 mg in the study by Thadani et al[78]) did not produce any significant improvement in total duration of exercised on ETT at trough.

Table EffDis-1. Comparison of change in mean total exercise time (SE) of the current study with other placebo-controlled double blind studies of single-dose, sustained-release diltiazem (results at trough)

	Test used	Treatment						
NDA 20-401			Placebo		Diltiazem QD doses			
					120 mg	240 mg	360 mg	540 mg
	TMT	2	14 (8.2) n=50		26 (6.4) n=52 P=0.332	42 (7.2) n=54 P=0.002†	33 (7.5) n=52 P=0.03†	32 (6.4) n=48 P=0.051†
Cutler et al. 1995[70]	Test used	Treatment	Placebo		Diltiazem QD doses			
					120 mg	240 mg		480 mg
	TMT	2	19.6 (7.8) n=50		36.5(8.4) n=42	49.2 (8.0) n=48 P<0.05†		56.1 (7.5) n=47 P<0.05†
Frances et al. 1995[71]	Test used	Treatment	Placebo		Diltiazem QD doses			
						200 mg	300 mg	
	EMP	1	37.3 (10.2) n=59			64.0 (12.1) n=54	71.4(10.5) n=66 P<0.05†	
Thadani et al. 1995[78]	Test used	Treatment	Placebo		Diltiazem QD doses			
				60 mg	120 mg	240 mg	360 mg	480 mg
	TMT	2	29 (8) n=38	40 (9) n=37‡	56 (11) n=37‡	51 (10) n=39‡	69 (12) n=40‡	68 (12) n=36‡

TMT = treadmill exercise time (total time or time to 1 mm ST-segment depression) and/or exercise workload; EMP = ergometric parameters; †: comparisons of diltiazem doses against placebo by ANOVA model without interaction; ‡: P = 0.004 for linear dose trend across all 6 study groups.

240 mg/day was the lowest dose of Diltiazem OD ER which produced a significant improvement in total duration of exercise on ETT observed in this submission as well as in the study by Cutler et al[70]; the study by Thadani et al[78] did not have sufficient power to detect significant improvements by pairwise comparisons (because of small sample size) at this dose.

At the next higher dose, a dose-related stepwise increase in improvement in the total duration of exercise on ETT was detected the studies by Frances et al[71] (using 300 mg, p<0.05) and Thadani et al[78] (using 360 mg, P=0.004). In this submission the improvement continues to be significant at the level of 360 mg (p=0.03) but a dose-related stepwise increase was not observed.

The dose-related improvement in total duration of exercise on ETT was maintained at 480 mg in the study by Cutler et al[70] ((P<0.05) and Thadani et al[78] (P=0.01). At the highest dose studied (540 mg in this submission), there was no further dose-related improvement in total duration of exercise on ETT.

At peak levels of extended-release diltiazem (Table EffDis-2), the mean improvements in total duration of exercise on ETT were found to be statistically significant at doses 240 mg and above in this submission and in the study by Cutler at al[70]. While this submission also showed a statistically significant (P=0.018) - albeit clinically small (16.4%) - improvement in total duration of exercise on ETT at the 120 mg dose, this effect was not demonstrated in the study by Cutler et al[70] that enrolled a smaller number of patients.

Table EffDis-3. Comparison of change in mean total exercise time (SE) of the current study with another placebo-controlled double blind study of single-dose, sustained-release diltiazem (results at peak)

NDA 20-401	Test used	Treatment duration	Placebo	Diltiazem QD doses 120 mg	240 mg	360 mg	540 mg
	TMT	2	13 (6.7) n=50	38 (7.8) n=52 p=0.018†	64 (9.0) n=54 P=0.001†	55 (8.6) n=52 P=0.001†	42 (9.1) n=48 P=0.004†
Cutler et al. 1995[70]	Test used	Treatment duration	Placebo	Diltiazem QD doses 120 mg	240 mg		480 mg
	TMT	2	18.1 (7.8) n=50	17.1(9.5) n=42	42.8 (9.1) n=48 P<0.05†		43.6 (9.0) n=47 P<0.05†

TMT = treadmill exercise time (total time or time to 1 mm ST-segment depression) and/or exercise workload;
†: comparisons of diltiazem doses against placebo by ANOVA model without interaction

6.9.2 Change in anginal attack rate/day

Significant reductions in the mean rates of anginal attack (Table EffDis-3) were observed in all dose levels in this submission as well as in two other comparable studies reporting this endpoint[70,78]. The study by Frances et al[71] also observed a 68% decrease in weekly anginal attacks with 200 mg and a 64% decrease with 300 mg, compared to only a 15% decrease with placebo.

Table EffDis-3. Comparison of change in mean (SE) daily anginal attack rate (frequency/day reported in a diary) from baseline observed in this submission with other placebo-controlled double blind studies of single-dose, extended-release diltiazem

NDA 20-401	Placebo		Diltiazem QD doses 120 mg	240 mg	360 mg	540 mg
	0.21 (0.13) n=49		-0.23 (0.06) n=51 P<0.001†	-0.23 (0.06) n=53 P=0.001†	-0.19 (0.08) n=49 P=0.001†	-0.24 (0.05) n=48 P=0.001†
Cutler et al. 1995	Placebo		Diltiazem QD doses 120 mg	240 mg		480 mg
	-0.1 (0.3) n=50		-1.3 (0.4) n=42 P<0.05†	-1.1 (0.3) n=48 P<0.05†		-1.2 (0.3) n=48 P<0.05†
Thadani et al. 1994	Placebo	60 mg	Diltiazem QD doses 120 mg	240 mg	360 mg	480 mg
	-1.9 (0.8) n=39	-0.6 (0.6) n=37‡	-1.5 (0.6) n=37‡	-2.7 (0.9) n=39‡	-2.9 (0.8) n=40‡	-1.8 (0.4) n=35‡

†: comparisons of diltiazem doses against placebo by ANOVA model without interaction
‡: p=0.04 for linear dose trend across all 6 dose groups.

6.9.3 Nitroglycerine consumption

A significant reduction in nitroglycerine tablets consumed per day was reported in this submission and in the study by Cutler et al[70] at 240 mg (Table EffDis-4); only this submission showed continuation of significant reductions in nitroglycerine tablet consumption at higher doses (360 mg and 540 mg). Thadani et al[78] reported that no significant reductions in nitroglycerine consumption were observed across the range of doses used. The study by Frances et al[71] reported a 70% reduction in nitroglycerine consumption with both (200 mg and 300 mg) dose levels whereas no reduction in nitroglycerine consumption was observed in the placebo group.

Table EffDis-4. Comparison of reduction in mean (SE) rate of nitroglycerine tablets used per day observed in the current study with other placebo-controlled double blind studies of single-dose, sustained-release diltiazem

NDA 20-401	Test used	Placebo	Diltiazem QD doses 120 mg	240 mg	360 mg	540 mg
	NT	0.09 (0.11) n=49	-0.13 (0.05) n=51 P=0.06†	-0.17 (0.07) n=53 P=0.018†	-0.16 (0.08) n=49 P=0.023†	-0.15 (0.07) n=48 P=0.026†
Cutler et al. 1995	Test used	Placebo	Diltiazem QD doses 120 mg	240 mg		480 mg
	NT	-0.4 (0.2) n=50	-0.9 (0.3) n=42 NS	-1.0 (0.2) n=48 P<0.05†		-0.5 (0.2) n=48 NS

NT: sublingual nitroglycerine tablets consumption; NS = not significant
†: comparisons of diltiazem doses against placebo by ANOVA model without interaction

6.9.4 Time to onset of angina

The submitted NDA and a comparable study by Thadani et al[78] showed no improvement in time to angina across all doses of extended-release diltiazem at trough (Table EffDis-5). The study by Thadani et al[78] showed significant increase in time to angina with linear dose trend at peak (4 hr) levels of all doses of diltiazem. In contrast, Frances et al[71] reported significant subjective improvement in time to angina by 93% to 96% at trough (22-26 hours after) 200 mg and 300 mg doses of diltiazem, respectively; however, they used ergometric parameters rather than the treadmill exercise test.

Table EffDis-5. Comparison of change in mean (SE) time (seconds) to angina of the current study with other placebo-controlled double blind studies of single-dose, sustained-release diltiazem

NDA 20-401	Test used	Placebo		Diltiazem QD doses 120 mg	240 mg	360 mg	540 mg
	TMT	28 (11.4) n=48		10 (9.0) n=50 P=0.140†	37 (10.5) n=52 P=0.376†	22 (9.3) n=48 P=0.823†	16 (9.3) n=45 P=0.364†
Frances et al. 1995 [71]	Test used	Placebo			Diltiazem QD doses 300 mg		
	EMP	43.9 (11.5) n=59			84.6 (13.2) n=54 P<0.05†	86.0 (11.9) n=66 P<0.05†	
Thadani et al. 1994 [78]	Test used	Placebo	60 mg	Diltiazem QD doses 120 mg	240 mg	360 mg	480 mg
	TMT	49 (10) n=38‡	40 (12) n=37‡	76 (15) n=37‡	69 (12) n=39‡	58 (15) n=40‡	82 (12) n=36‡

TMT = treadmill exercise time (total time or time to 1 mm ST-segment depression) and/or exercise workload; EMP = ergometric parameters; †: comparisons of diltiazem doses against placebo by ANOVA model without interaction; ‡ P = 0.08 for linear dose trends across all 6 study groups.

6.9.5 Time to onset of 1 mm ST-segment depression

No consistent results were found across different published studies for time to onset of 1 mm ST-segment depression (Table EffDis-6). The NDA submission found significant improvement in time to onset of 1 mm ST-segment depression only with the 360 mg dose of diltiazem. Cutler et al[70] reported significant improvements with 240 mg and 480 mg diltiazem, Frances et al[71] with 300 mg diltiazem, and Thadani et al[78] reported a statistically significant (P=0.007) linear dose trend for time to onset of 1 mm ST-segment depression.

Table EffDis-6. Comparison of change in mean (SE) time to 1 mm ST-segment depression of the current study with other placebo-controlled double blind studies of single-dose, sustained-release diltiazem

NDA 20-401	Test used	Placebo		Diltiazem QD doses 120 mg	240 mg	360 mg	540 mg
	TMT	6 (11.6) n=45		27 (9.7) n=43 P=0.136†	20 (9.6) n=51 P=0.148†	36 (10.9) n=48 P=0.041†	25 (10.2) n=48 P=0.219†
Cutler et al. 1995	Test used	Placebo		120 mg	Diltiazem QD doses 240 mg		480 mg
	TMT	19.6 (11.2) n=50		14.9 (12.0) n=42	48.0 (11.5) n=48 P<0.05†		62.6 (11.4) n=47 P<0.05†
Frances et al. 1995	Test used	Placebo			Diltiazem QD doses 240 mg	300 mg	
	EMP	47.0 (13.1) n=59			75.1 (14.5) n=54	91.5 (15.0) n=66 P<0.05†	
Thadani et al. 1994	Test used	Placebo	60 mg	Diltiazem QD doses 120 mg	240 mg	360 mg	480 mg
	TMT	34 (9) n=38‡	32 (12) n=37‡	55 (14) n=37‡	69 (14) n=39‡	65 (14) n=40‡	75 (13) n=36‡

TMT = treadmill exercise time (total time or time to 1 mm ST-segment depression) and/or exercise workload; EMP = ergometric parameters; †: comparisons of diltiazem doses against placebo by ANOVA model without interaction; ‡ P = 0.007 for linear dose trends across all 6 study groups.

7 SAFETY REVIEW

The safety update report included reports on patients from this study on angina pectoris as well as on two studies of diltiazem on hypertension, namely, study 103 (McMahon) and study 104 (Lacourciere) which were randomized, double-blind, placebo-controlled multicenter investigations of Tiazac™ in patients with mild to moderate hypertension. Also, the analysis for safety included all individuals entered into the trials (i.e., intent-to-treat patient population).

A total of 511 patients from the three Tiazac™ studies were included, of which 404 patients were exposed to the active medication. In the angina study, patients were exposed for 3 weeks and in the hypertension studies, patients were exposed for 8 weeks to the active medication. The dosage used in these studies ranged from 90 to 540 mg.

Safety was assessed in terms of physical examinations, clinical and laboratory parameters, ECG findings, incidence/severity of adverse reactions and discontinuations.

7.1 Deaths

There were no deaths in any of these three studies.

7.2 Serious Adverse Events (SAEs)

A total of four serious adverse events were reported in two of the three studies (Table Saf-1). There were no serious adverse events in the course of Hypertension Study 104 (Lacourciere).

Table Saf-1: Serious adverse events

Study	Serious Adverse Event	Comments	Outcome
Angina	worsening of ischemia	#7154 in Diltiazem 240 mg group	Recovery
Angina	acute bronchitis	Patient was not randomized	Recovery
HTN 103	allergic reaction	Possible drug related	Recovery
HTN 103	right lower lobe pneumonia	Patient on placebo	Recovery

HTN 103: Hypertension study 103 (McMahon)

Of the two subjects with serious adverse events in the angina study, one subject was hospitalized for acute bronchitis and, upon discharge, was still unable to walk on the treadmill because of cough and shortness of breath, and thus failed to qualify for randomization into the study.

The other subject (#7154), randomized to 240 mg Diltiazem, completed Visit 5 and developed worsening ischemia requiring hospitalization for angiography and angioplasty and stenting of Proximal LAD, and angioplasty of Diagonal and Ramus. He recovered completely from the event.

Thadani et al[78] reported serious adverse events (defined as events resulting in death, hospitalization, permanent disability, permanent or temporary discontinuation of therapy, dose reduction, treatment requiring a prescription drug, or an event of cancer, overdose or congenital anomaly) in 2% of their patients receiving once-daily formulation of diltiazem and 5% of placebo, resulting in discontinuation in 1.5% (3 of 197) of delayed release diltiazem recipients and 5% (2 of 40) of placebo recipients.

7.3 Withdrawals due to Adverse Events

In the angina study, 5 patients on active treatment were withdrawn due to adverse events (Table Saf-2). In addition, subject #2551 was withdrawn because "the investigator deemed it necessary".

In the two hypertension studies, 11 patients on active treatment were withdrawn due to adverse events.

Table Saf-2. Withdrawals due to adverse events

ID #	Treatment Group	Last visit completed	Adverse Event causing Withdrawal
5201	240 mg	4	Headache, rash, constipation; patient discontinued 4 days prior to notifying investigator
6102	540 mg	4	Pruritic rash on buttock which spread to chest and forearm. Study medication stopped.
6401	540 mg	4	Patient experienced abdominal bloating, shortness of breath, ankle edema and headaches
7154	240	5	Worsening ischemia. Hospitalized at Visit 5; had angiogram with angioplasty and stenting of Proximal LAD, and angioplasty of Diagonal and Ramus
7253	240 mg	5	Injured right knee; unable to complete Visit 6.
2551	540 mg	6	Ankle edema; investigator thought patient should go back on standard therapy rather than stay on placebo another week

7.4 Adverse Reactions

Adverse events were recorded at every visit. Regardless of the frequency of adverse events, subjects were counted only once in each adverse event and once in the corresponding body system.

Clinical adverse events were defined as any signs, symptoms, illnesses or diagnoses that appeared or worsened during the course of the study.

A total of 83 subjects reported at least one adverse event during the double blind phase of the study (Summarized in Table Saf-3). The number of subjects who developed adverse events increased as the dose increased with peripheral edema and dizziness bearing the strongest relationship to dose. A similar dose-related increase in incidence of peripheral edema and dizziness were also observed in the hypertension studies.

Only the two highest doses (360 mg/day and 540 mg/day of Diltiazem OD ER) were found to have significantly more subjects reporting an adverse event compared to placebo (Table Saf-3).

Table Saf-3: Summary of adverse events (AE) reported during the double blind phase of the study

		Diltiazem OD ER			
	Placebo	120 mg	240 mg	360 mg	540 mg
Number of Subjects	50	52	54	52	49
Number of adverse events	14	18	32	39	40
Subjects reporting an AE	9 (18%)	13 (25%)	19 (35%)	20 (39%)*	22 (45%)*
Body as a whole	1 (2%)	5 (10%)	9 (17%)	9 (17%)	10 (20%)
Cardiovascular	3 (6%)	1 (2%)	2 (4%)	5 (10%)	3 (6%)
Metabolic & nutritional	2 (4%)	3 (6%)	5 (9%)	2 (4%)	6 (12%)

*Statistically significant ($P<0.05$) compared to placebo

The most frequently reported adverse events in the Diltiazem OD ER groups were headaches (8.2%), dizziness (4.8%), peripheral edema (3.9%), pain (3.4%) and dyspepsia (2.4%). The remaining adverse events were generally only reported by one or two subjects in each of the active treatment groups.

The most common adverse events from the angina study are given in Table Saf-4a. There was a dose-related increase in the number of patients who had >1 adverse event. Also, a trend towards an increase in the frequency of common adverse events at higher doses of diltiazem was observed.

Table Saf-4a. Most common adverse events in double blind phase of the angina trial.

Adverse events	Placebo	Diltiazem (Tiazac™)			Tiazac™
Total number of patients in study	50	52	54	52	49	207
Patients with > 1 adverse event	9 (18%)	13 (25%)	19 (35%)	20 (39%)	22 (45%)	74 (36%)
Headache	1 (2%)	3 (6%)	5 (9%)	5 (10%)	4 (8%)	17 (8%)
dizziness	0 (0%)	1 (2%)	1 (2%)	3 (6%)	5 (10%)	10 (5%)
peripheral edema	1 (2%)	0	1 (2%)	2 (4%)	5 (10%)	8 (4%)
pain	1 (2%)	1 (2%)	3 (6%)	2 (4%)	1 (2%)	7 (3%)
dyspepsia	0	0	1 (2%)	1 (2%)	3 (6%)	5 (2%)
dyspnea	0	0	0	1 (2%)	3 (6%)	4 (2%)
pharyngitis	1 (2%)	0	1 (2%)	2 (4%)	1 (2%)	4 (2%)
bronchitis	0	0	0	1 (2%)	2 (4%)	3 (1%)
asthenia	0	0	1 (2%)	0	2 (4%)	3 (1%)
rash	0	0	2 (4%)	0	1 (2%)	3 (1%)
cough increased	0	1 (2%)	0	1 (2%)	1 (2%)	3 (1%)
gout	0	0	2 (4%)	0	1 (2%)	3 (1%)

Table Saf-4b. Common adverse events in double blind phase of hypertension and angina trials.

Most Frequent (COSARTs)	Placebo n=104	Up to 360 mg n=201	Up to 540 mg n=404
Headache	12 (11%)	42 (14%)	52 (13%)
peripheral edema	2 (2%)	11 (4%)	23 (6%)
pain	6 (6%)	16 (5%)	20 (5%)
dizziness	4 (4%)	12 (4%)	19 (5%)
asthenia	6 (6%)	10 (3%)	13 (3%)
dyspepsia	0	9 (3%)	13 (3%)
pharyngitis	3 (3%)	7 (2%)	10 (2%)
vasodilatation	1 (1%)	6 (2%)	8 (2%)
dyspnea	1 (1%)	4 (1%)	8 (1%)
infection	2 (2%)	4 (1%)	8 (2%)
rash	0	4 (1%)	7 (2%)
constipation	0	4 (1%)	5 (1%)
cough increased	0	3 (1%)	5 (1%)
palpitation	0	5 (2%)	5 (1%)
nausea	2 (2%)	3 (1%)	4 (1%)
paresthesia	2 (2%)	3 (1%)	4 (1%)
rhinitis	2 (2%)	4 (1%)	4 (1%)
nervousness	1 (1%)	3 (1%)	4 (1%)
edema	1 (1%)	3 (1%)	3 (1%)

The adverse events from the two hypertension studies and this angina study are summarized in Table Saf-4b. Without verification from raw data in a previous NDA of Diltiazem related to hypertension, it is noted from the above table submitted by the sponsor in the proposed labeling that headache, peripheral edema, and pain were more frequently reported in the hypertension studies (18%, 7.6% and 7%) than in the angina study (8.2%, 3.8% and 3%). The adverse events were combined in the categories "Up to 360 mg" and "Up to 540 mg" which would have reduced their proportions (percentages) in the above table due to relatively fewer adverse events at the lower doses.

In the two hypertension studies and the angina study, other cardiovascular adverse events such as tachycardia, first degree AV block and EKG abnormalities were seen at <1%, which is comparable to that reported in the study by Frances et al[71] and less than the reports of other diltiazem preparations such as Cardizem where the incidence of such adverse events were at a higher percentage (bradycardia = 3.3% - 4.6%, first degree AV block = 3.3% to 8.1% and EKG abnormalities = 1.6%)[64,67,78], higher rates of such adverse events been observed in patients exposed to the highest doses of sustained-release diltiazem[78].

7.5 Severe adverse events

Six severe adverse events were reported by five subjects as shown in Table Saf-5.

Table Saf-5. Subjects with severe adverse events

ID	Treatment Group	Severe Adverse Event
5354	360 mg	Bursitis
5355	Placebo	Headache
5853	540 mg	Dizziness
6401	540 mg	Peripheral edema, dyspnea
6703	360 mg	Migraine

7.6 Vital Signs

Supine blood pressure

There were no statistically significant differences in the supine systolic and diastolic blood pressure, and in the changes in supine systolic and diastolic blood pressures from baseline at each visit, between the active and placebo groups.

Supine heart rate

The mean supine heart rates remained clinically unchanged in all treatment groups with no statistically significant differences between the active and placebo groups at each visit.

Standing blood pressure

There were no statistically significant differences in the standing systolic and diastolic blood pressure, and in the changes in standing systolic and diastolic blood pressures from baseline at each visit, between the active and placebo groups.

Standing heart rate

The mean standing heart rates remained clinically unchanged in all treatment groups with no statistically significant differences between the active and placebo groups at each visit.

7.7 Resting Supine ECG abnormalities

There were no remarkable EKG abnormalities during the course of the study. The number of subjects with abnormal ECG readings remained unchanged within each treatment group during the course of the study (Table Saf-6). Similar absence of difference between treatment groups in ECG parameters has also be reported in the study by Frances et al[71].

While none of the patients on placebo had prolonged QT intervals, five patients on active treatment developed prolonged QT intervals which were not present at baseline before treatment was started.

They were:
(1) Patient # 2502 on Diltiazem 120 mg
(2) Patient # 0401 on Diltiazem 240 mg
(3) Patient # 2255 on Diltiazem 360 mg
(4) Patient # 0453 on Diltiazem 540 mg
(5) Patient # 6903 on Diltiazem 540 mg

Table Saf-6. Number of patients with ECG abnormalities

		Diltiazem ODER				
		Placebo	120 mg	240 mg	360 mg	540 mg
Number of Subjects		50	52	54	52	49
Baseline	Normal	13	16	24	11	11
	Abnormal	37	36	30	41	38
Visit 4	Normal	13	15	20	14	13
	Abnormal	36	36	34	37	35
	Not done	1	1	0	1	1
Visit 5	Normal	11	17	20	11	13
	Abnormal	38	34	32	41	33
	Not done	1	1	2	0	3
Visit 6	Normal	11	17	17	17	10
	Abnormal	36	34	33	34	36
	Not done	3	1	4	1	3
Endpoint	Normal	11	17	19	17	11
	Abnormal	38	34	35	35	37
	Not done	1	1	0	0	1

Baseline: ECG evaluation at Visit 2 or 2a. Endpoint: Last ECG evaluation from Visit 4, 5 or 6

7.8 Laboratory Studies

No clinically important changes occurred in the laboratory data, similar to reports in the published literature[78].

7.8.1 Hematology

There was no clinically relevant pattern of changes observed in any of the treatment groups. The number of laboratory results shifting from normal at baseline (Visit 2) to abnormal values at the end of the study (Visit 6) did not indicate any trend towards abnormal values as treatment was continued (summarized in Table Saf-7).

Table Saf-7 Number and list (ID numbers) of subjects shifting from normal to abnormal hematology laboratory values (from baseline to Visit 6)

	Diltiazem CD ER				
Test	Placebo	120 mg	240 mg	360 mg	540 mg
Number of Subjects	50	52	54	52	49
Hemoglobin	2 6052(L) 251(H)	2 5101(L) 6053(L)	0	0	2 0604(H) 6551(H)
Hematocrit	2 5251(H) 7101(H0	4 5101(L) 6053(L) 2404(H) 5253(H)	2 2451(H) 5655(H)	0	2 0604(H) 7255(H)
Red blood cells	3 5953(L) 5251(H) 7101(H)	0	2 2501(L) 7305(H)	0	2 2252(H) 5702(H)
White blood cells	1 1254(H)	2 5404(H) 5652(H)	1 5655(H)	3 5354(H) 5951(H) 6055(H)	3 5402(H) 6355(H) 7352(H)
Basophils	0	1 0655(H)	2 5252(H) 6752(H)	2 6502(H) 6952(H)	3 5804(H) 7153(H) 7255(H)
Eosinophils	2 0954(H) 5152(H)	2 2251(H) 5851(H)	3 0451(H) 6051(H) 6752(H)	3 5905(H) 6502(H) 6952(H)	4 0453(H) 2551(H) 5702(H) 6551(H)
Lymphocytes	1 5303(L)	0	0	4 5354(L) 0605(H) 6055(L) 6502(H)	2 0551(L) 1202(L)
Monocytes	0	3 1253(H) 5851(H) 5955(H)	0	2 0553(H(1254(H)	0
Segmented neutrophils	0	0	1 0653(L)	3 5354(H) 6002(H) 6055(H)	3 0902(L) 0551(H) 7301(H)
Platelets	2 5251(L) 1775(H)	1 0602(L)	1 2405(L)	0	0

ID numbers are those of patients who had shifts from normal at baseline to abnormal by Visit (6)
(H) = Higher than normal range; (L) = Lower than normal range

7.8.2 Urinalysis

There was no clinically relevant pattern of changes observed in any of the treatment groups. The number of laboratory results shifting from normal at baseline (Visit 2) to abnormal values at the end of the study (Visit 6) did not indicate any trend towards abnormal values as treatment was continued (summarized in Table Saf-9).

Table Saf-9 Number and list (ID numbers) of subjects shifting from normal at baseline (Visit 2 or Visit 2a) to abnormal Urinalysis values at Visit 6

Test	Placebo	Diltiazem QD ER 120 mg	240 mg	360 mg	540 mg
Number of Subjects	50	52	54	52	49
Urine pH	0	0	0	0	0
Specific gravity	0	0	0	0	0
Urine glucose	4 5303 6555 6354 7354	0	1 6554	1 6751	6 2403 6903 5254 7204 6801 7451
Urine protein	0	0	1 1802	5 1254 6952 1553 7203 1752	2 6355 7255
Urine RBC/hpf	3 1551 6802 6354	0	0	2 0951 7353	3 6951 7451 7301
Urine WBC/hpf	1 1551	1 1753	1 2501	1 6055	1 2252

ID numbers are those of patients who had shifts from normal at baseline to abnormal by Visit (6)

7.8.3 Blood Chemistry

No clinically relevant pattern of changes was observed in any of the treatment groups.

Slight increase in the mean alkaline phosphatase levels were noticed in the active treatment groups, particularly in the diltiazem 540 mg/day group (increase from 78.6 to 87.2 U/L, compared to a decrease in placebo group from 77.4 to 74.6 U/L). However, the mean values remain within the clinically normal range.

The number of laboratory results shifting from normal at baseline (Visit 2) to abnormal values at the end of the study (Visit 6) did not indicate any trend towards abnormal values as treatment was continued (summarized in Table Saf-8).

Table Saf-8 Number and list (ID numbers) of subjects shifting from normal to abnormal blood chemistry laboratory values (from baseline to Visit 6)

Test	Placebo		Diltiazem CD ER 120 mg		240 mg		360 mg		540 mg	
N=	50		52		54		52		49	
ALT	1	5654(H)	2	5253(H) 6151(H)	2	0401(H) 6103(H)	0		2	0654(H) 1554(H)
AST	0		0		0		0		0	
Alkaline Phosphatase	1	5603(H)	1	7252(H)	4	2253(H) 5252(H) 6901(H) 6954(H)	2	1553(H) 7254(H)	2	0453(H) 7255(H)
Bilirubin	1	1502(H)	0		0		0		0	
CO2 content	1	5904(L)	4	5652(L) 6004(L) 5703(H) 5902(H)	2	0601(L) 5852(L)	0		2	5901(L) 6801(H)
Calcium	0		0		0		0		0	
Chloride	0		1	7202(L)	0		1	0652(L)	0	
Cholesterol	2	5705(H) 6201(H)	1	7401(H)	4	1002(H) 1251(H) 6451(H) 7452(H)	2	1254(H) 5701(H)	5	0604(H) 1703(H) 5853(H) 6903(H) 7352(H)
Creatinine	0		1	5805(H)	2	1802(H) 5252(H)	0		3	6951(H) 5402(H) 6951(H)
Glucose	6	0455(H) 0954(H) 2254(H) 6354(H) 7152(H) 7252(H)	4	2352(L) 5404(L) 0584(H) 5253(H)	7	5302(L) 7051(L) 0952(L) 5852(L) 6005(H) 6554(H) 7355(H)	6	1001(L) 1254(L) 5951(L) 1205(H) 6703(H) 7353(H)	2	0504(H) 2551(H)
LDH	0		0		1	7051(H)	0		0	
Phosphorus	2	5904(L) 5802(H)	3	1555(H) 5652(H) 7401(H)	0		2	5905(L) 5951(H)	0	
Potassium	0		0		0		1	5752(L)	0	
Sodium	1	1055(L)	1	7202(L)	1	2253(L)	0		0	
Triglycerides	3	6052(H) 6354(H) 7402(H)	5	1203(H) 1753(H) 2502(H) 5902(H) 6151(H)	4	5153(H) 5852(H) 6554(H) 6655(H)	4	0951(H) 2351(H) 6055(H) 6351(H)	3	0851(H) 5353(H) 6205(H)
Urea Nitrogen	0		0		1	6202(H)	0		0	
Uric Acid	0		0		3	5954(L) 6103(L) 6954(L)	0		1	1703(L)
BUN	0		1	0953(L)	1	6501 (L)	1	5403(L)	1	7451(H)

N= number of subjects; (H) = Higher than normal range; (L) = Lower than normal range
ID numbers are those of patients who had shifts from normal at baseline to abnormal by Visit (6)

7.9 Miscellaneous

7.9.1 Concomitant medication use

Concomitant medication was defined as medication taken during the study period - Visit 0 to Visit 7, or to the termination visit. The drugs taken were coded using the following system:

Code	Drug	Number of times listed under concomitant medication
1	antiplatelet and anticoagulant drugs	208
1A	antihypertensive drugs	36 (31 = HCTZ, see below)
1B	antianginals	2 (see below)
2	lipid lowering drugs	100
3	drugs to control diabetes	57
4	analgesics and anti-inflammatory drugs	74
5	drugs acting on the GI system	65
6	drugs acting on the respiratory system	14
7	drugs acting on the central nervous system	23
8	hormone replacement therapy	21
9	dietary supplements, minerals, vitamins, K^+	36
10	anti-infectives	25
11	drugs for the treatment of glaucoma	6
12	cold remedies, decongestants, antitussives, antihistamines	38
13	other	60

Table Saf-10. Number of patients taking concomitant medication by treatment group

			Diltiazem OD LB				
Data entry code	Drug Code	Placebo	120 mg	240 mg	360 mg	540 mg	Total
Antiplatelet and anticoagulant drugs	1	40	40	45	42	41	208
Antihypertensives	1A	4	4	10	6	12	36
Antianginals	1B	2	0	0	0	0	2
Lipid lowering agents	2	23	21	24	14	18	100
Drugs to control diabetes	3	12	7	15	8	15	57
Analgesics and anti-inflammatory drugs	4	9	11	26	23	5	74
Drugs acting on the GI system	5	14	9	17	13	12	65
Drugs acting on the respiratory system	6	2	4	0	5	3	14
Drugs acting on the central nervous system	7	7	1	3	6	6	23
Hormonal replacement therapy	8	3	3	3	6	6	21
Dietary supplements: K^+, minerals, vitamins	9	4	8	10	7	7	36
Anti-infectives	10	1	9	3	5	7	25
Drugs for the treatment of Glaucoma	11	2	3	0	0	1	6
Cold remedies, decongestants, etc.	12	6	9	7	7	9	38
Others	13	7	4	14	25	10	60

Group 1A:	The antihypertensives were mostly hydroclorthiazide but 5 subjects had concomitant medications listed that are prohibited according to the protocol:
#5201:	early withdrawal. Last visit was on 7/7/95, last study medication taken on 7/8/95; she came back for her termination visit on 7/12/95. She started atenolol on 7/10/95. She was not on atenolol during the study period.
#6752:	atenolol was stopped prior to Visit 0; it was listed by investigator as "concomitant medication" but should not have been listed at all.
#6701:	Lotension was taken throughout the study; patient is recorded as a protocol violator.
#1004:	enalapril was stopped prior to Visit 0; it was listed by investigator as "concomitant medication" but should not have been listed at all.
#6801:	Lasix was taken throughout the study; patient is recorded as a protocol violator.
Group 1B:	Only one patient was associated with this.
#2401:	She was a drop-out who completed her last valid visit (Visit 5) on 2/28/95. She took her last study medication on 3/1/95 and started Cardizem CD and NTG patch also on 3/1/95. Thus, she did not take Cardizem CD nor NTG patch during the study assessment period.

The sponsor submitted that all of the above code groups 1 to 13 were fairly equally distributed between the 5 treatment groups with no effect on the efficacy results (Table Saf-10).

7.9.2 Pregnancy tests

No subject became pregnant during the study.

7.9.3 Overdosage

There was no report of any cases of overdose.

7.9.4 Drug abuse

There was no report of any cases of drug abuse.

APPEARS THIS WAY
ON ORIGINAL

8 SUMMARY OF EFFICACY

Tiazac™ (diltiazem hydrochloride) is a calcium ion cellular influx inhibitor (slow channel blocker) available for oral administration. The calcium channel blocking action decreases resting tone in vascular, including coronary, smooth muscle, and increases flow through them. In general, the calcium channel blocking agents decrease myocardial oxygen requirements by producing arterial dilatation and reducing arterial blood pressure and afterload, and by reducing myocardial contractility[1].

Tiazac™ capsules contain diltiazem hydrochloride in extended release beads at doses of 120, 180, 240, 300 and 360 mg.

8.1 Rationale

Over the last 20 years, multiple double-blind placebo-controlled clinical studies involving thousands of patients with stable effort angina have confirmed the efficacy of diltiazem and other calcium channel blocking agents[17,18]; patients show a reduction in chest pain attacks and nitroglycerine consumption, and improved exercise tolerance. Calcium-channel antagonists appear to be as safe and effective as ß-blockers and nitrates when used as monotherapies in patients with angina. There is no rebound symptoms upon abrupt withdrawal with verapamil, nifedipine or diltiazem[33,34].

Recently, 8 clinical trials (Table Lit-6) compared the efficacy of diltiazem once/day preparations with placebo[70,71,78], standard diltiazem given tid[72-74], sustained-released diltiazem given bid[75], with atenolol once/day[76] and with sustained-released isosorbide dinitrate[77]. In 666 patients with chronic stable angina, diltiazem once/day significantly decreased angina episodes, decreased nitroglycerin consumption, and increased time to ischemic threshold and time to angina threshold compared to placebo[70-72,78]. Diltiazem once/day was as effective and safe for chronic stable angina as immediate-release diltiazem given tid[72-74] or sustained-released diltiazem given twice/day[75]. Both diltiazem-R once/day and atenolol significantly prolonged the exercise time and time to onset of 1-mm ST-segment depression, with atenolol decreasing heart rate at maximal work levels while diltiazem did not[76]. Significantly more marked and sustained therapeutic effects were observed with sustained-release isosorbide dinitrate than with sustained-release diltiazem; combined therapy increased the therapeutic effects (ST depression at 2, 6, 12 hours) significantly over that of the individual drugs[77].

8.2 Summary of study protocol

To justify the claim (indication) as proposed by the sponsor, the following study was carried out.

A dose response study of the safety and efficacy of diltiazem once-daily extended release in the treatment of chronic stable exercise-induced angina pectoris (Protocol HR1321A/8/USA/301/AP)

8.2.1 Study design

The study was a 6 week multicenter, double-blind, randomized, placebo-controlled, parallel-group, dose-response trial. Following a 2 to 3 week single-blind placebo washout phase, all eligible subjects were enrolled into the double-blind treatment phase. Subjects were randomly assigned to receive either placebo or one of the Diltiazem OD ER dose groups: 120 mg, 240 mg, 360 mg or 540 mg. Subjects assigned to the higher dose groups were forcibly titrated over a 7 day period. All subjects then received their target dose of drug for the 2 week maintenance phase. Thus, subjects were on double-blind treatment (placebo or active drug) for a total of 3 weeks, their dose being stable for the last 2 weeks of that period (either placebo, 120 mg, 240 mg, 360 mg or 540 mg daily). Following the 2-week, multiple-dose, maintenance phase, there was a one-week follow-up placebo phase.

The Primary Efficacy Variable was Total duration of exercise (sec). This was defined as the total time the subject was able to exercise on the treadmill until he had to stop because of moderate angina (defined as the severity of pain that would ordinarily cause a subject to stop exercising during normal everyday activity), extreme fatigue, shortness of breath or the investigator believed that stopping the test was in the subject's best interests (e.g., >3 mm ST depression, arrhythmia, severe hypotension, etc.). Moderate angina must be the only reason the treadmill was stopped at Visits 1 and 2 (or 2a) or the patient was not eligible to participate in the double-blind phase of the study.

The Secondary Efficacy Variables were as follows:-

1. duration of exercise (sec) until the onset of angina
2. duration of exercise (sec) until the onset of ≥1 mm ST segment depression persisting ≥0.08 second beyond the J-point
3. angina attack rate (patients kept a diary of total number of anginal attacks/day)
4. nitroglycerine consumption (a diary of total nitroglycerine tablet consumption/day was kept by patients).

8.2.2 Sample size:

Based on a standard deviation of ±70 seconds[78], to detect an increase in total exercise time of 45 seconds or greater for Diltiazem OD ER over that of placebo with a power > 0.80 and alpha = 0.05 in two-tailed t-tests, the total sample size required was calculated to be 250 subjects (50 placebo and 50 in each of the four dose ranges of Diltiazem OD ER subjects).

8.2.3 Interim Analysis:

An interim analysis was to be done when one-half of the subjects completed the study, for the purpose of evaluating efficacy, to design a further study, or to terminate a negative study (using a very small alpha-level (0.0001) so that no alpha-level adjustment was necessary for the final analysis).

8.2.4 Population enrolled/analyzed:

388 subjects were enrolled. 12 dropped out or were withdrawn before they came for Visit 0 assessment and had CRFs completed. Thus, 376 entered the placebo washout phase.

119 subjects failed to meet the criteria for randomization for various reasons: 71 did not meet Inclusion/Exclusion criteria, 4 had adverse events, 8 were withdrawn by investigator for the patient's best interests, 5 subjects withdrew in their on interests, and 31 were withdrawn for "other" reasons including 15 who had exercise tolerance test results suggesting they were unlikely to qualify at Visit 1 for randomization.

There were 257 subjects randomized into 5 treatment groups. 12 subjects dropped-out prior to Visit 6 and one more dropped-out immediately after Visit 6. Thus, 244 subjects completed the study. Of the 13 who dropped-out, 3 subjects (#2204 Placebo group, #1451 Diltiazem 120 mg group, and #1003 - Diltiazem 540 mg group) withdrew prior to undergoing the ETT at Visit 4 (one week after randomization) and therefore data on these 3 subjects are not available for efficacy evaluation as defined by the protocol.

8.2.5 Centers:

36 of the 41 participating centers entered subjects. 32 of these 36 centers managed to randomize at least one subject. The number of randomized subjects per center varied between 1 and 24.

8.3 Summary of efficacy results

8.3.1 Baseline data comparability

There were no statistically significant differences between the treatment groups in medical history, history of angioplasty and/or coronary artery bypass graft surgery, findings at physical examination and Chest X-ray, and resting 12-lead ECG abnormalities.

Subjects in the 5 treatments groups were comparable at baseline for total duration of exercise, time to onset of angina and time to onset of 1-mm ST-segment depression.

8.3.2 Definitions

Baseline was the visit at which the subject was randomized (Visit 2 or 2a). The 3-week double blind treatment period began upon randomization.

Endpoint was considered Visit 6 (after 3 weeks of double blind study medication) for those who completed Visit 6 (n=245). For those subjects who completed Visit 4 or 5, but dropped out before Visit 6 (n=9), Endpoint was considered as Visit 4 or 5.

A **time point** analysis (for Visits 4, 5 and 6) was also performed for each variable. This analysis did not carry forward the last visit data for the drop-outs, and used data only from subjects who had values at these visits.

The outcome variable in the efficacy analysis was the *change* from a subject's baseline value to his or her endpoint. This is defined as *visit data minus baseline data*.

The **primary efficacy endpoint** was the *change* in total duration of exercise for the exercise tolerance test (ETT).

The **secondary efficacy endpoints** include *change* in duration of exercise until onset of angina and *change* in duration of exercise until onset of ≥ 1 mm ST-segment depression persisting ≥ 0.08 seconds beyond the J-point. The secondary efficacy endpoints also included *changes* in angina attack rate and in sub-lingual nitroglycerine use between baseline and endpoint. For this analysis, the baseline is the mean of the week prior to randomization and the endpoint is the mean of the week prior to subject's last valid visit (Visit 4 or 5 or 6).

For each variable, **"trough"** data is presented (i.e., data collected 24 hours after the last dose of study medication was taken).

For the primary variable, **"peak"** data was also presented (i.e., data from the ETT carried out 8 hours after the last dose of study medication was given at Visit 6).

8.3.3 Center interaction

Treatment by center interaction was not statistically significant (P>0.10) for all efficacy variables.

No statistically significant interaction was observed between treatment effect and stratum.

8.3.4 Primary Efficacy Variable

The endpoint analysis (Table Eff-1) showed that there was a significant increase (P = 0.024 overall) in the time subjects walked on the treadmill relative to their baseline total duration of exercise on ETT at trough (24 hours after dosing) by 14 seconds (4.1%), 26 seconds (8.0%), 41 minutes (12.7%), 33 seconds (9.9%) and 32 seconds (9.4%), respectively, with placebo and with Tiazac™ at the doses of 120 mg (P = 0.332, not significant), 240 mg (P = 0.002), 360 mg (P = 0.030) and 540 mg (P = 0.051, not significant).

The dose response curve was fairly flat, the change in walking times increasing by 12 seconds when the dose was doubled from 120 mg (mean improvement = 14 seconds) to 240 mg (mean improvement = 26 seconds). Increasing the dose to 360 mg and 540 mg did not change the mean walking time beyond that seen in the 240 mg group (Fig Eff-2).

The duration of exercise at "peak" levels (i.e., ETT carried out 8 hours post-dose at Visit 6) increased statistically significantly ($P < 0.001$ overall) from the baseline total duration of exercise on ETT by 13 seconds (3.8%), 38 seconds (11.6%), 64 minutes (19.8%), 55 seconds (16.69%) and 42 seconds (12.4%), respectively, with placebo and with Tiazac™ at single oral doses of 120 mg ($P = 0.018$), 240 mg ($P < 0.001$), 360 mg ($P < 0.001$) and 540 mg ($P = 0.004$) (Table Eff-3).

8.3.5 Secondary Efficacy Variables

Number of anginal attacks per day: At endpoint, while there were large variations in the response to diltiazem, the doses of 120 mg, 240 mg, 360 mg and 540 mg reduced the mean (range) number of anginal attacks statistically significantly ($P = 0.001$, overall) by -0.23 (-2.1 to -+0.3), -0.23 (-1.8 to 0.7), -0.19 (-2.4 to 1.4) and -0.24 (-1.4 to 0.1) respectively, whereas placebo increased the mean number of attacks by 0.21 (-1.4 to +4.4), (Table Eff-4).

Consumption of sublingual nitroglycerine per day: At endpoint there were no statistically significant differences overall ($P=0.098$) between the 5 treatment groups (Table Eff-6), but the 240 mg, 360 mg and 540 mg treatment groups showed statistically significant reductions in nitroglycerine tablet consumption compared to the placebo group which showed an increase.

Time to onset of angina: There are no statistically significant differences ($P= 0.144$) in the improvement in time to angina between placebo and the four diltiazem treatment groups at endpoint (Table Eff-8).

Time to onset of 1 mm ST-segment depression: There are no statistically significant differences ($P= 0.337$) in the improvement in time of onset of 1 mm ST-segment depression between placebo and the diltiazem treatment groups except the 360 mg treatment group at endpoint (Table Eff-10).

ETT Trough/Peak percentages: Trough/peak percentages for the four diltiazem treatment groups were similar, being 97.6%, 96.1%, 96.8% and 99.4%, respectively, for diltiazem 120 mg, 240 mg, 360 mg and 540 mg treatment groups (Table Eff-12) and not different from placebo (102.3%).

8.4 Conclusions

This study evaluated 4 doses (120 mg, 240 mg, 360 mg, 540 mg) of Diltiazem OD ER (Tiazac™) versus placebo. The primary efficacy variable was duration of exercise by exercise tolerance test; secondary efficacy variables included the number of anginal attacks per day and nitroglycerin consumption obtained from subjects' diaries, duration of exercise until the onset of angina, duration of exercise resulting in ≥ 1 mm ST-segment depression and trough/peak percentages.

Using an intent-to-treat analysis, endpoint analysis showed increases in the time subjects walked on the treadmill by 26 seconds (186%), 41 minutes (293%), 33 seconds (236%) and 32 seconds (228%) with Tiazac™ at trough at the doses of 120 mg ($P = 0.332$, not significant), 240 mg ($P = 0.002$), 360 mg ($P = 0.030$) and 540 mg ($P = 0.051$, not significant), respectively. This finding was supported by time point analyses at Visits 5 and 6 with the 240 mg group showing significance at both visits ($P = 0.011$ and $P = 0.002$, respectively) and 360 mg group being significant at Visit 5 ($P = 0.002$) compared

to placebo. The dose response was rather flat, with improvement increasing from 120 mg to 240 mg dose after which there was no further increase in effect at 360 mg and 540 mg. At peak, all four doses of Tiazac™ showed statistically significant improvement in walking times compared to placebo.

Improvements in secondary efficacy variables were also observed after 2-3 weeks of active medication. Tiazac™ 120 mg, 240 mg, 360 mg and 540 mg treatment groups reduced the mean number of anginal attacks significantly (P = 0.001 overall) by 55%, 53%, 46% and 62%, respectively, whereas placebo increased the mean number of attacks by 72%. Diltiazem 240 mg, 360 mg and 540 mg treatment groups showed statistically significant (P = 0.018, P = 0.023 and P = 0.026, respectively) reductions in nitroglycerine tablet consumption (57%, 70% and 60%, respectively) compared to the placebo group which showed an increase by 50%. There are no statistically significant differences in the improvements in time to angina and time of onset of 1 mm ST-segment depression between placebo and the four diltiazem treatment groups at endpoint.

The results of this study were also found to be consistent with those from 8 clinical trials which compared the efficacy of diltiazem once/day preparations with placebo[70,71,78], standard diltiazem given tid[72-74], sustained-release diltiazem given bid[75], with atenolol once/day[76] and with sustained-released isosorbide dinitrate[77]. In 439 patients with chronic stable angina in the reported literature, diltiazem once/day significantly decreased angina episodes, decreased nitroglycerin consumption, and increased time to ischemic threshold and time to angina threshold compared to placebo[70,71,72], which was also demonstrated in this study.

While the submission contained only one pivotal clinical trial, it was considered adequate to meet the regulatory requirements for approvability because of the following findings:-

1. the results of the current clinical are consistent with the known efficacy of other once/day sustained-release preparations of diltiazem[70-78],

2. statistical significance for the primary efficacy variable was demonstrated at an alpha level of 0.002 {for: (i) 240 mg Tiazac™ at endpoint, (ii) for 240 mg at time point at Visit 6, and (iii) for 360 mg at time point at Visit 5},

3. a dose-response (albeit only at 120 mg and 240 mg) on the primary efficacy variable was demonstrated, and

4. the secondary variables were also found to show significant improvements compared to placebo (P = 0.001 for reduction in number of anginal attacks overall, and P ≈ 0.026 - 0.018 for reductions in nitroglycerine tablet consumption).

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9. SUMMARY OF SAFETY

9.1 General considerations

A total of 83 subjects reported at least one adverse event in the double-blind phase of the study. Overall, the two highest doses of Tiazac™ - 360 mg and 540 mg - had a statistically significantly larger number of subjects reporting an adverse event compared to placebo. The incidence of adverse events increases with dose, peripheral edema and dizziness bearing the strongest relationship to dose.

9.2 Deaths

No death was reported in the study.

9.3 Withdrawals

Five subjects on active treatment were withdrawn due to adverse events (two due to rash, one for worsening ischemia (see below), one for edema, one for injury to right knee being unable to complete Visit 6, and one because "the investigator deemed it necessary").

The one randomized subject who had a serious adverse event (worsening of ischemia while on 240 mg Tiazac™ daily) required early withdrawal from the study; he recovered completely from the event.

9.4 Serious Adverse Events

Two subjects had serious adverse events.

One subject was hospitalized for acute bronchitis and, upon discharge, was still unable to walk on the treadmill because of cough and shortness of breath, and thus failed to qualify for randomization into the study.

The other subject (#7154) completed Visit 5 and developed worsening ischemia requiring hospitalization for angiography and angioplasty and stenting of Proximal LAD, and angioplasty of Diagonal and Ramus. He recovered completely from the event.

9.5 Severe Adverse Events

Six severe adverse events were reported by five subjects, namely: bursitis, headache, dizziness, peripheral edema with dyspnea, and migraine.

9.6 Adverse Events

A total of 83 subjects reported at least one adverse event during the double blind phase of the study. The number of subjects who developed adverse events increased as the dose increased with peripheral edema and dizziness bearing the strongest relationship to dose.

The two highest doses (360 mg/day and 540 mg/day of Diltiazem OD ER) were found to have significantly more subjects reporting an adverse event compared to placebo.

The most frequently reported adverse events in the Diltiazem OD ER groups were headaches (8.2%), dizziness (4.8%), peripheral edema (3.9%), pain (3.4%) and dyspepsia (2.4%).

9.7 Laboratory findings, ECGs, Vital signs

There were no statistically significant differences in the changes in supine or standing systolic and diastolic blood pressures from baseline between the active and placebo groups at each visit. The mean supine and standing heart rates remained clinically unchanged in all treatment groups with no statistically significant differences between the active and placebo groups at each visit.

There were no remarkable EKG abnormalities during the course of the study.

No clinically relevant pattern of changes in laboratory tests related to hematology, blood biochemistry or urinalysis were observed in any of the treatment groups. For these laboratory tests, the number of laboratory results shifting from normal at baseline (Visit 2) to abnormal values at the end of the study (Visit 6) did not indicate any trend towards abnormal values as treatment was continued.

No subject became pregnant during the study.

There was no report of any cases of overdose.

There was no report of any cases of drug abuse.

9.8 Conclusion

As submitted by the sponsor, the dose of 240 mg appears to achieve the optimal balance between beneficial effects and adverse events. The incidence of adverse events (particularly peripheral edema and dizziness) increase with dose, becoming statistically significant at the two highest dose levels (360 mg and 540 mg).

The type and frequency of adverse events reported in this study were not different from those reported in the literature for other currently marketed formulations of diltiazem[71,78] and are similar to those seen in previous studies in hypertensive patients with this formulation.

Overall, diltiazem OD ER (Tiazac™) provided statistically significant improvement in exercise tolerance time with an adverse event profile similar to that reported for other currently marketed formulations of sustained-release diltiazem.

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10. LABELING

10.1 Proposed labeling changes

For this NDA Supplement, the sponsor proposed to add the following in the labeling of Tiazac™:-

(1) Under *Mechanisms of Action:*

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 apical and subendocardial. Spontaneous and ergonovine induced coronary 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 n the configuration of the action potential. Diltiazem produces relaxation of the 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.

(2) Under *Pharmacodynamics:*

(3) Under *Dosage and Administration:*

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...

***Angina:** Doses 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.*

10.2 Rationale

Calcium channel antagonists decrease entry of calcium through the slow, voltage-sensitive calcium channels of vascular smooth muscle cells, decreasing the resting tone of blood vessels including coronary arteries and increasing the flow through them. They also decrease myocardial oxygen requirements. They are as effective as ß-blockers in stable angina pectoris, and are of special value in patients with asthma, chronic obstructive pulmonary disease or peripheral vascular disease where ß-blockers may not be used.

This study evaluated the efficacy of 4 doses (120 mg, 240 mg, 360 mg, 540 mg) of Diltiazem OD ER (Tiazac™) versus placebo on the duration of exercise by exercise tolerance test; secondary efficacy variables included the number of anginal attacks per day and nitroglycerin consumption obtained from subjects' diaries, duration of exercise until the onset of angina, duration of exercise resulting in ≥ 1 mm ST-segment depression and trough/peak percentages. Significant increases in the time subjects walked on the treadmill by 41 minutes (293%) with Tiazac™ at trough at the dose of 240 mg (P = 0.002), and by 33 seconds (236%) at the dose of 360 mg (P = 0.030) were found. Tiazac™ also reduced the mean number of anginal attacks significantly (P = 0.001 overall) by 55 to 62%, and reduced the number of nitroglycerine tablet consumption by 57-70%.

The positive effect of Tiazac™ on the primary efficacy variable was demonstrated at an alpha level of 0.002 {for: (i) 240 mg Tiazac™ at endpoint, (ii) for 240 mg at Visit 6, and (iii) for 360 mg at Visit 5} with a dose-response (albeit only at 120 mg and 240 mg). The secondary variables were also found to show highly significant improvements compared to placebo (P = 0.001 for reduction in number of anginal attacks overall, and P ≈ 0.026 - 0.018 for reductions in nitroglycerine tablet consumption). Thus, while the submission contained only one pivotal clinical trial, the efficacy findings were considered adequate to meet the regulatory requirements for approvability.

There was a dose-related response, with the duration of exercise by exercise tolerance test increasing from 120 mg to 240 mg after which there was no further increase in effect at 360 mg and 540 mg. The incidence of adverse events (particularly peripheral edema and dizziness) also increased with dose, becoming statistically significant at the two highest dose levels (360 mg and 540 mg). As submitted by the sponsor, the dose of 240 mg appeared to achieve the optimal balance between beneficial effects and adverse events.

The results of the current clinical trial were found to be consistent with the known efficacy of other once/day sustained-release preparations of diltiazem[70-78]. Also, the type and frequency of adverse events reported in this study were not different from those reported in the literature for other currently marketed formulations of diltiazem[71,78] and were similar to those seen in previous studies in hypertensive patients with this formulation.

Overall, diltiazem OD ER (Tiazac™) provided statistically significant improvement in exercise tolerance time with an adverse event profile similar to that reported for other currently marketed formulations of sustained-release diltiazem.

11. RECOMMENDATION

The proposed indication/labeling change is **approvable** with the following information added to provide more complete and accurate information:

(1) Under *Mechanisms of Action:*

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 apical and subendocardial. Spontaneous and ergonovine induced coronary 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 n the configuration of the action potential. Diltiazem produces relaxation of the 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.

(2) Under *Pharmacodynamics:*

Angina: *In a double-blind parallel group placebo controlled trial, Tiazac™ increased exercise tolerance times in patients with chronic stable angina as follows: at trough, 24 hours after dosing, exercise tolerance times using a Bruce exercise protocol, increased*

relative to the baseline total duration of exercise by 14 seconds (4.1%), 26 seconds (8.0%), 41 minutes (12.7%), 33 seconds (9.9%) and 32 seconds (9.4%), respectively, with placebo and with Tiazac™ at single oral doses of 120 mg (P = 0.332, not significant), 240 mg (P = 0.002), 360 mg (P = 0.030) and 540 mg (P = 0.051, not significant). *At peak, 8 hours after dosing, exercise tolerance times were statistically* significantly (P < 0.001 overall)

. relative to the baseline total duration of exercise on ETT by 13 seconds (3.8%), 38 seconds (11.6%), 64 minutes (19.8%), 55 seconds (16.69%) and 42 seconds (12.4%), respectively, with placebo and with Tiazac™ at single oral doses of 120 mg (P = 0.018), 240 mg (P < 0.001), 360 mg (P < 0.001) and 540 mg (P = 0.004). *Compared to baseline,* after 2-3 weeks of treatment with *Tiazac™, patients experienced statistically significant reductions in anginal attacks* by 55%, 53%, 46% and 62%, respectively for the 120 mg, 240 mg, 360 mg and 540 mg treatment groups *while the number of attacks increased by 72% in placebo treated patients. Similarly, patients* treated with Tiazac™ 240 mg, 360 mg and 540 mg *used* 57%, 70% and 60%, respectively, *less nitroglycerin compared to baseline while nitroglycerin use was increased by 50% in placebo treated patients.*

(3) Under *Dosage and Administration:*

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...

Angina: *Doses for the treatment of angina should be adjusted to each patient's needs, starting with a dose of 120 mg once daily.* In general, patients showed a dose-related response in exercise tolerance time up to 240 mg, after which there was no further increase in effect at 360 mg and 540 mg although *individual patients may respond to higher doses of up to 540 mg once daily.* The dose of 240 mg once a day appeared to achieve the optimal balance between beneficial effects and adverse events. *When necessary, titration should be carried out over 7 to 14 days.*

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REFERENCES

1. Schlant RC, Alexander RW. Ch. 58: Diagnosis and management of chronic ischemic heart disease. In: Hurst's The Heart, 8th Edition. Schlant RC and Alexander RW, Eds. McGraw-Hill, Inc., New York, 1994. Pp. 1055-82.
2. Palmer RMJ, Ferrige AG, Moncada S: Nitric oxide release accounts for the biologic activity of endothelium-derived relaxing factor. Nature 1987; 327: 524-6.
3. Parker JO. Nitrate therapy in stable angina pectoris. N Engl J Med 1987; 316: 1635-42.
4. Leier CV: Nitrate tolerance. Am Heart J 1985; 110: 224-32.
5. Thadani U, Davidson C, Singleton W, Taylor SH: Comparison of the immediate effects of five beta-adrenoreceptor-blocking drugs with different ancillary properties in angina pectoris. N Engl J Med 1979; 300: 750-5.
6. Yusuf S, Ramsdale D, Peto R, Furse L, Bennett D, Bray C, et al. Early intravenous atenolol treatment in suspected acute myocardial infarction. Lancet 1980; 2: 273-6.
7. Yusuf S, Wittes J, Friedman L. Overview of results of randomized trials in heart disease, II. Unstable angina, heart failure, primary prevention with aspirin, and risk factor modification. JAMA 1988; 260: 2259-63.
8. Muller JE, Turi ZG, Pearle DI, Schneider JF, Sekfas DH, Morrison J: Nifedipine and conventional therapy for unstable angina pectoris: a randomized, double-blind comparison. Circulation 1984; 69: 728-39.
9. Report of the Holland Interuniversity Nifedipine/Metoprolol Trial. Holland Interuniversity Nifedipine/Metoprolol Trial (HINT) Research Group: early treatment of unstable angina in the coronary care unit: a randomized, double blind, placebo-controlled comparison of recurrent ischemia in patients treated with nifedipine or metoprolol or both: Report of the Holland Interuniversity Nifedipine/Metoprolol Trial (HINT) Research Group. Br Heart J 1986; 56: 400-13.
10. Gerstenblith G, Ouyang P, Aschuff SC, Bulkley BH, Becker LC, Mellits ED, et al: Nifedipine in unstable angina: a souble-blind randomized trial. N Engl J Med 1982; 306: 885-9.
11. Gottlieb SO, Weisfeldt ML, Ouyang P, Schuff SC, Baughman KL, Traill TA, et al: Effect of the addition of propranolol to therapy with nifedipine for unstable angina pectoris: a randomized double-blind, placebo-controlled trial. Circulation 1986; 73: 331-7.
12. Schwartz A. A view of the latest concepts of the voltage dependent calcium channel and mechanism of action of calcium channel modulators. Cardiovasc Drugs Ther 1988; 1: 439.
13. Opie LH. Calcium channel antagonists. Part I: fundamental properties: mechanisms, classification, sites of action. Cardiovasc Drugs Ther 1987; 1: 411.
14. Zsoter TT, Church JG. Calcium antagonists - pharmacodynamic effects and mechanism of action. Drugs 1983; 55: 3C-7C.
15. Godfraind T. Classification of calcium antagonists. Am J Cardiol 1987; 59: 11B.
16. Schwartz A. McKenna E, Vaghy PL. Receptors for calcium antagonists. Am J Cardiol 1988; 62: 3G.
17 Frishman WH, Sonnenblick EH. Chapter 67. Calcium channel blockers. In: Hurst's The Heart, 8th Edition. Schlant RC and Alexander RW, Eds. McGraw-Hill, Inc., New York, 1994. Pp. 1291-1308.
18. Habib GB, Roberts R. Chapter 28. Calcium channel blockers as anti-ischemic agents. In: Cardiovascular Pharmacology and Therapeutics. Singh BN, Dzau VJ, Vanhoutte PM, Woosley RL (Eds). Churchill Livingstone, New York. 1994. Pp 425-48.
19. Braunwald E. Mechanism of action of calcium-channel blocking agents. N Engl J Med 1983; 307: 1618-1627.
20. Braunwald E. Calcium-channel blockers: pharmacologic considerations. Am Heart J 1982; 104: 665-71.
21. van Breeman C, Mangel A, Fahim M, Meisheri K. Selectivity of calcium antagonistic action in vascular smooth muscle. Am J Cardiol 1982; 49: 507-10.
22. Millard RW, Lathrop DA, Grupp G, Ashraf M, Grupp IL, Swhcartz A. Differential cardiovascular effects of calcium channel blocking agents: potential mechanisms. Am J Cardiol 1982; 49: 449-506.
23. Fleckenstein A. Specific pharmacology of calcium in myocardium, cardiac pacemakers, and vascular smooth muscle. Annu Rev Pharmacol Toxicol 1977; 17: 149-66.
24. Himori N, Ono H, Tiara N. Simultaneous assessment of effects of coronary vasodilators on the coronary blood flow and the myocardial contractility by using the blood perfused canine papillary muscle. Jpn J Pharmacol 1976; 26: 427-35.
25. Braunwald E, Stone PH, Antman EM, Muller JE. Calcium channel blocking agents in the treatment of cardiovascular disorders: II. Hemodynamic effects and clinical applications. Ann Intern Med 1980; 93: 886-904.
26. Ellrodt G, Chew CYC, Singh BN. Therapeutic implications of slow-channel blockade in cardiocirculatory disorders. Circulation 1980; 62: 669-79.
27. Frishman WH, Landau AJ, Charlap S, Lazar EJ. Calcium antagonists and heart failure. Heart Failure 1991; VII(4): 138-153.
28. Singh BN, Collet J, Chew CYC. New perspectives in the pharmacologic therapy of cardiac arrhythmias. Prog Cardiovasc Dis 1980; 22: 243-3-1.

29. Wit A. Cranefield P. The effects of verapamil on the sinoatrial and atrioventricular nodes of the rabbit and the mechanisms by which it arrests reentrant AV nodal tachycardia. Circ Res 1974; 35: 413-25.
30. Yamaguchi I, Obayashi K, Mandel WJ: Electrophysiologic effects of verapamil. Cardiovasc Res 1978; 12: 597-608.
31. Zipes DP, Fischer JC. Effects of agents which inhibit the slow channel on sinus node automaticity and atrioventricular conduction in the dog. Circ Res 1974; 34: 184-92,
32. Frishman WH, LeJemtel T. Electropharmacology of calcium channel antagonists in cardiac arrhythmias. PACE 1982; 5: 402-13.
33. Frishman WH, Klein N, Strom J, Cohen Mn, Shamoon H, Willens H, et al: Comparative effects of abrupt withdrawal of propranolol and verapamil in angina pectoris. Am J Cardiol 1982; 50: 1191-95.
34. Frishman WH, Charlap S, Kimmel B, Teicher M, Cinnamon J, Allen L, et al: Diltiazem compared to nifedipine and combination treatment in patients with stable angina: Effects on angina, exercise tolerance and the ambulatory ECG. Circulation 1988; 77: 774-86.
35. Koiwaya Y, Nakamura M, Mitsutake A et al: Increased exercise tolerance after oral diltiazem, a calcium antagonist in angina pectoris. Am Heart J 1981; 143: 101
36. Hossack KF, Bruce RA, Ritterman JB et al; Divergent effects of diltiazem in patients with exertional angina. Am J Cardiol 1982; 49: 538.
37. Wagniart P, Ferguson RJ, Chaitman BR et al. Increased exercise tolerance and reduced electrocardiographic ischemia with diltiazem in patients with stable angina pectoris. Circulation 1982; 66: 23.
38. Joyal M, Cremer K, Pieper J et al. Effects of diltiazem during tachycardia-induced angina pectoris. Am J Cardiol 1986; 57: 10.
39. Hossack KF, Pool PE, Steele P et al. Efficacy of diltiazem in angina on effort: a multicenter trial. Am J Cardiol 1982; 49: 567.
40. Hossack KF, Bruce RA. Improved exercise performance in persons with stable angina pectoris receiving diltiazem. Am J Cardiol 1981; 47: 95.
41. Pool PE, Seagren SC, Bonanno JA et al. The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. Chest 1980; 78: 234.
42. Go M, Hollenberg M. Improved efficacy of high-dose versus medium- and low-dose diltiazem therapy for chronic stable angina pectoris. Am J Cardiol 1984; 53: 669.
43. Khurmi NS, Bowles MJ, O'Hara MJ et al. Long-term efficacy of diltiazem assessed with multistage graded exercise tests in patients with chronic stable angina pectoris. Am J Cardiol 1984; 54: 738.
44. Weiner DA, Cutler SS, Klein MD. Efficacy and safety of sustained-release diltiasem in stable angina pectoris. Am J Cardiol 1986; 57:6.
45. Theroux P, Baird M, Juneau M et al. Effect of diltiazem on symptomatic and asymptomatic episodes of ST segment depression occurring during daily life and during exercise. Circulation 1991; 84:15.
46. Anderson JL, Wagner JM, Datz FL et al. Comparative effects of diltiazem, propranolol and placebo on exercise performance using radionuclide ventriculography in patients with symptomatic coronary artery disease: results of a double-blind randomized, cross-over study. Am Heart J 1984; 107: 698.
47. Cjaitman BR, Wagniart P, Pasternac A et al. Improved exercise tolerance after propranolol, diltiazem or nifedipine in angina pectoris: comparison at 1, 3 and 8 hours and correlation with plasma drug concentration. Am J Cardiol 1984; 53: 1.
48. Strauss WE, Parisi AF. Superiority of combined diltiazem and propranolol therapy for angina pectoris. Circulation 1985; 71: 951.
49. Johnston DL, Lesoway R, Humen DP et al. Clinical and hemodynamic evaluation of propranolol in combination with verapamil, nifedipine and diltiazem in exertional angina pectoris: a placebo-controlled, double-blind, cross-over study. Am J Cardiol 1985; 55: 680.
50. Subramaniam VB. Calcium antagonists in chronic stable angina pectoris. p.97. In: Excerpta Medica, Amsterdam, 1983.
51. El-Tamimi H, Davies GJ, Kaski J-C, et al. Effects of diltiazem alone or with isosorbide dinitrate or with atenolol both acutely and chronically for stable angina pectoris. Am J Cardiol 1989; 64: 717.
52. Humen DB, O'Brien P, Purves P, et al. Effort angina with adequate beta-receptor blockade: comparison with diltiazem alone and in combination. J Am Coll Cardiol 1986; 7: 329.
53. Hung J, Lamb IH, Connoly SJ et al. The effect of diltiazem and propranolol, alone and in combination, on exercise performance and left ventricular function in patients with stable effort angina: a double-blind, randomized, and placebo-controlled study. Circulation 1983; 68: 560.
54. Stone PH, Gibson RS, Glasser SP et al. Comparisonof propranolol, diltiazem and nifedipine in the treatment of ambulatory ischemia in patients with stable angina. Differential effects on ambulatory ischemia, exercise performance and anginal symptoms. Circulation 1990; 82: 1962.
55. Frishman W, Charlap S, Kimmel B et al. Diltiazem, nifedipine and their combination in patients with stable angina pectoris: effects on angina, exercise tolerance, and the ambulatory electrocardiographic ST segment. Circulation 1988; 77: 774.

56. Khurmi NS, Faftery EB. A comparison on nine calcium ion antagonists and propranolol: exercise tolerance, heart rate, and ST-segment changes in patients with chronic stable angina pectoris. Eur J Clin Pharmacol 1987; 32: 539.

57. Morse JR. Comparison of combination nifedipine-propranolol and diltiazem-propranolol with high dose diltiazem monotherapy for stable angina pectoris. Am J Cardiol 1988; 62: 1028.

58. Johnston AL, Lesoway R, Humen DP, Kostuk WJ. Clinical and hemodynamic evaluation of propranolol in combination with verapamil nifedipine and diltiazem in exertional angina pectoris: a placebo-controlled, double-blind, randomized, crossover study. Am J Cardiol 1985; 55: 680.

59. Schurtz CI, Lesbre JP, Kalisa A et al. Interet des inhibiteurs calciques dans l'angor d'effort stable: diltiazem versus nifedipine. Ann Cardiol Angelol 1983; 32: 337.

60. Weiner DA, McCabe CH, Cutler Ss et al. The efficacy and safety of high-dose verapamil and diltiazem in the long-term treatment of stable exertional angina. Clin Cardiol 1985; 7: 648.

61. Khurmi NS, Faftery EB. Comparative effects of prolonged therapy with four calcium ion antagonists (diltiazem, nicardipine, tiapamil and verapamil) in patients with chronic stable angina pectoris. Cardiovasc Drug Ther 1987; 1: 81.

62. Theroux P, Baird M, Juneau M, Warnica W, Klinke P, Kostuk W et al. Effect of diltiazem on symptomatic and asymptomatic episodes of ST segment depression occurring during daily life and during exercise. Circulation 1991; 84: 15-22.

63. Weiss RJ, Hicks D, Bittar N, Bowers J, Shah A, et al. A double-blind, placebo-controlled trial of sustained-release diltiazem in patients with angina. Clin Ther 1993; 15(6): 1069-75.

64. Vliegren HW, van der Wall EE, Kragten JA, Holwerda NJ, Schenkel WM, van de Moer WMM, et al. Comparison of diltiazem standard formulation and diltiazem controlled release in patients with stable angina pectoris: a randomized, double-blind, cross-over multicenter study. J Cardiovasc Pharmacol 1993; 21(4): 552-9.

65. Brorson L, Arvill A, Lofdahl P, Jorgensen E, Fraser T, Larsson H, et al. Conventional and controlled released diltiazem. Bioavailability in healthy volunteers and anti-anginal effects in combination with metoprolol in stable angina pectoris. Eur J Clin Pharmacol 1994; 47: 75-9.

66. Bowman K, Saetre H, Karlsson L-G, Ritter B, Marsell R, Wingman H, et al. Antianginal effect of conventional and controlled release diltiazem in stable angina pectoris. Eur J Clin Pharmacol 1995; 49: 27-30.

67. Vliegen HW, Van der Wall EE, Niemeyer MG, Holwerda NJ, Bernink PJ, et al. Long-term efficacy of diltiazem controlled release vs metoprolol in patients with stable angina pectoris. J Cardiovasc Pharmacol 1991; 18 (Suppl 9): S55-S60.

68. Steffensen R, Grande P, Pedersen F, Haunsø. Effects of atenolol and diltiazem on exercise tolerance and ambulatory ischemia. Internat J Cardiol 1993; 40: 143-53.

69. Borzak S, Fenton T, Glasser SP, Shook TL, MacCallum G, Young PM, Stone PH. Discordance between effects of anti-ischemic therapy on ambulatory ischemia, exercise performance and anginal symptoms in patients with stable angina pectoris. J Am Coll Cardiol 1993; 21: 1605-11.

70. Cutler NR, Eff J, Fromell G, Brass EP, Archer S, Chrysant SG, Fiddes R. Dose-ranging study of a new, once-daily diltiazem formulation for patients with stable angina. J Clin Pharmacol 1995; 35: 189-195.

71. Frances Y, Gagey S, Stalla-Bourdillon A, & the Dildurang Study Group. Twenty-four hour efficacy of two dose levels of a once daily sustained-release diltiazem formulation in stable angina: a placebo-controlled trial. Brit J Clin Pharmac 1995; 39: 277-82.

72. Klinke WP, Baird M, Juneau M, Waters D, Warnica W, Lakhani Z, et al. Antianginal efficacy and safety of controlled-delivery diltiazem QD versus an equivalent dose of immediate-release diltiazem TID. Cardiovasc Drugs Ther 1995; 9: 319-330.

73. Pool PE, Thadani U, Miller AB, Fromell GJ, Eff J. Conversion from immediate-release to extended-release diltiazem in angina pectoris. Clin Cardiol 1994; 17: 484-488.

74. Trimarco B, Radzik D, van Mieghem W, Neveux E, Wajman A, Attali P, Ponsonnaille J. Efficacy and safety of the 200-300 mg sustained release formulation of diltiazem administered once daily in patients with stable angina. Eur J Clin Pharmacol 1995; 47: 493-6.

75. Savard D, Lenis J, Juneau M, Jacob C, Boulet AP. Clinical efficacy and safety of once-daily diltiazem in patients with stable angina pectoris switched from twice-daily diltiazem. J Cardiovasc Pharmacol 1995; 26: 85-9.

76. Kaku T, Himeno E, Nakashima Y, Kuroiwa A. Effect of sustained release diltiazem (Diltiazem-R) in patients with stable effort angina. Artery 1994; 21(4): 193-207.

77. Lehmann G, Reiniger G, Haase H-U, Rudolph W. Enhanced effectiveness of combined sustained-release forms of isosorbide dinitrate and diltiazem for stable angina pectoris. Am J Cardiol 1991; 68 (10): 983-990.

78. Thadani U, Glasser S, Bittar N, Beach CL, and Diltiazem CD Study Group. Dose-response evaluation of once-daily therapy with a new formulation of Diltiazem for stable angina pectoris. Am J Cardiol 1994; 74: 9017.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20401/S-007

ADMINISTRATIVE DOCUMENTS

JAN 30 1998

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Public Health Service

Memorandum

DATE : January 26. 1998

FROM : Director, Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: NDA 20-401/S-007, Controlled Release Diltiazem, Tiazac, Biovail

TO : NDA File

Introduction

Diltiazem is well known to be antihypertensive and antianginal in man (here by well known I mean through **dozens** of publications in reputable, peer-reviewed medical journals as well as through having four other NDAs approved for the use of diltiazem as an antianginal, or as an antihypertensive, or for both indications, or for the treatment of supraventricular arrhythmias, each approval supported by clinical trials). The approved NDAs are:

1) NDA 18-602, Immediate Release Diltiazem, **Cardizem**, approved only for angina, Marion Merrell Dow, taken orally three-times-a-day, patent expired,
2) NDA 19-471, Controlled Release Diltiazem, **Cardizem SR**, approved only for hypertension, Marion Merrell Dow, taken orally twice-a-day, patent expires Jan. 26, 2005,
3) NDA 20--027, Intravenous Diltiazem, **Cardizem Injection**, approved only for paroxysmal supraventricular tachycardia and paroxysmal atrial flutter/fibrillation, Marion Merrell Dow, Intravenous,
4) NDA 20-062, Controlled Release Diltiazem, **Cardizem CD**, approved for angina and hypertension, Marion Merrell Dow, taken orally once-a-day, patent expires Jan. 16, 2007 & Mar. 26, 2008,
5) NDA 20-092, Controlled Release Diltiazem, **Dilacor XR**, approved only for hypertension, Rhone-Poulenc Rorer Pharmaceuticals, Inc, taken orally once-a-day, patent expires June 14, 2006.
6) NDA 20-401. Controlled Release Diltiazem,. **Tiazac**, approved for hypertension, taken orally, once-a-day. Biovail Corporation International. Patent holder Galephar P.R., Inc. Ltd., expires June 25, 2013. **Tiazac** was also approved in the United Kingdom in February, 1996 under the trade name **Viazem SR**.

Bolded names are Trade Names for the formulations of diltiazem.

NDAs 1 though 5 were full NDAs [505(b)(1)] in that they were supported by chronic animal toxicology and animal reproduction studies, as well as manufacturing & controls, in addition to the clinical trials that were requisite for approval. The 4 Marion Merrell Dow NDAs were supported by the original animal toxicology & reproduction data that were submitted with NDA 18-602. The Rhone-Poulenc Rorer NDA was supported by chronic animal toxicology & reproduction studies conducted by (in support of an immediate release formulation which never got to market), by right to reference.

Hoechst-Roussel developed another controlled release formulation of diltiazem (the product submitted as NDA 20-401, **Tiazac**) that was intended to control blood-pressure suitably when taken once-a-day. NDA 20-401 (the Hoechst-Roussel Pharmaceuticals NDA) and contained the results of studies that clearly demonstrate that **Tiazac** is **not bioequivalent** with immediate release diltiazem, **Cardizem CD** nor **Dilacor XR** (consequently, although not part of the empirical data, **Tiazac** would also not be bioequivalent to **Cardizem SR** and **Cardizem Injection**). Therefore **Tiazac** could not be approved as an ANDA (e.g., 505(j)), since it was known that it is bioinequivalent to any of the approved formulations of diltiazem.

NDA 20-401 was approved in September 1995 as a 505(b)(2) NDA on the basis of clinical trials that involved 281 patients or normal volunteers (133 volunteers to characterize the biopharmaceutical properties of their formulation [8 studies] and 148 patients with hypertension that were randomized to one of two placebo controlled, dose-ranging trials). In December 1995, Biovail obtained a right of reference for the pharmacology/toxicology data from Hoechst Marion Roussel, so NDA 20-401 was converted to a 505(b)(1) NDA. This right of reference supports NDA 20-401 and any NDAs or supplemental NDAs containing the diltiazem formulation that was originally submitted to NDA 20-401.

Biovail Corporation International acquired the manufacturing site (previously know as Galephar P.R., Inc. LTd. Galephar, the owner of the patent for this formulation), now called Biovail Laboratories, and transferred the ownership of the NDA to them. Biovail Laboratories manufactures Tiazac, and Forest Pharmaceuticals will be the distributor. Tiazac is currently listed in the 1998 PDR under Forest Pharmaceuticals name.

The applicant has submitted a 6 week randomized, double-blind, placebo-controlled, parallel-group, dose-ranging clinical trial. This trial randomized 257 subjects to one of 5 arms, placebo, 120 mg, 240 mg, 360 mg, or 540 mg of Tiazac, once-a-day. The primary endpoint was the duration of symptom limited exercise at trough, ST segment depression was also evaluated, diaries for counting angina attacks were kept and nitroglycerine consumption was recorded. The NDA supplement contained a full study report and an electronic data base that contained all variable recorded on case report forms.

The placebo subtracted increases in exercise time were 12, 27, 19 and 18 seconds for the 120 mg, 240 mg., 360 mg., and 540 mg dosage groups, respectively. More details can be found in the reviews conducted by Dr. U (completed October, 1997) and Dr. Karkowsky (also completed in October, 1997).

Further details relevant to NDA 20-401 related to the formulation can be found in my previous memoranda. NDA 20-401/S-007 is approvable for use in angina.

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

JAN 30 1998

EXCLUSIVITY SUMMARY FOR NDA # 20-401 SUPPL # 007

Trade Name Tiazac Generic Name diltiazem

Applicant Name Biovail HFD # 110

Approval Date If Known 1-30-98

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES / / NO /✓/

b) Is it an effectiveness supplement?

YES /✓/ NO / /

If yes, what type? (SE1, SE2, etc.) SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /✓/ NO / /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /✓/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /✓/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved.

Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /✓/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /✓/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not

independently support approval of the application?

YES /___/ NO /✓/

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /✓/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

1 HR 1321 A/8/USA/301/AP

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /~~___~~/ NO /✓/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /✓/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

HR 1321A/B/USA/301/AP _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /✓/ ! NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ ! NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

David Rosenberg
Signature
Title: RHPM

1-30-98
Date

Ray Lipicky
Signature of Office/
Division Director

1/30/98
Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

(11)

RHPM Package Overview

Application: NDA 20-401/S-007
Tiazac (diltiazem HCl) Capsules

Sponsor: Biovail Laboratories

User Fee Goal: January 27, 1998

Background

Tiazac is currently approved for the treatment of hypertension. This supplemental application provides for the use of Tiazac for the treatment of chronic stable angina. There are currently three other NDAs approved for the use of once-daily diltiazem formulations for the treatment of angina:

NDA 20-062: Cardizem CD (diltiazem HCl) Capsules

NDA 20-092: Dilacor XR (diltiazem HCl) Capsules

NDA 20-507: Tiamate (diltiazem malate) Tablets

Overview

Chemistry

Reviewer: Kathleen Jongedyk

Date: September 12, 1997

There are no Chemistry issues in this application.

Environmental Assessment

Reviewer: Florian Zielinski, Ph.D.

Date: March 17, 1997

The FONSI was completed

Medical

Reviewer: Khin Maung U, M.D.

Date: October 28, 1997

Dr. U recommends approval of the application. He has made several labeling recommendations on pages 60 and 61 of his review.

Secondary Review

Reviewer: Abraham Karkowsky, M.D., Ph.D.

Date: October 28, 1997

Dr. Karkowsky recommends approval of the application. He has provided a copy of marked-up labeling.

David Roeder
Regulatory Health Project Manager

dr/11-3-97

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

OCT 28 1997

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE:

FROM: Abraham Karkowsky, M.D., Ph.D. Group Leader HFD-110 Division of Cardio-Renal Drug Products a Karkowsky 10/27/97

SUBJECT: Approvability of Tiazac® (Diltiazem Hydrochloride) NDA 20-401 for Use in Angina Pectoris

TO: Dr. Raymond Lipicky, Director, Division of Cardio-Renal Drug products , HFD-110

This memo supports the approvability of Tiazac® for the treatment of chronic stable angina. My suggestions of labeling changes are appended. Since the approval of this formulation is based on only a single efficacy study I've toned down any labeling that would likely positively differentiate this product from any of the other sustained release diltiazem products that are approved for angina. Since we did not request a DSI audit of the study, none is pending.

Both immediate release and sustained release diltiazem hydrochloride formulations are already approved and marketed for the treatment of chronic stable angina. Tiazac® is already approved and marketed for the treatment of hypertension. Therefore, both the use of diltiazem hydrochloride for the treatment of angina pectoris as well as the safe use of Tiazac® are well established.

Tiazac® is not kinetically equivalent to other marketed sustained release formulations of diltiazem. The pharmacokinetic profile of Tiazac® was described in conjunction with this drug's approval as an antihypertensive. No additional kinetic studies were submitted for stable angina patients. Specifically, at a dose of 240 mg, the kinetics of Tiazac® differed from the equivalent doses of Cardiazem CD and Dilacor XR, two approved and marketed diltiazem sustained release formulations (see Table 1 for the kinetic profile). Both the AUC and C_{max} were substantially greater with the Tiazac® formulation than the other two formulations. Trough concentrations, however, were somewhat smaller with Dilacor XR than Tiazac®. Peak to trough differences in concentrations suggest that Tiazac® produces greater fluctuation in these concentrations over the day than the other two sustained release diltiazem formulations.

The dose range proposed for Tiazac® for the treatment of angina is equivalent to the range approved for hypertension.

Table 1 PK constants (SD) study 1242

	Tiazac®	Cardiazem	Dilacor
AUC 0-24	2400 (576)	1965 (587)	1901 (616)
C_{max}	183 (49)	152 (42)	131 (42)
C_{min}	46 (15)	46 (20)	44 (17)
Trough*	52 (4.3)	56 (5.1)	43 (3.6)
T_{max}	7.00 (1.8)	5.43 (1.4)	5.4 (2.0)

* Trough is defined as the average interdosing concentrations of days 4,5,6,7 an 8.

The only information that appears necessary for approval of Tiazac® for use in chronic stable angina is defining its useful dose range and dosing interval. The sponsor submits a single parallel group, dose-ranging, placebo-controlled, multicenter study (protocol HR 1321A/8/USA/301/AP) which supports both the dose range and once daily dosing interval for Tiazac®. This study was reviewed by Dr. Khin Muang U and the data in the tables are abstracted from his review.

A total of 257 patients were enrolled and randomized to placebo (n=50); or 120 mg (n=52); 240 mg (n=54); 360 mg (n=52) and 540 mg (n=49) of Tiazac ®. The study consisted of a 2-week single blind withdrawal period from previous medication. Eligible baseline treadmill testing was performed at the end of each of the two weeks of the placebo run-in phase. An additional single tread mill test was allowed after an addition 0.5 weeks, if the variability of the baseline treadmill measurement was > 15% of the higher measurement. Those randomized to all but the highest dose received their allocated medication for the next three weeks. Those randomized to the highest dose were forced titrated to that dose over a one week time span, with stable high dose given for two weeks. Each subject was, therefore, on their randomized dose for at least two weeks.

The results of ETT taken at trough and peak (8 hours after the dose) are shown below. Those who discontinued early had their last evaluable measurement carried forth. Overall there is a statistically significant increase in exercise capacity (maximal exercise time) on Tiazac® relative to placebo.

Table 2. Trough and Peak Exercise Tolerance study HR 1321A/8/USA/301/AP#.

Number of subjects randomized+	50	52	54	52	49	
Number discontinued/number with on therapy values	3/2	1/0	4/4	1/1	4/3	
Number with evaluable ETT (trough) in seconds	49	52	54	52	48	
Duration of Exercise (Baseline ±SE) in seconds	343 ±9.18	327 ±10.4	323 ±9.3	334 ±9.7	339 ±9.3	P=0.6
Change of ETT (trough ±SE) in seconds	14 ±8.2	26 ±6.4	41 ±7.2	33 ±7.5	32 ±6.3	P=0.024

Placebo subtracted (seconds)	———	12	**27**	**19**	18	
Number of subjects with peak values	47	51	50	50	46	
Baseline(peak ±SE) in seconds#	346 ±9.3	327 ±10.4	323 ±9.8	331 ±9.9	338 ±9.5	P=0.5
Exercise time (peak ±SE) in seconds	13 ±6.7	38 ±7.8	64 ±9.0	55 ±8.6	42 ±9.3	<0.001
Placebo subtracted (seconds)	———	**25**	**51**	**42**	**29**	

#Bold and underlined values indicates the individual dose compared to placebo has a $p < 0.05$, Bold without underline the p value is $0.1<p<0.05$.
+ subjects were stratified based on duration of exercise at baseline. Those with baseline ETT of between 3 to under 5 minutes were designated as stratum 1, those with baseline exercise of between 5-7 minutes as stratum 2.
* Overall two-way ANOVA. The terms in the model include treatment group, investigator and exercise duration (stratification) as fixed effects.

Maximum effect on both trough and peak exercise times are observed at 240 mg/day dose, there is little additional benefit at higher doses.

With respect to the effect of Tiazac ® on anginal attacks[1], the data are shown in Table 3 below. Among those with no anginal attacks at baseline, there was no difference in outcome whether subjects received placebo or active drug at any of the doses. Among those with some degree of angina at baseline, more subjects improved and fewer worsened while on active treatment. Nitroglycerine use paralleled angina frequency.

Table 3. Effects of Tiazac ® on Anginal frequency.

0	26	18 (72%)	7 (28%)		25	12 (48%)	2 (8%)	11 (44%)
120	21	17 (82%)	4 (19%)		29	25 (86%)	1 (3%)	3 (10%)
240	19	11 (59%)	8 (42%)		35	26 (74%)	1 (3%)	8 (23%)
360	18	13 (72%)	5(28%)		32	26 (81%)	2 (7%)	4 (13%)
540	25	23 (95%)	2 (5%)		23	23 (83%)	3(13%)	1 (4%)

Maximum benefit is again flat with respect to dose. There does not seem to be a particular benefit at doses greater than 120 mg in the improvement of anginal attacks.

Safety:

The safety of Tiazac ® in protocol HR 1321A/8/USA/301/AP was adequately summarized by Dr U. There were no deaths in the angina data base. There were six patients who discontinued during this study, three each in the 240 and 540 mg dose groups. The reason for discontinuation as per Dr. U's review is shown below.

[1] Occasionally, patient's measurements either at baseline or during active treatment were for intervals other than 7 days. The number of anginal attacks were, therefore, normalized to a one week period. When there were two weeks of baseline run-in, the anginal attack rate during the last week was considered the baseline measurement.

Table 4. Withdrawals for Adverse Events.

5201	240	4	Headache, rash, constipation. Patient discontinued 4 days prior to notifying investigator.
6102	540	4	Pruritic rash on buttocks which spread to chest and forearm. Study medication stopped.
6401	540	4	Patient experienced abdominal bloating, shortness of breath, ankle edema and headaches.
7154	240	5	Worsening ischemia. Hospitalized at Visit 5; had angiogram with angioplasty and stenting of Proximal LAD, and angioplasty of Diagonal and Ramus.
7253	240	5	Injured right knee; unable to complete visit 6.
2351	540	6	Ankle edema; investigator thought patient should go back to standard therapy.

Adverse events, as judged either by the number of events or subjects who had adverse events increased in a dose-related manner.

Table 5. Adverse Events.

Number at risk	50	52	54	52	49
Number of ADR	14	18	32	39	40
Subjects with ADR	9 (18%)	13 (25%)	19 (35%)	20 (39%)	22 (45%)
Headache	1 (2%)	3 (6%)	5 (9%)	5 (10%)	4 (8%)
Dizziness	0 (0%)	1 (2%)	1 (2%)	3 (6%)	5 (10%)
Peripheral edema	1 (2%)	0 (0%)	1 (2%)	2 (4%)	5 (10%)
Pain	1 (2%)	1 (2%)	3 (6%)	2 (4%)	1 (2%)
Dyspepsia	0 (0%)	0 (0%)	1 (2%)	1 (2%)	3 (6%)
Dyspnea	0 (0%)	0 (0%)	0 (0%)	1 (2%)	3 (6%)

In summary, this was a small data base, with a trend to increases in nuisance adverse events at higher Tiazac® doses.

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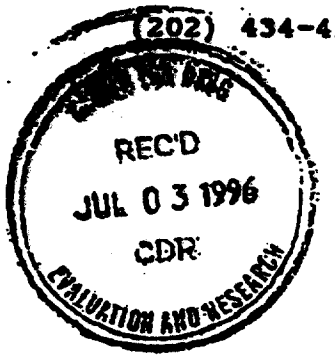

Via Hand Delivery

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
Park Building - Room 2-14
12420 Parklawn Drive
Rockville, Maryland 20857

Re: Time Sensitive Patent Information for Tiazac®
NDA No. 20-401

Dear Sir/Madam:

In accordance with 21 U.S.C. § 355(c)(2), 21 C.F.R. §§ 314.53(c) and (d), and 21 C.F.R. § 314.70(e), Biovail Corporation International hereby files the following information with the Food and Drug Administration (FDA) regarding a patent issued on June 25, 1996, covering the Company's Tiazac® (diltiazem hydrochloride), an approved new drug, NDA No. 20-401.

1. Patent Number: 5,529,791

2. Expiration Date: June 25, 2013

3. Type of Patent: Formulation

4. Patent Owner: Galephar P.R., Inc., Ltd., Carolina, Puerto Rico

Patent No. 5,529,791 is a newly-issued (June 25, 1996) patent that claims a formulation of the drug diltiazem hydrochloride which is marketed under the tradename Tiazac®. Biovail requests that FDA publish the patent information provided above in its List of Approved Drug Products (i.e., the Orange Book).

DECLARATION

The undersigned declares that Patent Number 5,529,791 covers a formulation of the drug diltiazem hydrochloride which is sold under the tradename Tiazac®. This product is currently approved under Section 505 of the Federal Food, Drug, and Cosmetic Act.

Sincerely,

John B. Dubeck
Counsel for Biovail Corporation International

cc: Division of Cardio-Renal Drug Products (HFD-110)

DEBARMENT CERTIFICATION

A debarment certification was filed with NDA 20,401. The reviewer is referred to the original NDA.