# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: NDA 20939

## MEDICAL REVIEW(S)

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DIVISION OF CARDIO-RENAL DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA Number: 20-939

Name of Drug: Diltiazem ER

Sponsor: Biovail Corporation International

Type of Submission: New Drug Application

Indication: Hypertension

Date of Submission: April 15, 1999

Date Received: April 16, 1999

Date Review Completed: July 23, 1999

Reviewer: Cristobal G. Duarte, MD

1.0. Title of Study: **"A Double Blind, Placebo-Controlled, Parallel Group, Fixed-Dose Study of the Efficacy and Adverse Event Profile of Diltiazem Extended Release (ER) in the Treatment of Essential Hypertension".**

2.0. Principal Investigators And Sites of Investigation:

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3.0. Objectives: The objectives of this study were:

- To determine efficacy and safety profile of a single daily dose formulation of diltiazem (diltiazem ER, Bioavail), given at doses ranging from 120 mg to 540 mg in patients with stable, mild [supine diastolic blood pressure (DBP) 95-104 mmHg] and moderate (supine DBP 105-114 mm Hg) hypertension.

- To determine the nature and degree of correlation between blood pressure changes and plasma diltiazem concentrations over one dosing interval.

- To determine if tolerance or treatment-limiting adverse events develop to the antihypertensive effect of diltiazem ER after 4 or 8 weeks of therapy.

4.0. Number of Patients: A total of 500 patients were planned to be screened in order to have 250 evaluable subjects.

5.0. Informed Consent Form: A sample of the Informed Consent Form is attached to the submission.

6.0. Institutional Review Board Approval: Stipulated.

7.0. Inclusion Criteria: Subjects were at least 18 years old. Women were of no reproductive potential. Male and female patients had no clinical or laboratory abnormalities. Controlled diabetes and increased lipids were acceptable.

8.0. Exclusion Criteria: Patients with the following conditions were not considered to fulfill the conditions to participate in the study:

- Known hypersensitivity to diltiazem.
- Malignant hypertension.
- Alterations in cardiac rhythm.
- Recent (6 months) history of cerebrovascular accident or myocardial infarction.
- Significant cardiovascular abnormalities (congestive heart failure, cardiogenic shock, non-controlled arrhythmias, acute myocarditis or pericarditis, valvular disease, unstable angina, atrioventricular block, atrial fibrillation or flutter).
- Significant renal insufficiency.
- Significant hepatic disease.
- Electrolytic imbalance.
- Terminal illness.
- Pregnancy or breast feeding.

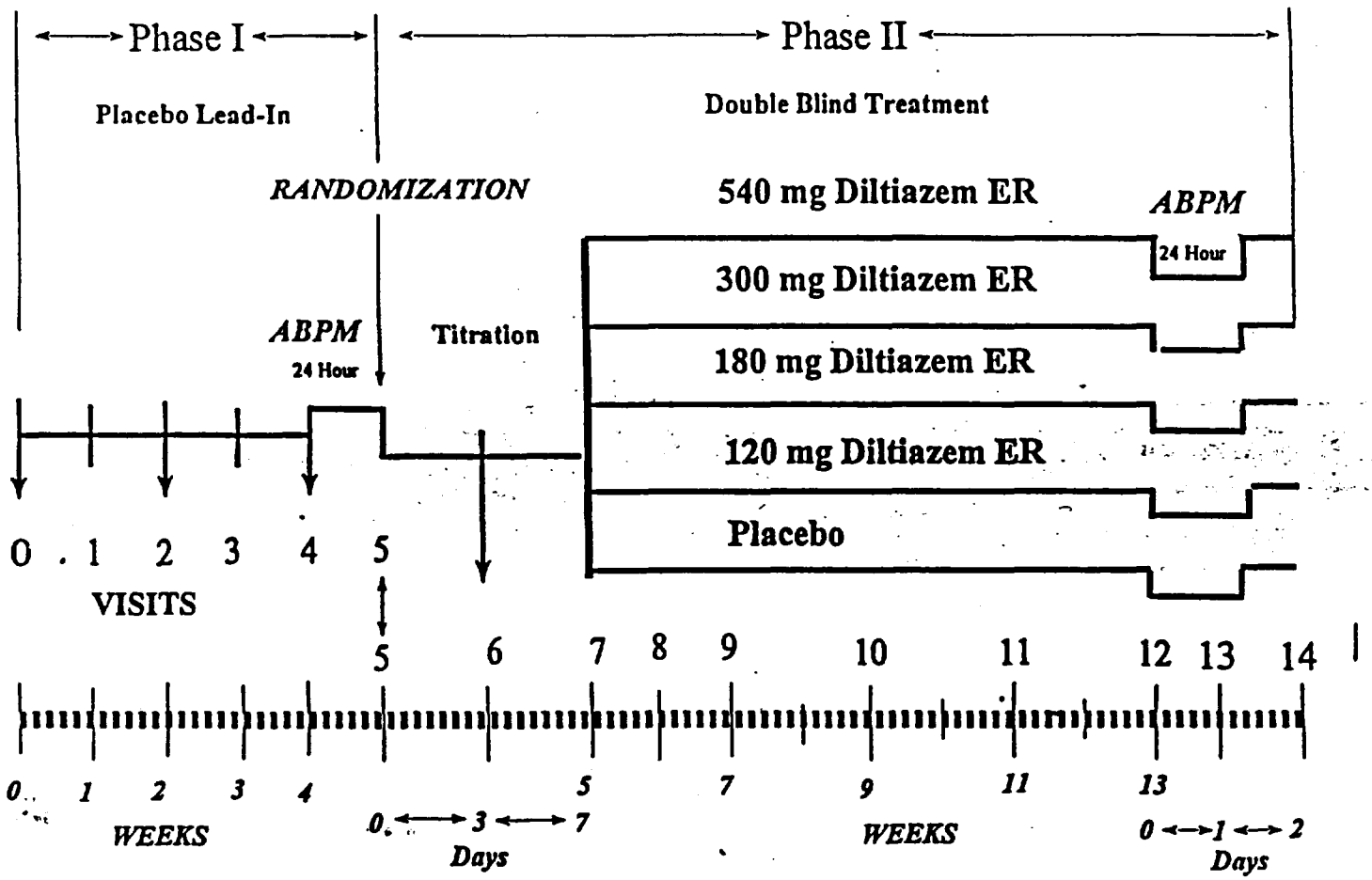
- Alcohol abuse or use of illicit drugs.
- Participation in an investigational study within 30 days.
- Use of the following drugs was discontinued and withheld during the study:
    - Diuretics, antihypertensives and potassium supplements.
    - MAO inhibitors, antiepileptics, cyclosporin, immunosuppressants.
    - Antiarrhythmics and digitalis.
    - Major tranquilizers and antidepressants.
    - Cimetidine, corticosteroids, antineoplastic agents, bile acid binding resins.
    - Macrolide antibiotics, grapefruit juice, ketoconazole, chronic NSAIDS, chronic asthma medications, any over-the-count medications that may affect the blood pressure.
- Elective surgery planned for the following 13 weeks.

9.0. Study Design. This was a randomized, double blind, forced titration, fixed dose, parallel group, placebo controlled trial consisting of a placebo lead-in period followed by a double-blind treatment period.

The protocol that initially was proposed to be followed is given in the following graph:

Figure 1

Study Design




The studies planned to be carried in the course of the investigation are given in the following Table:

Table 1

Plan of Study

| | VISITS | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | SCREEN | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
| STUDY DAYS | | —WEEKS— | | | | 1 | 3 | 7 | 14 | 21 | 35 | 49 | 63 | 64 |
| Pre-Dose B/P* | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Physical Exam** | X | | | | | X | | | | | | | | X |
| Chest X-ray*** | X | | | | | | | | | | | | | |
| ECG | X | | | | X | | | | X | | | | | X |
| Lab | X | | | | X | | | | | | | | | X |
| AE Evaluation | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| CC Meds | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Compliance | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Assign DB# | | | | | | X | | | | | | | | |
| Study Drug Issued | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Ambulatory B/P: | | | | | | | | | | | | | | |
| On | | | | | X | | | | | | | | X | |
| Off | | | | | | X | | | | | | | | X |

* 3 supine, 1 immediately erect, and 1 after 2 minutes erect.

** Visit 1 and Visit 13 full physical and Visit 5 brief PE only

*** If not within 12 months.

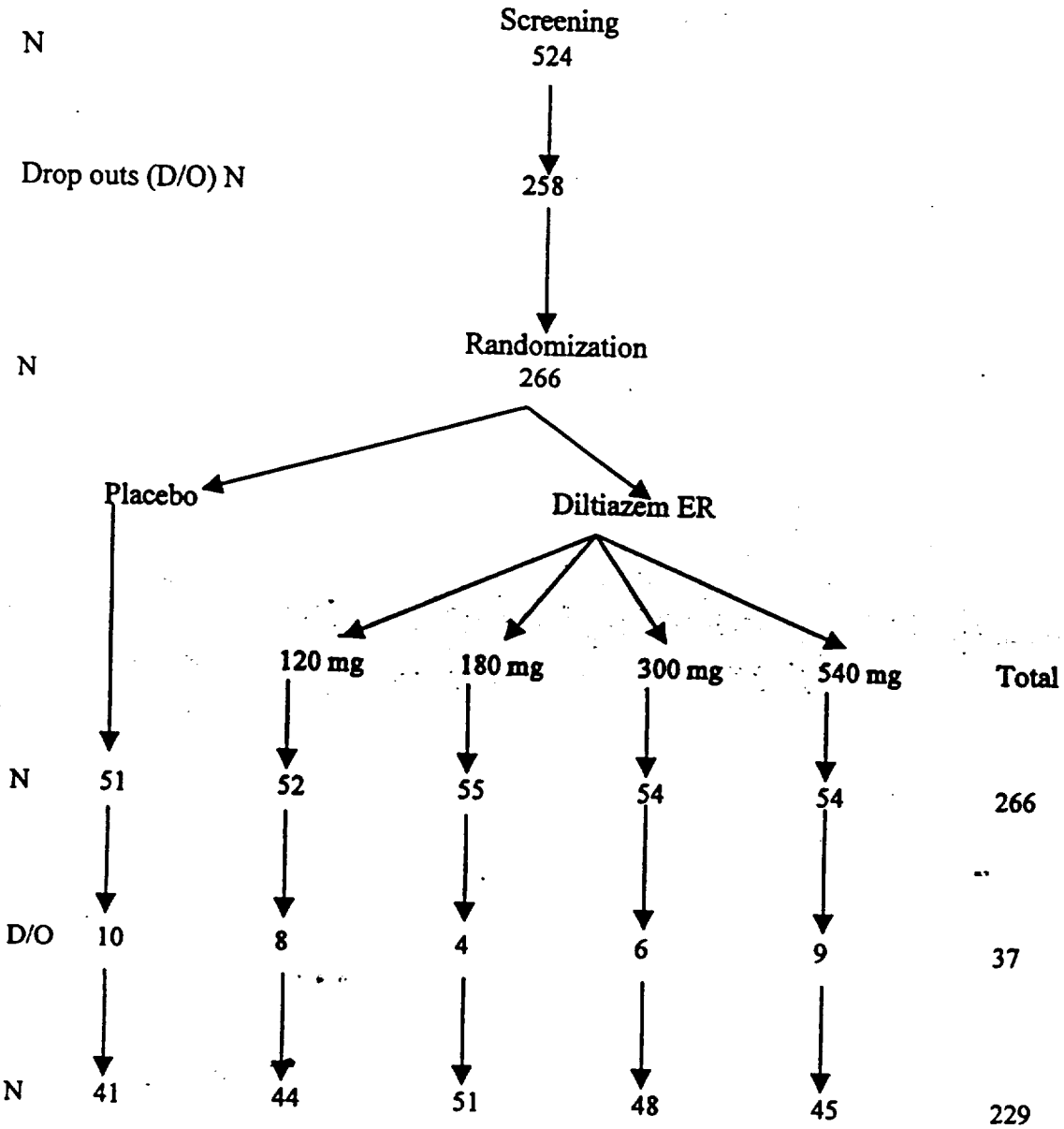
10.0 Results.

10.1. Disposition of Patients. At the beginning of the study, 524 patients were admitted for screening, 258 dropped out and 266 were selected for randomization. During the treatment period, 51 patients were given placebo and of the 215 patients that received the study drug, diltiazem ER, 52 patients were given the 120 mg dose, 55 patients the 180 mg dose, 54 patients the 300 mg dose and 54 patients the 540 mg dose. During the randomization period, 10 patients on placebo dropped out from the study and 41 reached the end of the study. Of the patients treated with diltiazem ER, 8 patients on the 120 mg dose dropped out, and 44 reached the end of the study; 4 patients on the 180 mg dose dropped out, and 51 reached the end of the study; 6 patients on the 300 mg dose dropped out, and 48 reached the end of the study; 9 patients on the 540 dose dropped out and 45 reached the end of the study.

The disposition of patients is given in the following Table:

Table 2

Disposition of Patients




The reasons for drop outs during the treatment period are given in the following Table:

Table 3

Reasons for Drop outs

| | Placebo | Diltiazem ER (mg/day) | | | | |
|---|---|---|---|---|---|---|
| | | 120 mg | 180 mg | 300 mg | 540m | Total |
| | (51) | (52) | (55) | (54) | (54) | (266) |
| | N (%) | N (%) | N (%) | N (%) | N (%) | N (%) |
| | 10 (20) | 8 (15) | 4 (7) | 6 (9) | 9 (19) | 37 (14) |
| Adverse Events | 2 | 0 | 1 | 3 | 5 | 11 |
| Lack of Efficacy | 3 | 6 | 0 | 3 | 0 | 12 |
| Patient withdrew | 1 | 1 | 1 | 0 | 3 | 6 |
| Protocol violation | 1 | 1 | 1 | 0 | 0 | 3 |
| Lost to follow up | 0 | 0 | 1 | 0 | 0 | 1 |
| Others | 3 | 0 | 0 | 0 | 1 | 4 |
| Total | 10 | 8 | 4 | 6 | 9 | 37 |

The clinic visit in which drop outs occurred is given in the following Table:

Table 4

Drop out Visit

| | Placebo | Diltiazem ER (mg/day) | | | | |
|---|---|---|---|---|---|---|
| | | 120 mg | 180 mg | 300 mg | 540m | Total |
| | (51) | (52) | (55) | (54) | (54) | (266) |
| | N (%) | N (%) | N (%) | N (%) | N (%) | N (%) |
| | 10 (20) | 8 (15) | 4 (7) | 6 (9) | 9 (19) | 37 (14) |
| Visit 5 | 0 | 1 | 1 | 0 | 1 | 3 |
| Visit 6 | 1 | 1 | 0 | 0 | 1 | 3 |
| Visit 7 | 0 | 0 | 0 | 1 | 1 | 2 |
| Visit 8 | 5 | 2 | 2 | 1 | 2 | 12 |
| Visit 9 | 2 | 2 | 1 | 2 | 1 | 8 |
| Visit 10 | 1 | 1 | 0 | 1 | 1 | 4 |
| Visit 11 | 0 | 1 | 0 | 1 | 2 | 4 |
| Visit 12 | 1 | 0 | 0 | 0 | 0 | 1 |
| Total | 10 | 8 | 4 | 6 | 9 | 37 |

The number of patients at endpoint and timepoint visits are given in the following Table:

Table 5

Number of Patients at Different Time Visits

| Timepoints (weeks post treatment initiation) | Placebo | Diltiazem ER (mg/day) | | | | |
|---|---|---|---|---|---|---|
| | | 120 mg | 180 mg | 300 mg | 540 mg | Total |
| Endpoint | 50 | 50 | 54 | 53 | 51 | 258 |
| Visit 8 (1) | 50 | 49 | 54 | 53 | 51 | 257 |
| Visit 9 (2) | 44 | 48 | 52 | 52 | 49 | 245 |
| Visit 10 (4) | 43 | 46 | 51 | 50 | 47 | 237 |
| Visit 11 (6) | 42 | 45 | 51 | 49 | 47 | 234 |
| Visit 12 (8) | 42 | 44 | 50 | 48 | 45 | 229 |
| Visit 13 (8+1 day) | 41 | 44 | 51 | 48 | 45 | 229 |

The adverse events that determined withdrawal from the study during the treatment period are given in the following Table:

Table 6

Adverse Events

| Number | Patient Initials | Treatment | Adverse Event |
|---|---|---|---|
| 1 | | Diltiazem ER 540 mg | Headache; Urinary frequency; Sinusitis; Edema; Increased Weight; Dyspnea |
| 2 | | Diltiazem ER 540 mg | Rash |
| 3 | | Diltiazem ER 300 mg | Headache; Epistaxis |
| 4 | | Diltiazem ER 180 mg | Headache;Pharyngitis;Amblyopia; EKG abnormality |
| 5 | | Diltiazem ER 540 mg | Rash |
| 6 | | Diltiazem ER 300 mg | Edema legs |
| 7 | | Diltiazem ER 540 mg | Arthralgia;Edema;Skin disorder |
| 8 | | Diltiazem ER 300 mg | Sinusitis;Jaundice |
| 9 | | Placebo | Dyspnea;Bundle branch block |
| 10 | | Placebo | Angina;Constipation |
| 11 | | Diltiazem ER 540 mg | Petechiae;Urinary infection;Rhinitis; EKG abnormality |

Comments. The most frequent causes for withdrawal from the study were lack of efficacy and adverse events (Table 3) and they took place more frequently after visit 8 (Table 4). There were 8 patients who did not have data beyond visit 5 and therefore endpoint in Table 5 shows a total of 258 patients. Most patients who had to be withdrawn from the study because of adverse events were being treated with Diltiazem ER, at the dose of 540 mg daily.

10.2. Demographic Characteristics. The demographic characteristics are given in the following Table:

Table 7

Demographic Characteristics

| Variable | Placebo (N=51) | Diltiazem ER 120 mg (N=52) | Diltiazem ER 180 mg (N=55) | Diltiazem ER 300 mg (N=54) | Diltiazem ER 540 mg (N=54) |
|---|---|---|---|---|---|
| | | | Mean±SD | | |
| Age (years) | 52.6±11.2 | 49.7±9.8 | 50.2±8.9 | 50.9±10.8 | 53±10.6 |
| Height (in) | 66.7±4.6 | 67.7±3.9 | 67.2±4.1 | 67.8±4.4 | 66.6±3.5 |
| Weight (lb) | 196.2±40.2 | 201.8±37 | 205±34.2 | 196.6±40.9 | 190.3±37.7 |
| | | | Number and (%) | | |
| Gender | | | | | |
| Male | 26 (51%) | 35 (67%) | 29 (53%) | 34 (63%) | 33 (61%) |
| Female | 25 (49%) | 17 (33%) | 26 (47%) | 20 (37%) | 21 (39%) |
| Race | | | | | |
| Black | 20 (39%) | 16 (31%) | 18 (33%) | 19 (35%) | 15 (28%) |
| Hispanic | 6 (12%) | 6 (12%) | 3 (5%) | 5 (9%) | 3 (6%) |
| White | 25 (49%) | 29 (56%) | 34 (62%) | 28 (52%) | 34 (63%) |
| Others | 0 (0%) | 1 (2%) | 0 (0%) | 2 (4%) | 2 (4%) |

Comment. The individuals were roughly well matched as to age, weight and height. Almost equal number of male and female patients were included in the placebo and diltiazem ER 180 mg groups, while in the other groups the proportions were roughly 2/3 males and 1/3 females. In the distribution by race, whites predominated in all groups.

10.3. Plan of Study. The study consisted of a Phase 1, Placebo Lead-In Period and a Phase II Double-Blind Treatment Period (see Figure 1, page 4).

10.3.1. Phase I-Placebo Lead –In Period. All patients participated in a single-blind placebo run-in of 4 weeks duration in order to establish the presence of mild to moderate hypertension (supine diastolic blood pressure (SuDBP) ≥95-≤114 mmHg inclusive) in the untreated condition. Newly diagnosed patients and those under present treatment entered the study provided, in case of the latter, current medication was washed out.

Patients were assigned to a single blind study number and instructed to take two capsules of placebo medication daily between 7 am and 11 am with the exception that on clinic visit days they did not take their medication until they were seen by the investigator and the necessary study measurements have been taken. Placebo medication was dispensed at visit 0 and again at 1, 2, 3 and 4 weeks. At the end of Phase I the patient was eligible for randomization to Phase II-Double-Blind Treatment Period provided the following two conditions were met:

- SuDBP measured during the last two visits were within 8 mmHg of each other and within the target hypertensive range (≥95-≤114 mmHg inclusive).

- The 24-hour ambulatory blood pressure monitoring (ABPM) recording taken at the last visit (day 28 plus or minus 2 days) indicated a daytime average diastolic blood pressure (DBP) of ≥ 90 mmHg).

The last Phase I manually determined SuDBP measurement was used as baseline for statistical analysis. If goal stability was not achieved at last visit of Phase I the patient was considered ineligible to participate in the study.

10.3.2. Phase II-Double-Blind Treatment Period. In this phase of the study of 9 weeks duration, patients who qualified were assigned to one of five treatment groups: 120 mg, 180 mg, 300 mg and 540 mg diltiazem or placebo.

All patients underwent forced treatment titration during the first week of double-blind medication which comprised an initial dose, step one titration at day 3 and step 2 titration at day 7 (Figure 1, page 4).

The dose escalation is given in the following Table:

Table 8

Dose Escalation Schedule

| Treatment Group | | Double Blind Treatment Week One | | |
|---|---|---|---|---|
| | | Day 0 | Day 3 | Day 7 |
| Placebo | | Placebo | Placebo | Placebo |
| Diltiazem | 120 mg | Placebo | Placebo | 120 mg |
| | 180 mg | Placebo | Placebo | 180 mg |
| | 300 mg | Placebo | 180 mg | 300 mg |
| | 540 mg | 180 mg | 300 mg | 540 mg |

Diltiazem hydrochloride was used in the following strengths:

- 120 mg capsule
- 180 mg capsule
- 240 mg capsule
- 300 mg capsule

Placebo capsules matched for size, shape and color were provided for the placebo group. During both phases of the study all patients took two capsules each day which comprised active treatment or placebo according to the treatment group they were assigned. The two study capsules were taken once daily between 7 am and 11 am except on day of clinic visit when they took their medication after they were seen by the investigator and the necessary study measurements were taken.

Titration only proceeded in the absence of dose limiting adverse events and when SuDBP did not became too low (≤75 mmHg) or too high (> 114 mmHg) to support safe patient management. Patients not able to reach their assigned dose level were dropped from the study and placed on appropriate antihypertensive therapy.

For the next eight weeks treatment was held constant while clinic visits to measure effect and safety were held once a week or once every two weeks.

10.4.0. Efficacy Evaluation. 10.4.1. Primary efficacy variable was:

- Supine diastolic blood pressure

10.4.2. Secondary efficacy variables were:

- Supine systolic blood pressure
- Immediate standing both systolic and diastolic blood pressure
- Standing blood pressure (after 2 minutes) both systolic and diastolic
- Responder analysis

The last observed value (endpoint) was the primary variable for the efficacy evaluation. The analysis conducted on the change from baseline (visit 5) for the last observed values was called endpoint analysis. Also, statistical analysis was conducted on the change from baseline at each visit for those subjects who had values at that visit. This is called timepoint analysis.

10.5. Efficacy Results. 10.5.1. Primary Endpoint. Supine Diastolic Blood Pressure. The endpoint analysis for supine diastolic blood pressure is given in the following Table:

Table 9

Baseline and Mean Reduction (mmHg) in Supine Diastolic Blood Pressure

Endpoint Analysis- (Mean ±SE)

Diltiazem ER (mg/day)

| Parameter | Placebo (50) | 120 mg (50) | 180 mg (54) | 300 mg (53) | 540 mg (51) |
|---|---|---|---|---|---|
| Baseline | 101±0.79 | 102±0.88 | 102±0.69 | 102±0.75 | 102±0.74 |
| Reduction | 3±1.12 | 3±1.17 | 6±1.15 | 7±1.04 | 9±1.06 |
| P-value* | ------- | 0.736 | 0.058 | 0.014 | <0.001 |

*Comparison of mean reduction against placebo.

Timepoint Analysis. The timepoint analysis on mean reduction in supine diastolic blood pressure is given in the following Table:

Table 10

Mean Reduction (mmHg) in Supine Diastolic Blood Pressure

Timepoint Analysis-[Mean±SE (n)]

Diltiazem ER (mg/day)

| Visit (Weeks post-treatment initiation) | Placebo | 120 mg | 180 mg | 300 mg | 540 mg |
|---|---|---|---|---|---|
| 8 (1) | 5±1.01 (50) | 4±1.01 (49) | 5±0.94 (54) | 11±1.46* (53) | 10±1.34* (51) |
| 9 (2) | 5±0.97 (44) | 4±0.89 (48) | 6±1.06 (52) | 10±1.05* (52) | 9±1.26* (49) |
| 10 (4) | 5±1.09 (43) | 4±1.05 (46) | 6±0.91 (51) | 10±1.16* (50) | 10±1.52* (47) |
| 11 (6) | 4±1.06 (42) | 5±1.32 (45) | 6±0.94 (51) | 12±1.71* (49) | 12±1.37* (47) |
| 12 (8) | 3±1.15 (42) | 1±2.06 (44) | 5±1.11 (50) | 10±1.05* (48) | 9±1.35* (45) |
| 13 (8+ 1 day) | 2±1.09 (41) | 3±1.28 (44) | 6±1.19* (51) | 7±1.00* (48) | 9±1.16* (45) |

* Statistically significant ($p<0.05$) when compared to placebo

Comment. Values of SuDBP at baseline in all five study groups were almost identical (Table 9, page 12). Statistically, the 120 mg of diltiazem ER lacked efficacy (Table 10, this page). The 180 mg dose showed efficacy only at the end of the study and doses of 300 mg and 540 mg demonstrated significant efficacy at all timepoints.

10.5.2. Secondary Endpoints. 10.5.2.1. Supine Systolic Blood Pressure. Changes in mean reduction in supine systolic blood pressure are given in the following Tables:

Table 11

Baseline and Mean Reduction (mmHg) in Supine Systolic Blood Pressure

Diltiazem ER (mg/day)- [Mean±SE (n)]

Endpoint Analysis

| Parameter | Placebo (50) | 120 mg (50) | 180 mg (54) | 300 mg (53) | 540 mg (51) |
|---|---|---|---|---|---|
| Baseline | 157±2.47 | 155±2.06 | 157±1.73 | 159±2.07 | 161±2.31 |
| Reduction | 1.9±1.83 | 0.3±2.14 | 6.6±1.69 | 7.4±1.92 | 11±2.54 |
| P-value* | ---------- | 0.477 | 0.096 | 0.054 | 0.002** |

* Comparison of mean value reduction versus placebo.** $p<0.05$

Table 12

Mean Reduction (mmHg) in Supine Systolic Blood Pressure

Diltiazem ER (mg/day)- [Mean±SE (n)]

Timepoint Analysis

| Visit (Weeks post-treatment initiation) | Placebo | 120 mg | 180 mg | 300 mg | 540 mg |
|---|---|---|---|---|---|
| 8 (1) | 5±2.01 (50) | 3±1.92 (49) | 6±1.72 (54) | 12±1.98*(53) | 11±2.14*(51) |
| 9 (2) | 4±1.97 (44) | 2±2.05 (48) | 5±1.72 (52) | 12±1.99*(52) | 13±2.01*(49) |
| 10 (4) | 5±2.26 (43) | 1±2.11 (46) | 7±1.77 (51) | 12±1.89*(50) | 15±2.5*(47) |
| 11 (6) | 4±1.89 (42) | 4±2.41 (45) | 7±1.78 (51) | 13±2.21*(49) | 15±2.58*(47) |
| 12 (8) | 4±2.23 (42) | -1.2±2.11 (44) | 4±1.74 (50) | 13±2.07*(48) | 11±2.7*(45) |
| 13 (8+1 day) | 1±1.75 (41) | 0.3±2.35 (44) | 7±1.7* (51) | 8±2* (48) | 11±2.74*(45) |

* Statistically significant ($p<0.05$) compared to placebo.

Comment. As shown with results of measurements of SuDBP (Tables 11-12, previous page), the doses of 300 and 540 mg diltiazem ER elicited the greatest efficacy.

10.5.2.2. Heart Rate. Mean reductions in supine heart rate by endpont and timepoint analysis are given in the following Tables:

Table 13

Mean Reduction in Supine Heart Rate

Endpoint Analysis

Diltiazem ER (mg/day)

| Parameter | Placebo (50) | 120 mg (50) | 180 mg (54) | 300 mg (53) | 540 mg (51) |
|---|---|---|---|---|---|
| Baseline | 78±1.37 | 74±1.38 | 75±1.23 | 76±1.34 | 75±1.29 |
| Reduction | 0±1.23 | 2±1.69 | 1±1.30 | 3±1.13 | 6±1.10 |
| P value* | ------ | 0.2002 | 0.5808 | 0.0444** | <0.0003** |

* Comparison of mean value reduction versus placebo ** $p<0.05$

Table 14

Mean Reduction in Supine Heart Rate

Timepoint Analysis

| Visit (Weeks post-treatment initiation) | Placebo | Diltiazem ER (mg/day) | | | |
|---|---|---|---|---|---|
| | | 120 mg | 180 mg | 300 mg | 540 mg |
| 8 (1) | 1±1.19 (50) | 2±1.29 (49) | 1±1.14 (54) | 1±1.34 (53) | 4±0.97(51) |
| 9 (2) | 1±1.62 (44) | 2±1.42 (48) | 1±1.72 (52) | 2±1.10 (52) | 4±1.24 (49) |
| 10 (4) | -1±1.64 (43) | 1±1.28 (46) | 0±1.77 (51) | 2±1.23 (50) | 3±1.20*(47) |
| 11 (6) | -1±1.66 (42) | 2±1.34 (45) | 1±1.29 (51) | 1±1.36 (49) | 4±1.22*(47) |
| 12 (8) | -1±1.61 (42) | 0±1.46 (44) | 1±1.37 (50) | 3±1.34 (48) | 4±1.10*(45) |
| 13 (8+1 day) | -1±1.27 (41) | 2±1.87 (44) | 1±1.28 (51) | 3±1.21*(48) | 6±1.19* (45) |

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

Comment. The 300 mg and 540 mg doses of diltiazem ER elicited the greater reductions in heart rate.

10.5.2.3. Other Secondary Endpoints. Measurements of diastolic blood pressure, systolic blood pressure, hear rate, immediately after standing and two minutes later after standing, were similar to those obtained when measurements were obtained with the patient in supine position.

10.6. Responders. A responder was defined as any patient with a post-treatment supine diastolic blood pressure ≤ 90 mmHg or any patient with a reduction in supine diastolic blood pressure of 10 mmHg or more.

A comparison of placebo and treatment groups according to the response rate at endpoint and different timepoint is given in the following Tables:

Table 15

Responders-Number (%)

| Time | Placebo | Diltiazem ER | | | |
|---|---|---|---|---|---|
| | | 120 mg | 180 mg | 300 mg | 540 mg |
| Endpoint | 13 (26) | 12 (24) | 22 (41) | 24 (45) | 26 (51) |
| Timepoints | | | | | |
| Visits (Weeks post treatment initiation) | | | | | |
| 8 (1) | 17 (34) | 17 (35) | 12 (22) | 26 (49) | 29 (57) |
| 9 (2) | 16 (36) | 12 (25) | 17 (33) | 31 (60) | 28 (57) |
| 10 (4) | 16 (37) | 14 (30) | 19 (37) | 30 (60) | 27 (58) |
| 11 (6) | 14 (33) | 19 (42) | 17 (33) | 30 (61) | 33 (70) |
| 12 (8) | 9 (21) | 8 (18) | 16 (32) | 28 (58) | 27 (60) |
| 13 (8+1 Day) | 10 (24) | 12 (27) | 22 (43) | 21 (44) | 21 (47) |

Comment. When considered either at endpoint, or at different stages at tiempoints, there was a response relationship between the dose of diltiazem ER administered and the proportion of responders.

10.7. Plasma Levels of Diltiazem and Blood Pressure. In a subset of patients, after eight weeks of therapy, pharmacokinetic studies (plasma levels of diltiazem and metabolites,desacetyl and desmetyldiltiazem) and pharmacodynamic studies (manual measurements of blood pressure) were performed. Results are shown in the following Table in which baseline values are included for comparison:

Table 16

Plasma Diltiazem and Supine Diastolic and Systolic Blood Pressure

| | Diltiazem 120 mg (8) (M±SD) | | | Diltiazem 180 mg (9) (M±SD) | | |
|---|---|---|---|---|---|---|
| | DTZ Level ng/ml | SuDBP mmHg | SuSBP mmHg | DTZ Level ng/ml | SuDBP mmHg | SuSBP mmHg |
| Baseline | | 102±6.7 | 155±14.6 | | 102±5 | 157±12 |
| Hour Post- Dose | | | | | | |
| 0 | 20±15 | 96±12 | 152±14 | 45±22 | 94±12 | 147±11 |
| 1 | 20±15 | 96±16 | 152±23 | 47±26 | 96±13 | 155±22 |
| 2 | 21±14 | 97±12 | 151±15 | 47±23 | 94±8 | 155±16 |
| 4 | 24±14 | 94±14 | 156±10 | 58±24 | 93±11 | 151±12 |
| 6 | 39±23 | 93±13 | 151±12 | 90±50 | 94±9 | 151±8 |
| 8 | 51±25 | 94±5 | 146±11 | 107±63 | 91±9 | 148±11 |
| 12 | 44±25 | 96±47 | 150±9 | 98±47 | 94±13 | 150±16 |
| 24 | 20±13 | 100±6 | 149±11 | 47±24 | 93±10 | 150±15 |
| | Diltiazem 300 mg (7) (M±SD) | | | Diltiazem 540 mg (8) (M±SD) | | |
| Baseline | | 102±5.4 | 159±15 | | 102±5.2 | 160±16 |
| Hour Post- Dose | | | | | | |
| 0 | 127±33 | 97±10 | 165±19 | 169±85 | 94±6 | 153±11 |
| 1 | 133±34 | 95±11 | 152±21 | 169±83 | 92±10 | 153±16 |
| 2 | 138±36 | 90±12 | 155±16 | 175±83 | 91±4 | 149±13 |
| 4 | 155±59 | 88±9 | 150±13 | 213±78 | 93±4 | 152±11 |
| 6 | 188±76 | 87±5 | 153±15 | 306±84 | 86±6 | 150±10 |
| 8 | 192±51 | 89±6 | 154±11 | 359±124 | 88±6 | 143±13 |
| 12 | 201±81 | 89±9 | 156±21 | 359±127 | 91±7 | 147±11 |
| 24 | 108±54 | 92±9 | 148±16 | 177±69 | 94±5 | 154±14 |

10.8. Trough/Peak Ratios of Diltiazem and Diastolic Blood Pressure. Calculations of trough/peak ratios of plasma diltiazem level and supine diastolic blood pressure are given in the following Tables:

Table 17

Plasma Diltiazem Trough/ Peak Ratios

| Treatment Group | n | Diltiazem Trough/Peak Ratios* | | | |
|---|---|---|---|---|---|
| | | Mean | SE | Min | Max |
| Diltiazem 120 mg | 8 | 0.35 | 0.05 | 0.21 | 0.70 |
| Diltiazem 180 mg | 9 | 0.41 | 0.09 | 0.00 | 1.00 |
| Diltiazem 300 mg | 7 | 0.59 | 0.03 | 0.47 | 0.70 |
| Diltiazem 540 mg | 8 | 0.43 | 0.05 | 0.26 | 0.63 |

Supine Diastolic Blood Pressure Trough/Peak Ratios **

| Treatment Group | n | SuDBP Trough/Peak Ratios in percent | | | |
|---|---|---|---|---|---|
| | | Mean | SE | Min | Max |
| Diltiazem 120 mg | 8 | 0.98 | 0.04 | 0.86 | 1.22 |
| Diltiazem 180 mg | 9 | 0.98 | 0.04 | 0.76 | 1.16 |
| Diltiazem 300 mg | 7 | 0.93 | 0.04 | 0.77 | 1.02 |
| Diltiazem 540 mg | 8 | 0.96 | 0.03 | 0.79 | 1.07 |

* Pre-dose diltiazem level/maximum diltiazem level

** Blood pressure measurements at maximum diltiazem level/blood pressure measurement at pre-dose diltiazem level.

Comment. Table 16, previous page, indicates that the effective doses of diltiazem ER are the 300 and 540 mg concentration. The peak effect is at hours 6 to 8 after dose administration, is still present at hour 12, and coincides in time with the highest plasma concentrations of diltiazem. Unfortunately, ambulatory blood pressure monitoring, that was initially planned (see Figure 1, page 4), was not performed at this stage of the study and, therefore, events that may have occurred during the 12-24 hour interval are unknown.

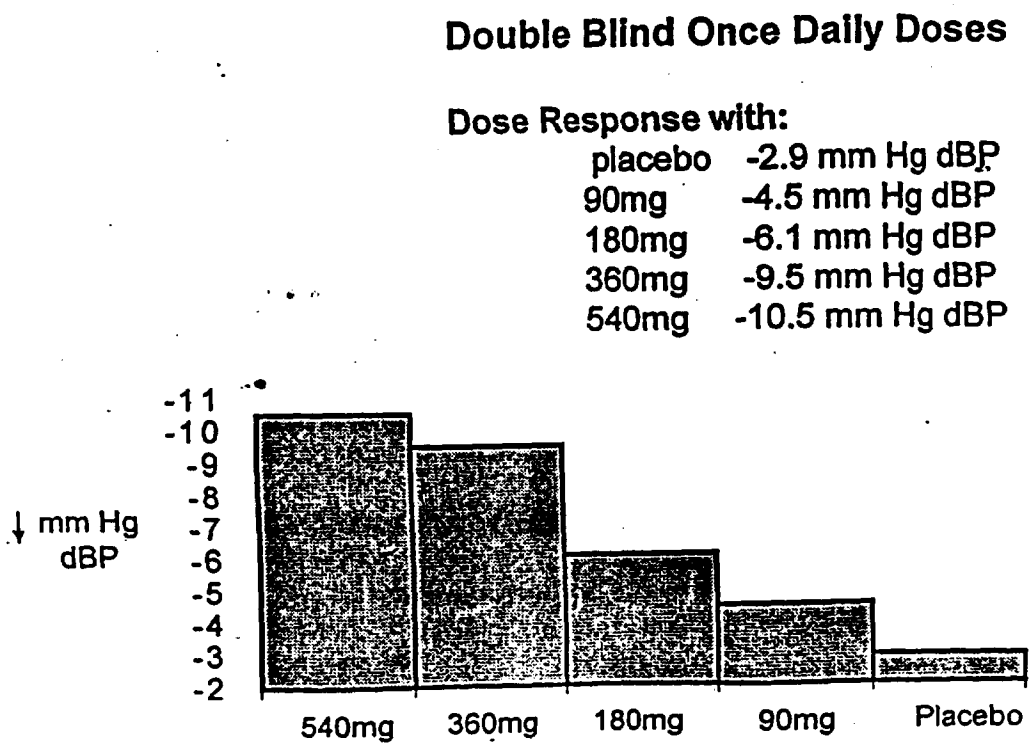
Results shown in the upper portion of Table 17 indicate that by calculating trough/peak ratios of drug concentration, there was significant concentrations of the drug in plasma given once daily at the 300 mg dose at trough and lower levels at the other doses. Trough/peak ratios of supine diastolic blood pressure were almost 1 for all doses of diltiazem ER.

10. 9. Dose Response Curves. In general, as the concentration of a drug in plasma increases, the efficacy also increases until a plateau is reached or toxicity demands discontinuation of treatment. Some information can be collected considering the range of doses used in the present study. As shown in Table 10, page 13, the efficacy of the 120 mg dose of diltiazem ER was not different from placebo. The 180 mg dose showed efficacy only in the last week of the study. The 300 and 540 mg doses of diltiazem ER elicited significant reductions in supine diastolic blood pressure at all times in the course of the study as compared to placebo and there were no differences between both doses. Therefore, a plateau was reached with the 300 mg dose.

The sponsor also reviewed the literature searching for results of dose response of long acting diltiazem formulations. The single best response reported was taken from package insert of the drug. Placebo reduced the diastolic blood pressure by 2.9 mmHg, 90 mg a day by 4.5 mmHg, 180 mg a day by 6.1 mmHg, 360 mg a day by 9.5 mmHg and 540 mg a day by 10.5 mmHg. Results of this study are shown in the following graph.

Figure 2

Cardizem CD-Dose Response Curve



11.0. Safety. 11.1. Adverse Events. Any unfavorable, unintended events (signs, symptoms, changes in laboratory data) temporally associated with the administration of the study drug whether or not drug related were considered as adverse events. All adverse events were considered in terms of severity and relationship to study treatment.

The adverse event rates of the placebo and four treatment groups were measured in both phases of the study. Results are shown in the following Tables:

Table 18

Adverse Events Rate

| | Placebo | Treatment Level | | | | |
|---|---|---|---|---|---|---|
| | | 120 mg | 180 mg | 300 mg | 540 mg | Total |
| N | (51) | (52) | (55) | (54) | (54) | (266) |
| Placebo | 24* | 23* | 27* | 26* | 30* | 130 |
| | (47 %) | (44 %) | (49 %) | (48 %) | (56 %) | (49 %) |
| P Value | | | 0.828 | | | |
| Active | (50) | (50) | (54) | (53) | (51) | (258) |
| Treatment | 30* | 27* | 24* | 27* | 28* | 136* |
| Period | (60 %) | (54 %) | (44 %) | (51 %) | (55 %) | (53 %) |
| P Value | | | 0.602 | | | |

* Number of patients who reported at least one adverse event during each of the two study periods.

Comment. There were no significant differences between the five groups during the placebo lead-in period (Chi-square test p=0.828) and the active treatment period (Chi-square test p=0.602).

The number of adverse events increased in the placebo group from 24 (47 %) in the placebo period to 30 (60 %) in the double-blind, randomization period, although patients were not receiving any treatment in the course of the study. Adverse events increased from 48 % in the placebo period to 51 % in patients treated with diltiazem ER 300 mg from 44 % to 54 % in those receiving diltiazem ER 120 mg, decreased from 49 % to 44 % in those given diltiazem ER 180 mg and remained essentially unchanged in the group treated with diltiazem ER 540 mg.In summary, more patients reported adverse events during the treatment period ( 49 %) than during the placebo phase of the study (53 %).

The five more frequent adverse events during the placebo and treatment periods are given in the following Tables:

Table 19

More Frequent Adverse Events

| Term | Treatment Level | | | | | |
|---|---|---|---|---|---|---|
| | Placebo (51) | 120 mg (52) | 180 mg (55) | 300 mg (54) | 540 mg (54) | Total (266) |
| **Placebo period** | | | | | | |
| Headache | 5 (10%) | 10 (19%) | 9 (16%) | 12 (22) | 12 (22%) | 48 (18 %) |
| Pharyngitis | 5 (10%) | 4 (8%) | 5 (9%) | 3 (6%) | 6 (11%) | 23 (9%) |
| Infection | 1 (2%) | 3 (6%) | 3 (5%) | 3 (6 %) | 4 (7%) | 14 (5%) |
| Pain | 2 (4%) | 2 (4%) | 1 (2%) | 0 (0%) | 1 (2%) | 6 (2% |
| Edema | 0 (0%) | 1 (2%) | 0 (0%) | 2 (4%) | 2 (4 %) | 5 (2 %) |
| Rhinitis | 1 (2%) | 0 (0%) | 2 (4%) | 0 (0%) | 2 (4%) | 5 (2%) |
| **Treatment Period** | | | | | | |
| | (50) | (50) | (54) | (53) | (51) | (208) |
| Headache | 9 (18%) | 10 (19%) | 5 (9%) | 6 (13%) | 6 (11%) | 27 (13%) |
| Pharyngitis | 5 (10%) | 3 (6%) | 5 (9%) | 2 (4%) | 6 (11%) | 16 (8%) |
| Edema | 0 (0%) | 1 (2%) | 3 (6%) | 4 (8%) | 6 (12%) | 14 (7%) |
| Pain | 1 (2%) | 2 (4%) | 5 (9%) | 2 (4%) | 2 (4%) | 11 (5%) |
| Infection | 4 (8%) | 1 (2%) | 0 (0%) | 2 (4%) | 5 (10%) | 8 (4%) |

Values in parenthesis=n

Headache was the most common adverse reaction in all subjects during the placebo period and in those receiving placebo and the 120 mg dose of diltiazem ER during the treatment period. In all other groups, the incidence of headache declined during the treatment period. Edema was absent in patients on placebo, but was detected in all patients treated with diltiazem ER and its incidence progressed in proportion to the increase in strength of study drug. In general, the drug was well tolerated.

11.2. Serious Adverse Events. A serious adverse event was defined as one that constituted a definite hazard or handicap to the patient (or off spring) including, but not limited to, an adverse experience which resulted in:

- Death
- Permanent or severe disability
- In-patient hospitalization or prolongation of existing in-patient hospitalization
- Cancer
- A congenital anomaly
- Is life threatening
- Resulted in an overdose

There were four reported cases of serious adverse reactions.

A 70-year-old male patient with non-insulin dependent diabetes who was receiving diltiazem ER 300 mg for seven weeks developed a posterior wall myocardial infarction. He also had a history of coronary artery disease and in this admission had a triple bypass surgery. Although the event was life threatening and required hospitalization, was not considered to be drug related.

The other three subjects were enrolled in the study but were withdrawn previous to randomization.

A 53-year-old white male with non-insulin dependent diabetes mellitus, essential hypertension, mild stable coronary artery disease not requiring anti-anginal therapy was found slumped in a car, blue, unresponsive. Paramedics attempted to resuscitate the patient but he was pronounced dead one hour later.

A 52-year-old white male with history of type II diabetes and status post transuretral resection was diagnosed as having cancer of the lung in a screening chest X-ray. He was recovering after right pneumonectomy.

A 39-year-old black male was hospitalized after complaining of abdominal pain and was recovering after laparotomy for acute gangrenous appendicitis.

Comment. Adverse events reported in this study are similar to those recognized after administration of calcium channel blockers.

11.3. Electrocardiogram. Results of changes in PR and QTc by electrocardiogram during placebo and end of treatment periods are shown in the following Table:

Table 20

Electrocardiogram

| Treatment Groups | Group Mean Electrocardiogram Parameters | | | | | |
|---|---|---|---|---|---|---|
| | Baseline | | End of Treatment | | Difference | |
| | PR | QTc | PR | QTc | PR | QTc |
| Placebo | 171.6 (51) | 414.5 (51) | 166.2 (44) | 424.9 (44) | 4.3 (44) | -12.2 (44) |
| 120 mg | 161.2* (52) | 411.5 (52) | 161.7* (43) | 412.8* (43) | -1.07* (43) | -2.7 (43) |
| 180 mg | 161.1* (54) | 413.7 (54) | 167.6 (51) | 416.7 (51) | -6.7* (50) | -6.8 (50) |
| 300 mg | 166.3 (54) | 408.2 (54) | 170.7 (48) | 413.7* (48) | -2.5 (48) | -6.5 (48) |
| 540 mg | 158.0* (54) | 413.2 (54) | 167.7 (47) | 417.2 (47) | -12.6* (47) | -4.9 (47) |

* Indicates p value < 0.05

Values in parenthesis = n

Comment. As compared to placebo, at baseline values of PR intervals in groups to be randomized to treatment were lower (in most cases significantly lower) than placebo and, therefore, matching at baseline was poorly done.

Statistical results were apparently obtained by comparing values at baseline with those at end of treatment. PR segment barely increased by 0.5 msec (1.07, according to the sponsor with the 180 mg dose of diltiazem ER and this change was considered statistically significant while greater changes (decrease of almost 5 msec for placebo, and more than 4 for the 300 mg dose) did not reach statistical significance. The known effect of calcium channel blocking agents prolonging the PR interval was evident in these results, but the critical limit of 200 msec was not exceeded in these calculations of mean values.

All groups were well matched for QTc intervals at baseline. There was a tendency to a prolongation of QTc intervals, but mean values did not exceed the normal range of 350-440 msec.

11.4. Laboratory Analysis. Samples of blood and urine were obtained at periodic intervals throughout the study (see Table 1, page 5) and the following tests were performed:

- CBC with differential and platelet count
- Blood chemistries including:
  - Total bilirubin
  - Creatinine
  - SGOT or SGPT
  - Alkaline phosphatase
  - BUN
  - Serum glucose
  - Total protein
  - Electrolytes including:
    - Sodium
    - Potassium
    - Chloride
  - Blood lipids including:
    - Cholesterol
    - Triglycerides
- Routine urinalysis
- Pregnancy test for women of childbearing potential: serum at visits 0 and post-study (visit 13 or 14) and urine at visit 5.

The baseline laboratory parameters were contrasted with the end of treatment measurements to determine whether there were any increases in the number of subjects with abnormal results. The normal to abnormal shifts were then calculated.

In blood chemistry the highest normal to abnormal shifts were noted in the cholesterol, triglycerides and glucose for all the five study groups. The magnitude of the shifts was minimal. The same parameters were also observed to have the highest numbers of abnormal to normal shifts. However, there were more subjects whose laboratory parameters shifted back to normal compared to those who demonstrated normal to abnormal shifts.

In hematology the shifts were minimal. The highest magnitude in shifts from normal to abnormal was in hematocrit for all treatment groups.

The most common abnormal results in urinalysis in all treatment groups were the presence of bacteria in the urine and abnormalities in the sediment. There were no differences in the normality shifts for the five treatment groups. The magnitude of the normal to abnormal shifts was less than that of the abnormal to normal shifts.

Comment. This is an unusual way of presenting laboratory abnormalities by showing the number of patients shifting from normal to abnormal results or vice versa rather than the changes in absolute values of the concentration of determined substances. However, since the adverse reactions of this calcium channel blocker has already been extensively reported probably there were no life threatening changes in laboratory results.

12. Pharmacokinetic and Pharmacodynamic Studies. A subset of patients participated in this portion of the study. Blood samples were collected at 0 hour predose and at 1, 2, 4, 6, 8, 12 and 24 hours post-dose. The sampling was accompanied by manual blood pressure measurements that provided data for a pharmacokinetic/pharmacodynamic correlation analysis. These data were collected at baseline and at the end of eight weeks of treatment. Plasma samples were analyzed for diltiazem, desmethyldiltiazem and desacetyldiltiazem concentrations.

Results of the pharmacodynamic studies are given in Table 16, page 17, Table 17, page 18, and discussed in pages 17-18. For results of the pharmacokinetic studies see the review by Biopharmaceutics.

13. 0. Label. The sponsor submits a label for diltiazem HCl extended release capsules. The writing was compared with those for Cardizem CD (1), Cardizem Injectable (2), Cardizem SR (3) and Cardizem Tablets (4). For the most part, the label of the sponsor is a literal transcription of the labels for Cardizem in sections corresponding to description, clinical pharmacology, contraindications, warnings, precautions, overdose and dosage and administration.

13.1. Contraindications. Diltiazem is contraindicated in the following conditions:

- Patients with sick sinus syndrome, except in the presence of a functioning ventricular pacemaker.
- Patients with second or third degree AV block except in the presence of a functioning ventricular pacemaker.
- Patients with hypotension.
- Patients with hypersensitivity to the drug.
- Patients with acute myocardial infarction and pulmonary congestion by x-ray.

13.2. Warnings:

- Defects in cardiac conduction.
- Congestive heart failure.
- Hypotension.

13.3. Precautions. 13.3.1. General.

- Impaired renal or hepatic function.
- Dermatological reactions.

13.3.2. Drug Interactions.

- Beta blockers.
- Cimetidine.
- Digitalis.
- Anesthetics.
- Cyclosporine
- Carbamazepine

13.4. Adverse Reactions. The sponsor submits the following Table as illustrating the most frequent adverse reactions:

| Adverse Reaction | Placebo n=50 | Diltiazem HCl ER 120-300 mg n=157 | 540 mg n=51 |
|---|---|---|---|
| | # patients (%) | # patients (%) | # patients (%) |
| Headache | 9 (18) | 21 (13) | 6 (11) |
| Pharyngitis | 5 (10) | 10 (6) | 6 (11) |
| Edema | 0 (0) | 8 (5) | 6 (12) |
| Pain | 1 (2) | 9 (6) | 2 (4) |
| Infection | 4 (8) | 3 (2) | 5 (10) |
| Rhinitis | 2 (4) | 6 (4) | 2 (4) |

In clinical trials of 3200 patients receiving different diltiazem preparations, most common events (greater than 1 %) were: edema (4.6 %), headache (4.6 %), dizziness (3.5 %), asthenia (2.6 %), first degree AV block (2.4 %), bradycardia (1.7 %), flushing (1.4 %), nausea (1.4 %) and rash (1.2 %).

In addition, adverse events have been reported infrequently (less than 2 %) in the following systems: cardiovascular, nervous system, gastrointestinal, dermatological, and other systems.

13.5. Drug Overdose. There have been 29 reports of diltiazem overdose in doses ranging from less than 1 gm to 10.8 gm. Most of them involved multiple drug ingestion. Twenty-two patients recovered. Seven patients had a fatal outcome, the amount ingested was unknown, and, in six patients, multiple drug ingestion was confirmed.

In cases of drug overdose or exaggerated response, supportive measures and gastrointestinal decontamination are recommended. Diltiazem is not removed by peritoneal or hemodialysis. Plasmapheresis or charcoal hemoperfusion may help.

The following measures are recommended in some particular cases:

Bradycardia. Atropine and, if there is no response, isoproterenol.

High Degree AV Block. Treat as in bradycardia. Cardiac pacing in case of fixed high degree AV block.

Hypotension. Vasopressors.

13.6. Dosage and Administration. Patients controlled on diltiazem alone or in combination with other medications may be switched to diltiazem HCl ER capsules at the nearest equivalent total daily dose. Higher doses may be needed in some patients.

Hypertension. Starting doses of 180 to 240 mg diltiazem ER are recommended for the treatment of hypertension. Maximum effect usually is seen after 14 days of daily therapy. Dosage adjustment should be done accordingly.

It may be taken with nitroglycerine.

It has an additive effect when added to other antihypertensive agents.

13.7. How Supplied. Diltiazem HCl ER will be supplied with the following strengths and characteristics:

| Strength | Quantity | Description |
|---|---|---|
| 120 mg | 30 btl<br>90 btl<br>500 btl<br>1000 btl | Light green opaque capsule imprinted with 'BVF 120' |
| 180 mg | 30 btl<br>90 btl<br>500 btl<br>1000 btl | Dark green opaque/light green opaque capsule imprinted with 'BVF 180' |

| | | |
|---|---|---|
| 240 mg | 30 btl<br>90 btl<br>500 btl<br>1000 btl | Dark green opaque<br>capsule imprinted with<br>'BVF 240' |
| 300 mg | 30 btl<br>90 btl<br>500 btl<br>1000 btl | Ivory opaque/dark green<br>opaque capsule<br>imprinted with 'BVF<br>300' |

14.0. Amended Label. In response to a request made by the Agency (Biopharmaceutics, attachment 1), Hoechts Marion Roussel Inc. made modifications to the printed label of Cardizem (attachment 2) that are not incorporated in the 1999 version of the PDR or in present submission by the sponsor. These changes are as follows:

- Possible treatment modalities were added to the section Overdosage
- Benzodiazepines, Rifampin and Lovastatin have been added to Precautions-Drug Interactions
- A Geriatric Use subsection has been added to Precautions
- Myopathy has been added to Adverse Reactions.

15.0. Proposed Amendments to Label. In addition, the Agency (Biopharmaceutics) has made the following recommendations:

- That the labeling of the section Precautions-Drug Interactions be amended according to the wording given in their report.
- That a more specific writing, provided in their report, be inserted in the section Precautions-Drug Interactions referring to Rifampin.
- That the extent of the pharmacokinetic changes resulting of the exposure of midazolam and triazolam to diltiazem be made more specific in terms suggested in their report.

16.0. Other Unrecognized Drug Interactions. In addition, a review of the literature revealed the following possible drug interactions:

Buspirone is an anxiolytic agent (5) with an extensive first-pass metabolism which makes it potentially susceptible to drug interactions (6). In a pharmocokinetic study co-administration of diltiazem increased the area under the buspirone plasma concentration-time curve 5.5 fold ($p<0.001$) (6). The peak plasma concentration of buspirone was increased 4.1 fold ($p<0.001$) (6). The elimination half-life of buspirone was not changed by diltiazem (2). Side effects of buspirone occurred more frequently with diltiazem than with placebo ($p<0.05$) (6).

Because same enzymes in the liver catalyze the metabolism of quinidine and diltiazem it is reasonable to anticipate an interaction between these two drugs. (7). Pretreatment with diltiazem significantly increased the AUC of quinidine by 51 %, prolonged its elimination $t_{1/2}$ by 36 % and decreased $Cl_{oral}$ by 33 % (7) . A slight but not significant increase in $C_{max}$ of quinidine was observed in presence of diltiazem (7).

Pretreatment with quinidine did not significantly alter any of the pharmacokinetic parameters of diltiazem (7).

Pretreatment with diltiazem significantly prolonged the PR interval compared with the effect of quinidine alone ($p = 0.035$) (7). Analysis of QRS indicated no significant difference between treatments but a significant difference was measured for QTc between treatments ($p = 0.018$) (7). Pretreatment with diltiazem induced a significant decrease in diastolic blood pressure ($p = 0.02$) and heart rate ($p = 0.01$) without changes in systolic blood pressure (7).

For ethical and safety reasons the dosages used for quinidine and diltiazem in this study in normal volunteers were at subtherapeutic levels (7). Much higher doses of both agents could be used in patients with affected cardiac function, and higher concentrations could be reached after repeated drug administration (7). Therefore the authors suggest that there is a need for monitoring drug concentrations and/or reducing the doses of quinidine when there is co-administration of quinidine and diltiazem in order to prevent drug accumulation that may cause toxicity (7).

Experimental studies have shown that when diltiazem was added to animals infused with FK 506, the blood levels of FK 506 rose by a four-fold (8). Plasma levels of FK 506 may have to be monitored in patients also receiving diltiazem (8).

There is a report of subcutaneous lupus related to the administration of calcium channel blockers for hypertension (9). Four patients treated with diltiazem, four patients receiving verapamil and one patient on nifedipine developed photoinduced annular or papulo-squamous cutaneous lesions consistent clinically with subacute cutaneous lupus erythematosus (9). The diagnosis was confirmed by serology and pathology and, on dechallenge, the lesions resolved (9).

14. Conclusions. Results submitted in this placebo control, forced titration, five arms study over a 8-week period in patients with essential hypertension indicate that diltiazem HCl ER showed efficacy in significantly reducing the supine diastolic blood pressure.

Efficacy became evident at the 180 mg daily dose of diltiazem ER and increased at the 300 mg daily dose (Table 10, page 13 and Table 15, page 16). The 120 mg daily dose lacked efficacy and increasing the dose to 540 mg did not provide additional advantage (Table 10, page 13 and Table 15, page 16). Therefore a plateau seems to have been reached at the 300 mg dose.

Pharmacokinetic-pharmacodynamic studies indicated a correlation between a reduction in supine diastolic blood pressure and increasing plasma blood levels at higher doses of diltiazem (Table 16, page 17). Calculations of peak/trough ratios showed that the effect of diltiazem lowering the supine diastolic blood pressure persisted over a 24-hour period (Table 17, page 18).

The adverse events related to diltiazem were not significantly different to those in the placebo group or those known to occur with similar diltiazem preparations or other calcium channel blockers (Table 18, page 20, Table 19, page 21, pages 20-22), (1-4), (Attachment 1).

Thus, the sponsor succeeded in meeting the objectives for this study (see pages 1-2, Objectives):

- Diltiazem HCl ER showed efficacy when administered once daily to patients with mild to moderate hypertension.

- There was a correlation between the plasma concentration of diltiazem and the lowering effects on blood pressure

- Diltiazem HCl ER was safe and there were no treatment limiting side effects.

Label. The label submitted by the sponsor (NDA 20-939, Vol. 2 of 19, pages 83-98) needs to be reconciled with the amendments already inserted in the labels of the cardizem preparations (Attachment 1) and the suggestions of the Division of Biopharmaceutics (Attachment 2) and this review (pages 28-30).

15. Recommendations. The recommendations relate to changes that should be made in the label of diltiazem HCl ER.

The label of diltiazem HCl ER (NDA 20-939, Vol. 2 of 19, pp. 83-98) should be amended according to the changes introduced in the label of Cardizem (Attachments 1 and 2).

The recommendations made by the Division of Biopharmaceutics (Attachment 2) for the sponsor should consider further changes in the label of cardizem (Attachment 1).

The sponsor with a wording must consider the insertion of buspirone in the subsection Precautions-Drug Interactions of diltiazem similar to the following:

Buspirone. Co-administration of diltiazem with buspirone the AUC of buspirone by a 5.5 fold and the $C_{max}$ of buspirone by a 4.1 fold. Thus, enhanced effects and adverse effects of buspirone are possible when used with diltiazem.

Considering should be given to adding quinidine in the subsection Precautions-Drug Interactions with a wording similar to the following:

Quinidine. Pretreatment with diltiazem significantly increased the AUC and elimination $t_{1/2}$ of quinidine and a prolonged the PR and QTc intervals with a decrease in diastolic blood pressure and heart rate. Blood levels of quinidine should be monitored when given with diltiazem and the dose of quinidine may have to be lowered accordingly.

The subsection Cyclosporine of Precautions-Drug Interactions (Vol. 2 of 19, pp.269-271) should be amended the following way (characters in bold are the suggested changes or additions):

Title in the first line of third paragraph (page 271):

A third paragraph should be added to the subsection

Consideration should be given to adding: subacute subcutaneous lupus erythematosus to the subsection: Adverse Reactions-Dermatological of diltiazem.

/S/

Cristobal G. Duarte, MD – HFD-110

CC.

ORIG. NDA-20-939
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HFD-110/Dr.Duarte/21July99
Encls

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