

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**21-392**

**Medical Review(s)**



Douglas C. Throckmorton, M.D.  
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857  
Tel (301) 594-5365, FAX (301) 594-5494

### Memorandum

DATE: 6.10.02

FROM: Douglas C. Throckmorton, M.D., Director  
Division of Cardio-Renal Drug Products (DCRDP), HFD-110

SUBJECT: NDA 21-392

NAME OF DRUG: Diltiazem Hydrochloride Extended Release Tablets

SPONSOR: Biovail Laboratories, Inc.

#### DOCUMENTS USED FOR MEMO:

1. Medical Review by Norman Stockbridge, M.D., dated 6.07.02.
2. Chemistry Reviews #1, 2 and 3 by Ram Mittal, Ph.D., dated 5.22.02, 5.22.02, and 6.07.02 respectively.
3. Clinical Pharmacology and Biopharmaceutics Review by Gabriel Robbie, dated 5.31.02.
4. Draft Labeling, prepared by Norman Stockbridge dated 6.06.02.
5. Statistical Review by John Lawrence, dated 2.13.02.
6. Review of proposed labeling by Cheryl Cropp, Pharm. D., BCPS, dated 5.24.02.
7. Summary of Biopharmaceutics Deficiencies by Angelic Dorantes, dated 6.07.02.
8. Proprietary Name review by Carol Holquist, R. Ph., Division of Medication Errors and Technical Support (DMETS), dated 5.10.02.

#### CONCLUSIONS

This memorandum constitutes the secondary review for the named supplement as well as the Divisional memorandum for the approvability of Diltiazem Hydrochloride Extended Release Tablets at the 240, 360 and 420 mg dose strengths to be administered in the morning or evening. While the clinical effects of the Diltiazem Hydrochloride Extended Release Tablets have been adequately demonstrated (that is, it is an antihypertensive), there are several issues remaining to be resolved prior to approval of this supplement, all of them discussed in the sections to follow:

- 1) Adequate demonstration of the bioequivalence of the 420 mg dose. While the current supplement adequately demonstrates the bioequivalence of the 360 mg dose to an approved product as well as dose-proportionality between several doses of Diltiazem Hydrochloride Extended Release Tablets (thus allowing for approval of lower doses than 360 mg), additional data are needed for approval of the 420 mg dose in the form of bioequivalence testing against an approved 420 mg sustained release diltiazem (or a combination of two lower doses of an approved drug).
- 2) Adequate comparative dissolution testing is needed to support the approval of the 120, 180, 240 and 300 mg tablets. While the timing of the dissolution testing submitted by the sponsor is acceptable, future testing should be conducted using a modified schedule recommended by the Agency to better characterize the dissolution profile of the product.

- 3) Additional comparative dissolution testing in support of a biowaiver for the proposed site-change for producing the 120, 180, 240, 300 and 360 mg tablets.
- 4) Additional comparative dissolution testing between the scored tablets (used for the trials submitted in the supplement) and unscored tablets (proposed for marketing) for the 120, 180, 240, 300, and 360 mg tablets.
- 5) Additional information regarding the identity of the drug substance to be used, and comparative analyses from the two manufacturers ( [ ] )
- 6) Agreement as to the product labeling, including choice of the proprietary name and the description of the trial conducted and submitted as part of the current supplement.

#### BACKGROUND

The source of the current supplement is an interest on the part of the current sponsor to develop a diltiazem extended release product [ ] There is a belief structure held by clinicians, not supported by clinical data, that a drug that prevents the early morning rise in blood pressure (BP) will be more effective at preventing cardiovascular events than one that has its major effects in the afternoon and evening (where the majority of other agents work). Based on this interest, the sponsor had proposed to develop and market a formulation that is identical to the currently approved Cardiazem CD, called Cardiazem [ ] Their hope was [ ]

[ ] To examine the effects of diltiazem when given in the evening, they conducted the clinical trial summarized in the Medical Review, examining (among other endpoints) the early morning effects of this compound compared with the effects of a sustained release drug administered in the morning.

The Division's view is that there are not sufficient data demonstrating a relationship [ ] hence to allow such claim in labeling would inappropriately influence physician prescribing by falsely implying a clinical benefit to where none has been demonstrated.

What follows is a summary of the reviews submitted for the supplement.

#### CHEMISTRY

There are three chemistry reviews, reflecting a series of submissions by the sponsor in support of this supplement. At the time of this action there remain several deficiencies that are enumerated in the last review, dated 6.7.02. They are enumerated below, along with their relevance to the approvability of the application at this time.

##### Reference Standard

1. The sponsor needs to provide additional information regarding the Reference Standard, including the list found on page 10 of Dr. Mittal's latest review. These materials have been requested of the sponsor (6.4.02) who has agreed to provide them. They have also agreed to reformat and resubmit the specification tables as requested by the Agency.

Insufficient reference standard information will be transmitted as a deficiency.

##### Drug Substance

1. The sponsor provided inadequate data on their analyses of the drug substance obtained from two different sources. It isn't clear from the submitted materials whether the sponsor conducted the analyses of impurity profiles for the two products [ ] or whether the respective companies did them. Without additional data on the two sources of drug substance, the observed differences in the diltiazem from the two sources (especially the particle size distribution data, see Dr. Mittal's last review page 12) cannot be interpreted except to suggest the two drug substances are different. Such a conclusion would require additional testing before the two could be accepted as acceptable, interchangeable sources of drug substance.

Insufficient information on the drug substance composition from these two companies will be transmitted as a deficiency.

#### Drug Product

1. The sponsor submitted stability testing through \_\_\_\_\_ for both standard and accelerated stability (see Dr. Mittal's second review, page 21-23). The standard stability data support a \_\_\_\_\_ but the \_\_\_\_\_ data were obtained using a product that differs from the to-be-marketed formulation (see Dr. Mittal's third review, page 20). Additionally, there are concerns about cracks noted in the coating from the samples stored at 40 degrees C/ 75% relative humidity. Given these deficiencies, a \_\_\_\_\_ expiration date is approvable pending additional standard stability data, and a warning is to be placed into the label against storage at >30 degree centigrade.

\_\_\_\_\_ The proposed Diltiazem Hydrochloride Extended Release Tablets dosages are approvable with a stability.

2. The stability testing was evaluated using 2, 8, 14 and 24 hour sampling. The Office of Biopharmaceutics has found these time points inadequate, and proposed new points to be used in the future (2, 6, 12 and 18 hours), as discussed in the review by Dr. Robbie and Dr. Dorantes. The stability testing conducted to date is acceptable, provided that future testing on the first three post-marketing batches includes these additional time points and be submitted to the Annual Report.

The need for additional time points during stability testing of future lots will be transmitted to the sponsor.

3. The dissolution and stability testing to date were done on scored tablets, but the sponsor proposes to market unscored tablets (Dr. Mittal's third review, page 17-18). The sponsor needs to provide comparative dissolution specifications for the scored and unscored tablets.

Insufficient comparative dissolution for the scored and unscored tablets will be transmitted as a deficiency in the approvable letter.

#### Environmental Assessment, Microbiology, Closure Container System, Compliance Inspections

Per Dr. Mittal's reviews the sponsor's proposal for an exemption from the Environmental Assessment is satisfactory. The reviews of Microbiology and Closure Container System, and the Inspections completed by Compliance have identified no approvability issues.

#### **PHARMACOLOGY TOXICOLOGY**

There was no Pharmacology Toxicology review of this supplement and no issues identified.

#### **CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS**

The conclusions for the Biopharmaceutics review rely on both the formal review by Dr. Robbie as well as additional reviews by his supervisor, Dr. Dorantes, who summarized her conclusions in a memo dated 6.07.02.

#### Proposed 420 mg Strength

The data submitted by the sponsor adequately demonstrated the bioequivalence of the 360 mg Diltiazem Hydrochloride Extended Release Tablets with 2 x 180 mg approved extended release capsules. The highest proposed dose for the tablets (420 mg) was not tested for bioequivalence and a biowaiver cannot be granted on the basis of bioequivalence data from the 360 mg dose.

The need for a bioequivalence study using the 420 mg dose is identified as a deficiency.

#### Dissolution Testing

The Biopharmaceutics Division had reservations about the dissolution specifications proposed by the sponsor (see Dr. Robbie's review for details, recommendations page 3). In short, the time points chosen were sub-optimal for defining the dissolution profile of the Diltiazem Hydrochloride Extended Release Tablets. Having reviewed the dissolution data (see Dr. Robbie's review starting on page 74), the use of the time points proposed by Biopharmaceutics (2, 6, 12 and 16 hours) will give slightly different, but not dramatically different results from those obtained using the sponsor's time points (2, 8, 14, 24 hours). While an issue to be addressed in future stability testing, this does not affect the approvability of this supplement.

There are issues related to the extent of the dissolution testing submitted by the sponsor; as summarized by Biopharmaceutics there is inadequate dissolution data to support presently the approval the 120, 240 300 and 360 mg doses of the Diltiazem Hydrochloride Extended Release Tablets (see Dr. Robbie's review, starting on page 74 and Dr. Dorantes' summary). This includes inadequate data to support the proposed site change for drug product manufacturing.

The need for changes in the dissolution specifications (changes in the time points used), and the need for additional dissolution data in different media are identified as a deficiency.

#### MEDICAL/STATISTICAL REVIEW

Both Dr. Stockbridge and Dr. Lawrence concluded that Diltiazem Hydrochloride Extended Release Tablets demonstrated antihypertensive efficacy, although Dr. Lawrence expressed concern about the lack of robust statistical findings for several of the doses short of the 540 mg dose. There is at present no approved trademarked name for this product. The sponsor proposed Cardiazem — but the implied claim for nighttime efficacy is not allowable absent clinical data of its relevance (see DMETs review by Dr. Holquist).

#### Efficacy

The sponsor submitted a single randomized, double blind, placebo-controlled, forced titration, parallel group study in patients with mild-to-moderate hypertension, comparing Diltiazem Hydrochloride Extended Release Tablets at doses of 120, 240, 360 and 540 mg to placebo. The primary endpoint was change in trough diastolic blood pressure (DBP) as recorded by ambulatory blood pressure monitoring (ABPM) between 6 p.m. and 10 PM the night after administration of study drug. As reviewed by Dr. Lawrence (Table 2), all doses had a negative point estimate for effect on BP, and doses of 240, 360 and 540 mg achieved nominally significant effects on BP relative to placebo, ranging between -1.9 mmHg for the 120 mg dose to -8.0 mmHg for the 540 mg dose. He concluded that while the 240 and 360 mg doses 'appeared to effective relative to placebo' with p Values of 0.034 and 0.020 respectively, their strength of evidence was not as great as that seen for the 540 mg dose (p Values <0.001).

The sponsor also explored a number of other time points and comparisons for BP lowering. One comparison the sponsor was particularly interested in was the effect of a.m. versus p.m. administration of Diltiazem Hydrochloride Extended Release Tablets on BP. The pharmacology of diltiazem was predictable in both groups: the maximal blood pressure reduction occurred approximately 12 hours after taking the drug, whether taken in the am or at night. Despite some observed differences in the bioavailability of the Diltiazem Hydrochloride Extended Release Tablets when taken at night, however, no significant differences in 24-hour mean BP control were seen (see Dr. Lawrence's review, table 3).

Of interest, the 120 mg dose did not demonstrate a significant antihypertensive effect (for instance, see Dr. Stockbridge's review Appendix one, Figure one), measured as change in DBP; all of the relevant measures of antihypertensive effect were well less than 50% of those recorded for the 240 mg tablet (*ibid*, table 2).

#### Safety

The safety review from this study revealed no new safety concerns for diltiazem (see Dr. Stockbridge's review, section 12.2.1.4.3).

#### SUMMARY

When administered in the evening, Diltiazem Hydrochloride Extended Release Tablets is clearly effective as an antihypertensive, with anti-hypertensive efficacy demonstrated in the one trial submitted in the NDA at doses of 240, 360, 420 and 540 mg. Dr. Lawrence is correct that the most robust effects were seen with the 540 mg dose, but there is a clear dose-related effect present at the lower dose. For the 120 mg dose, no clear antihypertensive effect was demonstrated. As predicted by the pharmacokinetics of the drug's release, peak effects occur after approximately 12 hours, so that taking the drug in the late evening means that the trough BP effect will be maximal in the morning, while taking it in the morning results in peak BP effects in the evening. Taking Diltiazem Hydrochloride Extended Release Tablets in the evening did not have a significantly greater effect on BP than taking it in the am, when integrated over the entire 24 hours using ABPM.

Regarding the Biopharmaceutics and Chemistry issues, significant additional data are needed to buttress the approval of several of the doses of the Diltiazem Hydrochloride Extended Release Tablets. Most significantly, additional bioequivalence data are needed for the 420 mg dose, and additional dissolution data are needed to support the biowaivers for the lower doses.

The issue, then, is whether to issue an 'Approvable' or a 'Not Approvable' letter, given the deficiencies noted above. The trial demonstrated clinical efficacy for the Diltiazem Hydrochloride Extended Release Tablets, such that this supplement is approvable. Diltiazem Hydrochloride Extended Release Tablets are effective as antihypertensive drug product, and can be taken in the morning or at night without demonstrable differences in efficacy. The consequences of taking the medication in the morning or at night are manifest by the timing of the peak antihypertensive effect: whether the timing of this peak has any clinical relevance is unknown.

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Doug Throckmorton  
6/11/02 07:34:43 AM  
MEDICAL OFFICER



## DIVISION OF CARDIO-RENAL DRUG PRODUCTS

### Primary Clinical Review

NDA: 21-392

Sponsor: Biovail Laboratories

Submission: Supplement consisting of one clinical study supporting antihypertensive effectiveness. [

Review date: June 7, 2002

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Summary: Cardizem CD (extended release diltiazem) is an effective antihypertensive given once daily morning or evening.

Distribution: NDA 21-392

HFD-110/Project Manager

#### Table of contents

1	Executive summary .....	3
1.1	Recommendations .....	3
1.1.1	Recommendation on approvability .....	3
1.1.2	Recommendation on Phase 4 studies and risk management steps .....	3
1.2	Summary of clinical findings .....	3
1.2.1	Brief overview of clinical program .....	3
1.2.2	Efficacy .....	3
1.2.3	Safety .....	3
1.2.4	Dosing .....	3
1.2.5	Special populations .....	3
2	Introduction and background .....	4
2.1	Drug established and proposed trade name, drug class, sponsor's proposed indication(s), dose, regimens, age groups .....	4
2.2	State of armamentarium for indication(s) .....	4
2.3	Important milestones in product development .....	4
2.4	Other relevant information .....	4
2.5	Important issues with pharmacologically related agents .....	4
3	Clinically relevant findings from chemistry, animal pharmacology and toxicology, microbiology, biopharmaceutics, statistics and/or other consultant reviews .....	5
4	Human pharmacokinetics and pharmacodynamics .....	6
4.1	Pharmacokinetics .....	6
4.2	Pharmacodynamics .....	6
5	Description of clinical data and sources .....	7
5.1	Overall data .....	7
5.2	Tables listing the clinical trials .....	7
5.3	Postmarketing Experience .....	7
5.4	Literature Review .....	8
6	Clinical review methods .....	9
6.1	Describe how review was conducted .....	9
6.2	Overview of materials consulted in review .....	9
6.3	Overview of methods used to evaluate data quality and integrity .....	9
6.4	Were trials conducted in accordance with accepted ethical standards .....	9

- 6.5 Evaluation of financial disclosure ..... 9
- 7 Integrated review of efficacy..... 10
  - 7.1 Briefly present conclusions and any critical differences from sponsor's proposed label claims..... 10
  - 7.2 General approach to review of the efficacy of the drug..... 10
  - 7.3 Detailed review of trials by indication ..... 10
  - 7.4 Efficacy conclusions ..... 10
- 8 Integrated review of safety..... 11
  - 8.1 Brief statement of conclusions ..... 11
  - 8.2 Description of patient exposure (i.e., number of patients at given duration, dose, demographic, distribution, country)..... 11
  - 8.3 Methods and specific findings of safety review ..... 11
  - 8.4 Adequacy of safety testing..... 11
  - 8.5 Summarize critical safety findings and limitations of data..... 11
- 9 Dosing, regimen, and administration issues ..... 12
- 10 Use in special populations ..... 13
  - 10.1 Critically evaluate sponsor's gender effects analyses and adequacy of investigation..... 13
  - 10.2 Critically evaluate evidence for age, race, or ethnicity effects on safety or efficacy ..... 13
  - 10.3 Evaluate pediatric program..... 13
  - 10.4 Comment on data available or needed in other populations such as renal or hepatic compromised patients, or use in pregnancy..... 13
- 11 Conclusions and recommendations ..... 14
  - 11.1 Conclusions..... 14
  - 11.2 Recommendations ..... 14
- 12 Appendix..... 15
  - 12.1 Other relevant materials ..... 15
  - 12.2 Individual studies ..... 15
    - 12.2.1 B00.CT3.011.DIL G99: A double-blind, randomized, parallel-group, dose-response, multicenter study to compare the safety and efficacy of diltiazem HCl extended-release capsules (G99) to placebo dosed at bedtime and to G99 dosed in the morning in patients with moderate to severe essential hypertension..... 15
      - 12.2.1.1 Study dates ..... 15
      - 12.2.1.2 Source materials reviewed ..... 15
      - 12.2.1.3 Protocol ..... 15
      - 12.2.1.4 Results..... 15
        - 12.2.1.4.1 Conduct..... 15
        - 12.2.1.4.2 Effectiveness ..... 16
        - 12.2.1.4.3 Safety ..... 17

**List of Tables**

- Table 1. Demographics in phase II (PATH-I)..... 16
- Table 2. Vital sign changes from baseline and placebo with evening dosing..... 16
- Table 3. Common adverse events (%) ..... 18

## **1 Executive summary**

### **1.1 Recommendations**

#### **1.1.1 Recommendation on approvability**

There are no clinical barriers to approval of Cardizem™ as an antihypertensive for use once daily in the morning or evening. The various unresolved chemistry and biopharmaceutics issues should result in an "approvable" action at this time.

#### **1.1.2 Recommendation on Phase 4 studies and risk management steps**

No phase 4 studies are recommended. No risk management steps are recommended.

### **1.2 Summary of clinical findings**

#### **1.2.1 Brief overview of clinical program**

The evening dosing of diltiazem in the treatment of hypertension is supported by a single clinical study. This study was a double-blind, parallel study in which subjects with moderate diastolic hypertension ( $100 < \text{DBP} < 114$  mmHg by cuff) were randomized (70-100 subjects per group) to placebo or diltiazem 120, 240, 360, or 540 mg once daily in the evening or diltiazem 360 mg once daily in the morning. Follow-up was at 7 weeks.

#### **1.2.2 Efficacy**

Diastolic pressure by ABPM (primary) or cuff (secondary) was statistically significantly reduced in the 240- to 540-mg groups compared with placebo. The magnitude of effect at trough was similar to that previously reported for once-daily dosing in the morning. These doses also reduced systolic pressure, somewhat more than diastolic pressure, and there was a clinically insignificant effect on heart rate.

Not surprisingly, when effects of morning and evening dosing on morning blood pressure were compared, the more proximal evening dosing had a greater effect.

#### **1.2.3 Safety**

Conventional safety monitoring was performed. There were no findings suggestive of differences in risk between morning and evening dosing.

#### **1.2.4 Dosing**

The study collected data over the dosing range approved for once-daily administration in the morning. Dose-limiting side effects were not demonstrated; it may be true that higher doses could be tolerated.

#### **1.2.5 Special populations**

Not applicable.

## **2 Introduction and background**

### **2.1 Drug established and proposed trade name, drug class, sponsor's proposed indication(s), dose, regimens, age groups**

The calcium channel blocker diltiazem (Cardizem CD) is approved for treatment of hypertension and angina in adults. The approved dose range is 180 to 360 mg, with "limited general clinical experience" with 540 mg, once-daily, without specification of the timing of the dose. The sponsor proposed to market a formulation identical to Cardizem CD, called Cardizem — [ The Cardizem — name is used throughout this review; however, it has been found unacceptable, as was the concept of identical products distinguished only by recommended time of dosing.

### **2.2 State of armamentarium for indication(s)**

Of the many drug approved for hypertension, none have a claim for nighttime use.

### **2.3 Important milestones in product development**

The sponsor's NDA for Cardizem — was converted to a supplement to the NDA for cardizem extended release tablets.

### **2.4 Other relevant information**

Not applicable.

### **2.5 Important issues with pharmacologically related agents**

Not applicable.

**Appears This Way  
On Original**

### 3 Clinically relevant findings from chemistry, animal pharmacology and toxicology, microbiology, biopharmaceutics, statistics and/or other consultant reviews

There are no reviews of pharmacology, toxicology, or microbiology.

Three Chemistry reviews from Dr. Mittal, two dated 5 June 2002 and one dated 6 June 2002 (all much too close to the regulatory decision date) enumerate numerous deficiencies, but conclude that the data support an "approvable" action. Deficiencies include the following:

- There is no information on the drug substance reference standard.
- Drug substance from two suppliers needs to be shown to have similar physical properties.
- Stability data support a — expiration, not the — ; requested by the sponsor, for all six dosage strengths.
- Product label should describe the known effects of high-temperature storage (cracked coatings or broken tablets).
- "Once-a-day-dosage" should not appear on packaging.

Many other 'deficiencies' are complaints about the organization of the NDA.

Environmental assessment information was satisfactory.

Facility inspection was satisfactory

The Biopharmaceutics review dated 31 May 2002 (much too close to the regulatory decision date) found no clinical issues.

The 360-mg tablet is bioequivalent to the extended release capsule (2x180 mg). The proposed 420-mg tablet would require a bioequivalence study; upward extrapolation is not acceptable. The 240- and 300-mg tablets are dose proportional with the 360-mg tablets and a bioequivalence waiver can be granted provided the sponsor demonstrates acceptable dissolution data for 0.1 N HCl. Dissolution data in water and 0.1 N HCl are needed for the 120- and 180-mg tablets<sup>1</sup>.

Appears This Way  
On Original

---

<sup>1</sup> Although the Biopharmaceutics review does not say so, the Chemistry review shows all tablet strengths to have a composition proportional to the dose.

## 4 Human pharmacokinetics and pharmacodynamics

Comments on pharmacokinetics are based on the Clinical Pharmacology and Biopharmaceutics Review by Dr. Robbie, dated 31 May 2002.

### 4.1 Pharmacokinetics

The sponsor proposes to market 120-, 180-, 240-, 300-, 360-, and 420-mg extended release tablets.

The sponsor's proposed 360-mg extended release tablets were found to be bioequivalent to the approved 360-mg extended release capsules and to 2x180-mg extended release capsules.

Single evening administration of diltiazem tablets resulted in 10% higher C<sub>max</sub> and 15% higher AUC than did morning administration (both times fasting). Similar effects were seen with repetitive dosing. The explanation for this difference is not known.

Food did not significantly affect bioavailability.

Biopharmaceutics recommends changes in the proposed dissolution specifications.

### 4.2 Pharmacodynamics

Not applicable.

Appears This Way  
On Original

## 5 Description of clinical data and sources

### 5.1 Overall data

The reviewed data came from the sponsor's development program.

### 5.2 Tables listing the clinical trials

There was one study of antihypertensive effectiveness: *B00.CT3.011.DIL G99: A double-blind, randomized, parallel-group, dose-response, multicenter study to compare the safety and efficacy of diltiazem HCl extended-release capsules (G99) to placebo dosed at bedtime and to G99 dosed in the morning in patients with moderate to severe essential hypertension.* This study is described in detail in section 12.2.1 on page 15.

The following were studies of biopharmaceutics, reviewed elsewhere:

- Study 2433: A two-way, crossover, open-label, single-dose, night time administration, fasting comparative bioavailability study of diltiazem hydrochloride 360 mg extended-release bead tablets versus diltiazem hydrochloride 2 x 180 mg extended release capsules in normal healthy non-smoking male and female subjects.
- Study 2489: A two-way, cross-over, open-label, single-dose, night time administration, fed, comparative bioavailability study of diltiazem hydrochloride 360 mg extended-release bead tablets versus diltiazem hydrochloride 360 mg extended release capsules in normal healthy non-smoking male and female subjects.
- Study 2435: A two-way, crossover, multiple-dose, open-label, night time administration, fasting, comparative bioavailability study of diltiazem hydrochloride 360 mg extended-release bead tablets versus diltiazem hydrochloride 2 x 180 mg extended release capsules in normal healthy non-smoking male and female subjects.
- Study 2492: A two-way, crossover, multiple-dose, open-label, night time administration, fasting, comparative bioavailability study of diltiazem hydrochloride 360 mg extended-release bead tablets versus diltiazem hydrochloride 360 mg extended release capsules in normal healthy non-smoking male and female subjects.
- Study 2434: A two-way, crossover, open-label, single-dose, fasting, comparative bioavailability study of diltiazem hydrochloride 360 mg extended-release bead tablets under morning administration versus evening administration conditions in normal healthy non-smoking male and female subjects.
- Study 2463: A two-way, crossover, open-label, multiple-dose, fasting, comparative bioavailability study of diltiazem hydrochloride extended-release capsules (2 x 180 mg) with morning drug administration and diltiazem hydrochloride extended-release capsules (2 x 180 mg) with evening drug administration in normal healthy non-smoking male and female subjects.
- Study 2438: A four-way, crossover, single-dose, open-label, fasting pharmacokinetic study of three formulations of diltiazem hydrochloride extended-release bead tablets 360 mg (q.d.) and one formulation of an oral diltiazem hydrochloride solution 120 mg (q.d.) in normal, healthy, non-smoking male subjects.

### 5.3 Postmarketing Experience

Not applicable.

**5.4 Literature Review**

No literature was supplied. No search was made.

Appears This Way  
On Original

## **6 Clinical review methods**

### **6.1 Describe how review was conducted**

The one non-biopharmaceutics study was reviewed in detail. See section 12.2.1 on page 15. There were no integrated summaries of efficacy and safety, and there is no integrated review of efficacy or safety.

### **6.2 Overview of materials consulted in review**

Only paper documents were provided. There was no original protocol for the one study in hypertensive subjects; the description is based on the final study report. The review made some use of the electronic datasets.

The IND record was not consulted.

### **6.3 Overview of methods used to evaluate data quality and integrity**

No DSI audit was requested or performed.

### **6.4 Were trials conducted in accordance with accepted ethical standards**

Yes.

### **6.5 Evaluation of financial disclosure**

The sponsor categorically denies inappropriate financial arrangements with investigators for study B00.CT3.011.DIL G99 (the only study for which such assurance is needed), as defined in 21CFR54.2(a), (b), and (f).

Appears This Way  
On Original

## 7 Integrated review of efficacy

### 7.1 Briefly present conclusions and any critical differences from sponsor's proposed label claims.

There was only one study. The sponsor's proposed description of its results in the proposed label is consistent with the reviewer's view of the study.

### 7.2 General approach to review of the efficacy of the drug

Not applicable.

### 7.3 Detailed review of trials by indication

A detailed review of study B00.CT3.011.DIL G99: *A double-blind, randomized, parallel-group, dose-response, multicenter study to compare the safety and efficacy of diltiazem HCl extended-release capsules (G99) to placebo dosed at bedtime and to G99 dosed in the morning in patients with moderate to severe essential hypertension.* This study is described in detail in section 12.2.1 on page 15. Briefly, this was a parallel study with hypertensive subjects randomized to one of six arms: placebo, diltiazem given in the evening at 120, 240, 360, or 540 mg, or diltiazem 360 mg given in the morning. Primary end points were changes from baseline and placebo for trough diastolic pressure by ABPM for the nighttime dosing regimens, and comparisons of morning and evening doses for morning diastolic pressure, also by ABPM. Doses above 120 mg were clearly effective. Dosing the night before produces greater blood pressure reduction in the morning compared with dosing 24 hours earlier.

The Statistical review by Dr. Lawrence, dated 13 February 2002, is consistent with this interpretation of the study<sup>2</sup>.

### 7.4 Efficacy conclusions

There is a high prior expectation that once-daily dosing at different times of day should result in similar changes in trough blood pressure, and that dosing in the evening would result in greater blood pressure reduction in the morning, about 12 hours later, than would dosing the previous morning.

This one study might have sufficed to show diltiazem was an effective antihypertensive, even in the absence of strong priors, but with these priors, the study's results are certainly compelling.

Appears This Way  
On Original

---

<sup>2</sup> Dr. Lawrence does, however, note that the persuasiveness of the results at low doses are not what one would want to see if they were, individually the basis of approval.

## **8 Integrated review of safety**

### **8.1 Brief statement of conclusions**

Safety findings with once-daily dosing at night were similar to those seen with morning administration in this study and others.

### **8.2 Description of patient exposure ( i.e., number of patients at given duration, dose, demographic, distribution, country)**

See section 12.2.1 on page 15.

### **8.3 Methods and specific findings of safety review**

Not applicable.

### **8.4 Adequacy of safety testing**

There is no a priori reason to expect that the risk of nighttime dosing is greater than for daytime dosing, so the sponsor's safety evaluation program is adequate.

### **8.5 Summarize critical safety findings and limitations of data**

The safety data from nighttime dosing did not reveal unusual risks.

Appears This Way  
On Original

## **9 Dosing, regimen, and administration issues**

Once daily administration of extended release diltiazem in the evening at doses of 240 to 540 mg produced antihypertensive effects consistent with existing data, which is probably substantially based on daytime administration. Dosing instructions can simply indicate that either time may be used.

Appears This Way  
On Original

**10 Use in special populations**

**10.1 Critically evaluate sponsor's gender effects analyses and adequacy of investigation**

Not applicable.

**10.2 Critically evaluate evidence for age, race, or ethnicity effects on safety or efficacy**

Not applicable.

**10.3 Evaluate pediatric program**

Not applicable.

**10.4 Comment on data available or needed in other populations such as renal or hepatic compromised patients, or use in pregnancy.**

Not applicable.

Appears This Way  
On Original

## 11 Conclusions and recommendations

### 11.1 Conclusions

Extended release diltiazem is an effective antihypertensive when administered once daily in the morning or evening.

### 11.2 Recommendations

The Dosage and Administration section should say that the product can be administered once daily in the morning or evening.

There is no good reason to include a description [ ] in the clinical trials section.

The approval letter should state that any promotion of nighttime use should be balanced with the statement that better outcome has not been demonstrated.

Appears This Way  
On Original

## 12 Appendix

### 12.1 Other relevant materials

Not applicable.

### 12.2 Individual studies

#### 12.2.1 B00.CT3.011.DIL G99: A double-blind, randomized, parallel-group, dose-response, multicenter study to compare the safety and efficacy of diltiazem HCl extended-release capsules (G99) to placebo dosed at bedtime and to G99 dosed in the morning in patients with moderate to severe essential hypertension.

##### 12.2.1.1 Study dates

10 August 2000 to 22 June 2001.

##### 12.2.1.2 Source materials reviewed

Final study report: Vol 106, page 003.

Fully amended protocol and amendments: Not in evidence.

##### 12.2.1.3 Protocol

The study population was to be 462 subjects, age 18 to 70 years, with seated diastolic pressure 100 to 114 mmHg by cuff and mean ABPM diastolic pressure 90-114 mmHg. Exclusions were made for (1) nightshift work schedule, (2) childbearing potential without adequate contraception, (3) within one year of hypertensive encephalopathy, stroke or TIA, (4) within one year of myocardial infarction or unstable angina, (5) resting sinus bradycardia or other rhythm disturbances, (6) heart failure, left ventricular dysfunction, or cardiac valvular disease, (7) evidence of chronic renal or hepatic impairment, and (8) pulmonary hypertension or other pulmonary disease. There were other criteria concerning ability to complete study.

The study was double-blind. Subjects discontinued antihypertensive treatment and underwent a 3-4 week single-blind run-in, at the end of which they had to meet requirements for stable hypertension. Qualified subjects were randomized to placebo or to evening doses (10 pm  $\pm$  1 h) of diltiazem 120, 240, 360, or 540 mg, or the morning doses (8 am  $\pm$  1 h) of diltiazem 360 mg. Subjects randomized to diltiazem 540 mg received 360 mg the first week. Follow-up was 7 weeks. Cuff blood pressure was assessed at each visit. ABPM was assessed over 36 hours at baseline and after the last dose. Cuff blood pressure was also obtained.

Study drug was commercial diltiazem capsules and matching placebo.

The primary analyses were (1) change from baseline and placebo in trough diastolic pressure, as assessed by ABPM, using Dunnett's procedure to correct for multiple comparisons for the evening doses, and (2) comparison of mean diastolic pressure between 6 am and noon for the two 360-mg dose groups. The primary analysis group was intent-to-treat.

##### 12.2.1.4 Results

###### 12.2.1.4.1 Conduct

Thirty-nine US centers enrolled 1 to 29 subjects for a total of 478 subjects, of whom 426 (89%) completed (83% on placebo). The most common reasons for withdrawal were adverse events (n=16), noncompliance (10), withdrawn consent (8), and "other" (10). No category appeared to be dose-related. Data from 4 subjects appear to have been excluded from the ITT analyses, 2 for noncompliance and 2 for use or concomitant medication.

Demographics are summarized in Table 1.

**Table 1. Demographics in phase II (PATH-I)**

	Placebo N=69	Diltiazem				
		120 mg PM N=67	240 mg PM N=68	360 mg AM N=102	360 mg PM N=103	540 mg PM N=69
Age ± SD	52±10	52±10	53±9	54±10	53±8	51±10
Male (%)	65	69	62	60	67	58
Caucasian (%)	65	52	62	65	65	68
Black	23	33	35	28	27	20

Discrepancies among treatment groups were about what was to be expected in a study of this size.

Baseline blood pressures were similar across all groups.

**12.2.1.4.2 Effectiveness**

Effects on blood pressure are summarized in Table 2.

**Table 2. Vital sign changes from baseline and placebo with evening dosing<sup>3</sup>**

		120 mg	240 mg	360 mg	540 mg
ABPM <sup>4</sup>	DBP	-1.9	-5.1	-3.1	-8.0
	SBP	-3.3	-8.6	-5.1	-10.4
	HR	1.3	0.0	-3.1	-3.9
Cuff <sup>5</sup>	DBP	0.3	-3.2	-4.8	-8.6
	SBP	-1.5	-6.1	-4.6	-12.3
	HR	-2.1	-3.8	-2.9	-3.2

Most of the effects at doses above 120 mg were nominally statistically significant. The primary analysis of ABPM diastolic pressure by ANCOVA showed statistical significance at these doses as well.

The ABPM time course data are shown in Figure 1. The curves generally order by dose. The data for 360 mg morning and evening dosing are very similar to one another. The peak effects on systolic and diastolic pressure occur 8 to 12 hours after dosing.

Appears This Way  
On Original

<sup>3</sup> Data from sponsor's tables 8, 16, 18, 20, 23, and 26.

<sup>4</sup> Values shown are ABPM means from 6pm-10pm (near trough). They are not from the ANCOVA model.

<sup>5</sup> Values shown are from assessments at 6pm ± 1 h. They are not from the ANCOVA model.

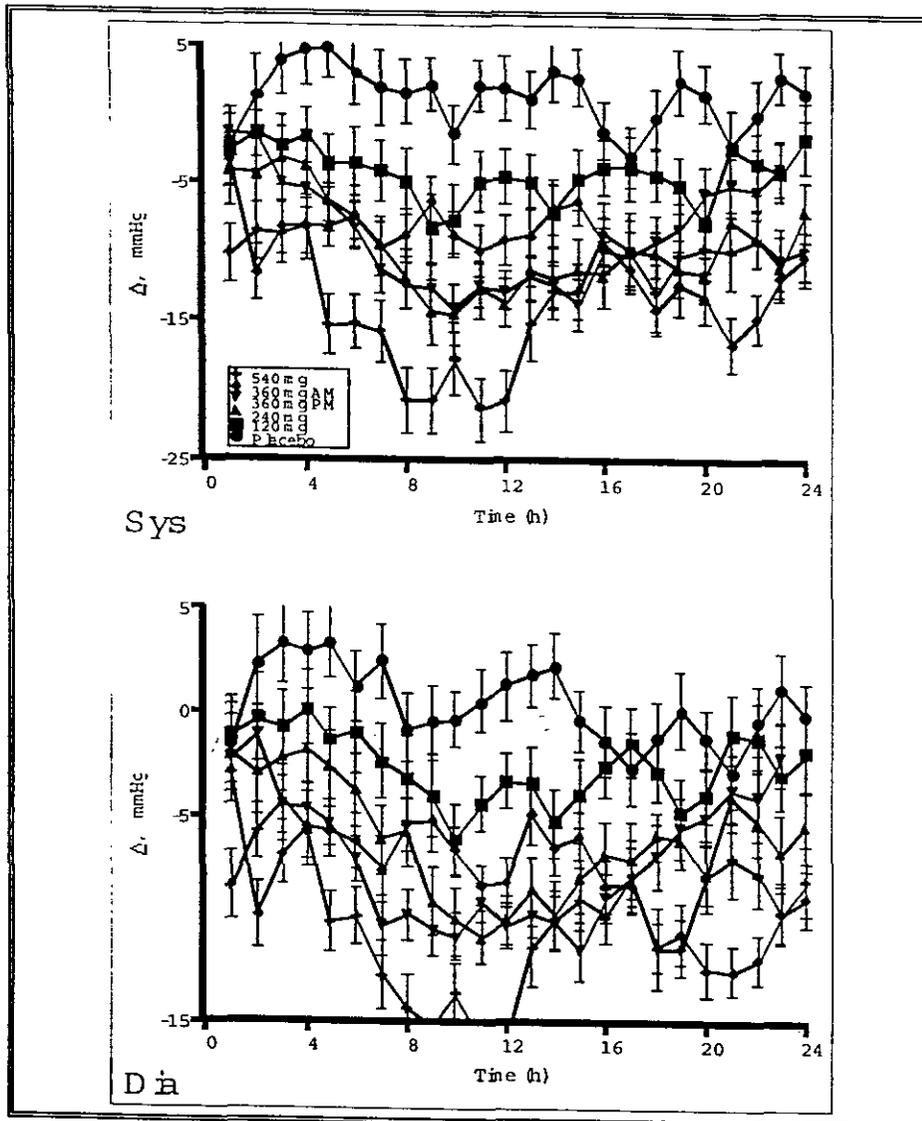


Figure 1. Hourly average ABPM data

Hourly averaged ABPM data were provided in the sponsor's dataset. Subjects with both a baseline and on-treatment ABPM contributed to this analysis. Each subject's diurnal variation was subtracted by taking the differences between on-treatment and baseline aligned by time of day. Then the curves were obtained for the average ( $\pm$ SE) response by treatment group and hour from dosing. The curve for the placebo group is shown; the data for the other doses are not placebo-subtracted.

The second primary end point, a comparison of morning diastolic pressure following morning or evening dosing with 360 mg demonstrated about a 3 mmHg greater reduction ( $p=0.0004$ ) after the evening dose (12 hours previous) compared with the morning dose (24 hours previous).

#### 12.2.1.4.3 Safety

There were no deaths.

Adverse events led to discontinuation from randomized treatment for 4% of subjects on placebo, 120 mg, or 240 mg, 5% on 540 mg, and 1.5% on the two 360-mg regimens

combined. Events leading to the withdrawal of more than one subject from active treatment groups were headache (n=4), edema (3), and dermatitis (2).

Two adverse events were considered serious: chest pain and dizziness, the latter of which led to the subject's withdrawal.

Events reported in at least 5 subjects on active treatment and more common on study drug than on placebo are shown in Table 3.

**Table 3. Common adverse events (%)**

	Plcbo N=69	Dilt N=409		Plcbo	Dilt
URI	2.9	5.6	Dizziness	0	1.5
Nasopharyngitis	1.4	2.7	Nausea	0	1.5
Dermatitis	0	2.0	Back pain	1.4	1.5
Fatigue	1.4	2.0	Bronchitis	0	1.2
Cough	0	1.7			

A variety of laboratory abnormalities were reported, all non-serious, and generally consistent with existing labeling.

Appears This Way  
On Original

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Norman Stockbridge  
6/7/02 12:14:14 PM  
MEDICAL OFFICER

**Memo to the file**

Date: January 24, 2002  
From: Colleen LoCicero, RHPM  
To: IND 63,787  
Subject: 30-day safety evaluation

This IND is for a study of a tablet extended-release formulation of diltiazem that the Sponsor indicates (in the cover letter of the submission) is the formulation filed in pending NDA 21-392. Mr. Wayne Kreppner of Biovail clarified in a telephone communication that the clinical efficacy studies submitted in NDA 21-392 were done with a capsule extended-release formulation of diltiazem, for which there is an existing IND. He indicated that bioequivalence studies to bridge the capsule and tablet formulations are provided in NDA 21-392. The Sponsor wishes to perform the study proposed in this December 10, 2001 submitted IND using the tablet extended-release formulation that is pending approval (NDA 21-392) and for which there is no existing IND. Therefore, they submitted this IND.

In light of the above information, Dr. Stockbridge decided that a 30-day safety meeting would not be needed for this application.

Both Drs. Stockbridge (medical reviewer) and Koerner (pharmacology reviewer) identify no safety concerns with the proposed study in their reviews dated December 27, 2001 and January 4, 2002, respectively. Both recommend proceeding with the proposed study.

While Dr. Mittal's review of the IND is not completed yet, Dr. Srinivasachar informed me that Dr. Mittal did not have any safety concerns with the proposed study.

**Appears This Way  
On Original**

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Colleen LoCicero  
1/24/02 04:09:35 PM  
CSO