CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-392

Clinical Pharmacology and Biopharmaceutics Review

Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation I

NDA 21-392/N000BZ	SUBMISSION DATE:	July 16, 2002
N000BB		August 1, 2002
N000BZ		September 5, 2002
N000BL		October 7, 2002
N000BB		October 24, 2002
N000BB		November 20, 2002
N00BC		December 2, 2002
N000BB		December 13, 2002
FAX		October 17, 2002
FAX		October 23, 2002
FAX		December 12, 2002
FAX		December 30, 2002

TYPE:	RESPONSE TO APPROVABLE LETTER
BRAND NAME:	Cardizem® Tablets
GENERIC NAME:	Diltiazem Hydrochloride
DOSAGE STRENGTH:	120, 180, 240, 300, 360, and 420 mg oral Extended-Release Tablets
SPONSOR:	Biovail Technologies, Ltd.
PRIMARY REVIEWER:	Lydia Velazquez, Pharm.D.
TEAM LEADER:	Patrick Marroum, Ph.D.

SUBMISSIONS:

Biovail Technologies has responded to the approvable letter for NDA 21-392 dated June 11, 2002 in eight submissions and three faxes. The submissions are dated July 16th, August 1st, September 5th, October 7th and 24th, November 20th, 2002, and December 2nd and 13th, 2002. The four faxes are dated October 17th and 23rd, and December 12th and 30th, 2002. Each submission addresses specific issues that the Agency has advised will be necessary for the sponsor to address before the original application may be approved. Amendment to the NDA dated August 1st, 2002 is an additional amendment with justification for widening the Agency's interim upper dissolution limits at the 8-hour time point that was established in the approvable letter dated June 11th, 2002 and Agency correspondence dated July 11th, 2002. Issues numbered 2, 3, 4 (a and b), and 5 from the same approvable letter were specific to Clinical Pharmacology and Biopharmaceutics (CPB). This review will address each of the sponsor's responses to the mentioned issues.

Issue #2:

FDA

"Lack of bioequivalence data on the 420 mg strength. Additional data are needed for the approval of the 420 mg strength in the form of bioequivalence testing against an

approved 420 mg sustained release diltiazem (or a combination of two lower strengths of an approved drug)."

Biovail Response
"Biovail wishes to obtain approval for the 420 mg strength as part of this new drug application. Protocol B02-599PK-G99B1, entitled 'A two-way, cross-over, single-dose, open-label, fasting, evening administration, comparative bioavailability study of diltiazem hydrochloride extended-release tablets (420 mg) vs diltiazem hydrochloride extended –release capsules (420 mg) in normal, healthy, non-smoking male volunteers' is a bioequivalence study comparing the 420 mg strength tablet to a combination of two lower strengths of an approved sustained-release diltiazem drug product. This study is currently ongoing. The applicant intends to file the final report to the Division for review on the 16th of August 2002."

FDA Response
The sponsor submitted a bioequivalence study in Submission No. N000 (BZ) dated September 5th, 2002 which has demonstrated bioequivalence of the 420 mg strength extended-release tablet to the approved extended-release capsules in the form of two 120 mg capsules and one 180 mg capsule for a total strength of 420 mg administered in the evening after a two-hour fast. In the future, the sponsor should be aware that females should not be an exclusion criteria in a bioequivalence study. Please refer to Appendix I for study review.

Issue #3:
FDA
"Inadequate time of dissolution sampling. Your proposed dissolution method (USP Apparatus 2 (paddle), 100 rpm, and 900 mL of phosphate buffer pH 5.8 at 37°C) is acceptable. However, the proposed dissolution sampling points of 2, 8, 14 and 24 hours are not appropriate. We consider that sampling at 2, 6, 12, and 16 hours will provide more adequate information on the dissolution/release characteristics of your product.

Taking into account that your dissolution-stability data were generated using 2, 8, 14, and 24 hours and submitted to this supplement, your dissolution time points are acceptable pending submission of further stability and lot-release data on the primary stability lots as well as the first three post-marketing production lots as a part of your initial Annual Report. This dissolution testing should include testing at the timepoints you have used as well as those listed above (i.e., 2, 6, 8, 12, 14, 16, and 24 hours).

Biovail Response
"Please note that further stability and lot-release data on the primary stability lots as well as the first three post-marketing production lots will include results of dissolution testing conducted at the 6, 12, and 16 hour timepoints using the interim specifications, for information purposes only, in addition to the timepoints currently approved for release of the finished product. The interim specifications for all of the timepoints will be as requested by Dr. Patrick Marroum:

2 hours	*NMT*	*%*
6 hours		*%*
8 hours		*%*
12 hours		*%*
14 hours		*%*
16 hours	*NLT*	*%*
24 hours	*NLT*	*%*

Attached to this response are finished product release specifications and stability specifications for each strength, revised to include the additional timepoints and interim specifications."

FDA Response

We remind the sponsor that data gathering of timepoints at 6, 12, and 16 hours is not just for information gathering purposes only. The collection of these additional dissolution timepoints is for the purposes of setting final dissolution specifications for the product at a later time. These timepoints have been chosen because the Office of Clinical Pharmacology and Biopharmaceutics considers that dissolution sampling at these new timepoints will provide more appropriate information on the release characteristics of the product. The timepoints chosen by the sponsor at 8, 14, and 24 hours is inappropriate because of almost complete dissolution at earlier timepoints being observed.

Issue #4:

FDA

"Lack of adequate dissolution testing for some of the strengths. The testing listed below is necessary to support the biowaivers, both for approval of the proposed strengths and to support a biowaiver for the proposed manufacturing site changes for the individual strengths of diltiazem hydrochloride extended-release tablets. Note that this dissolution testing should be conducted at 2, 6, 12, and 16 hours.

a. ***For the 300 and 360 mg strengths, you did not perform comparative dissolution studies in 0.1N HCl because you asserted that diltiazem degrades substantially in this medium. We do not accept this, noting that your NDA for diltiazem hydrochloride extended release capsules (NDA 20-939) included dissolution data in this medium. Therefore, before a biowaiver for the 240 and 300 mg extended release tablets can be granted, you should provide additional dissolution profile comparison data in 0.1N HCl under the same dissolution conditions (i.e., USP Apparatus 2 and 100 rpm).***

b. ***For the 120 and 180 mg diltiazem extended release tablets, you should provide dissolution profile comparisons in the application dissolution medium (phosphate buffer pH 5.8) and in the following three dissolution media: 0.1N HCl, buffer pH 4.2, and buffer pH 6.8. The dissolution profiles***

should be generated using 12 units/lot of the test and reference products and the same dissolution conditions."

Biovail Response
"Attached please find comparative dissolution studies conducted in 0.1N HCl on the 240 mg strength, Lots Nos. 001002 and 001A185, 300 mg strength, Lot Nos. 001005 and 01A186, and the 360 mg strength, Lot Nos. 001004 and 01A176. Also attached are comparative dissolution profiles for the 120, 180, and 420 mg strengths, Lot Nos. 01M171, 01M173 and 01M170, in the following media: 0.1N HCl, pH 4.2, pH 5.8, and pH 6.8."

FDA Response
Issue 4a:
Upon reviewing the data submitted in amendment dated July 16th, 2002 from the sponsor, no F2 similarity factor calculations were performed. Additionally, the sponsor did not generate dissolution data for every time point. This was communicated to the sponsor on October 15th, 2002 resulting in additional data faxed on October 17th, 2002. However, the data addressing issue 4a did not coincide with the submitted data from July 16th, 2002 and no indication was given in the fax that the data generated was performed in 0.1N HCl. This was communicated to the sponsor on November 15th, 2002 via a telephone conversation. On November 20th, 2002 the sponsor responded to the identified deficiencies via fax and subsequently sent as an amendment dated November 20th, 2002. Upon reviewing the new faxed data, a biowaiver is granted for the 240 and 360 mg diltiazem extended-release tablets. Please refer to Appendix II for further details.

Issue 4b:
Dissolution data submitted on October 17th, 2002 did not have proper titles for identification of lot numbers and dissolution specifications used. Only one F2 similarity factor calculation table summary was provided for one medium when 4 different media were requested in the June 11th, 2002 approvable letter. As a result, a telecon was held between the Agency and the sponsor identifying further deficiencies on November 19th, 2002. On November 20th, 2002 the sponsor faxed the required data and subsequently submitted the data as an amendment to the NDA. Upon reviewing the data, insufficient dissolution time points were provided for the comparison of the 180 mg to the 360 mg strength in pH 6.8. A telephone message identifying this issue was left for the sponsor on November 22nd, 26th, and December 9th, 2002 resulting in data being faxed on December 12th, 2002. However, only summary tables were submitted. When the summary table was verified, the mathematical calculations were performed incorrectly. This error was communicated to the sponsor via a telephone conversation on December 13th, 2002 resulting in an additional fax with new calculations and the raw data missing later that day. Upon reviewing the newly faxed data on December 13th, 2002, a biowaiver is granted for the 120 and 180 mg extended-release strength of diltiazem hydrochloride tablets. The fax has been subsequently submitted as an amendment

to the NDA dated December 13th, 2002. Please refer to Appendix III for further details.

Issue #5:

FDA

"Inadequate data supporting the marketing of the unscored diltiazem extended release tablets. We note that you used scored extended release tablets to generate all the bioequivalence and dissolution data submitted in this application, but propose to market an unscored tablet form. Before this change may be approved, you should provide additional comparative dissolution profile data in the application data medium (phosphate buffer pH 5.8), showing that this change does not affect your product for each of the proposed strengths."

Biovail Response

"Provided overleaf is a comparative dissolution profile filed in the original submission, pages 223 to 258, to support the change in commercial manufacturing sites from Biovail Technologies, Ltd., site of manufacture of scored 240 and 360 mg strength tablets, to Biovail Corporation, Manufacturing Division, Steinbach, Manitoba, where unscored 240 and 360 mg strength tablets were manufactured. This dissolution profile, comparing Lot Nos. 001002, 01A185, 001005, 01A186, 001004, 01A176, not only demonstrates the equivalency of the manufacturing sites, but also of the scored and unscored tablets. Please note that only the 240 and 360 mg strengths were originally manufactured as scored tablets, therefore it was not necessary to conduct comparative tests on the 120, 180, 300, or 420 mg strengths, although a comparison is made between the 300 mg strength tablets manufactured at the Biovail Technologies facility and those manufactured at the Biovail Corporation facility in this profile."

FDA Response

Dissolution F2 similarity factor calculations seem to indicate that there should not be any bioavailability issues with the unscored tablet even though clinical trials were performed with a scored version of diltiazem HCl extended release tablets and a new manufacturing site will be utilized for the unscored, to be marketed product. Please refer to Appendix IV for further details.

Biovail's Justification For Widening The Upper Dissolution Limits

The sponsor has submitted an amendment to the NDA dated August 1st, 2002 in which they address the revision of the dissolution specifications recommended by the Agency in their approvable letter dated June 11th, 2002. In support of this request, the sponsor has submitted: 1) dissolution profiles for a "Fast", "Slow", and "Targeted" formulation for diltiazem hydrochloride extended release tablets; and 2) a bioavailability study (study# 2547 entitled – "A four-way, crossover, open-label, single-dose, fasting, pharmacokinetic study of three formulations of diltiazem HCl extended-release bead tablets 360 mg (once daily) and one formulation of an oral diltiazem HCl solution 120 mg (once daily) in normal, healthy non-smoking male subjects"). The sponsor believes they have demonstrated bioequivalence between the "Fast" release and the "Targeted" formulation even though the "Fast" formulation is dissolving at a faster rate in vitro than the recommended interim specifications that have been set by the Agency. The sponsor

believes that since bioequivalence has been established, a widening of the specifications at the [ ] time point is justified.

FDA Response

Upon reviewing the submitted study and dissolution data, the following information was missing:

1. **The study describes 3 formulations ("Fast", "Slow", and "Target") were studied in order to develop an IVIVC in study 2547; but no data was submitted describing the components of each formulation.**
2. **Appendices 1.3 and 1.4 (pages 147 to 169) are missing from study 2547. The missing pages are necessary for review of the study.**
3. **It is unclear whether "Treatment B" used a scored tablet from the description of the three treatments given. That information is required in evaluating the outcome of the studies (dissolution and clinical bioavailability study 2547).**
4. **No raw data accompanied the summarized dissolution table provided of the "Fast", "Slow", and "Targeted" formulations. Information on lot numbers of each of these formulations was not provided either. So it is not possible to discern if the same biobatches used in study #2547 were used to generate the dissolution profiles in question. This information is crucial to the evaluation of the analysis performed by the sponsor to justify their request.**

All of these deficiencies were communicated to the sponsor on October 18th, 2002 via a telephone conversation. The sponsor assured us that this information would be forthcoming as soon as possible.

On October 21st, the sponsor faxed the above mentioned request for data and subsequently submitted the data as an amendment to the NDA on October 24th, 2002. However, it was not possible to discern which lots were the scored tablets and which were not since interchangeable names were used for the scored and unscored tablets. In certain areas of the faxed and submitted data, lot numbers were used without mentioning if the lot came from a scored batch of tablets or not. In other areas of the data sets the tablets were referred to in terms of manufacturing site, not by lot number or whether the tablet was scored or not. This deficiency was communicated to the sponsor on October 23rd resulting in an additional fax with a reference table of all the terms used on the same day (October 23rd, 2002).

Upon reviewing all submitted data, the sponsor has demonstrated that the "fast" formulation is bioequivalent to the "targeted" formulation even though the dissolution profiles demonstrated a deviation at the 8-hour time point to that of the Agency's recommended interim dissolution specifications. As a result, the sponsor may widen the interim dissolution specification as requested at the 8-hour time point. Since the "fast" formulation is bioequivalent to the "targeted" formulation, safety concerns with the wider 8-hour specification does not seem to be a concern at this time. However, as per the approvable letter dated June 11th, 2002, the sponsor will be required to submit dissolution data for the time points they have proposed of 2, 8, 14, and 24 hours and time points of 6, 12, and 16 hours as part of your initial Annual Report. The additional time points of 6, 12, and 16 hours were originally

requested in the approval letter dated June 11th, 2002 in order to provide more adequate information on the dissolution/release characteristics of their product (item number 3 of the approvable letter dated June 11th, 2002). Please refer to Appendix V for further details.

Labeling

Biovail has submitted a new version dated October 7th, 2002 electronically. Below are the Agency's recommendations regarding their changes from the Clinical Pharmacology and Biopharmaceutics perspective:

CLINICAL PHARMACOLOGY

FDA Recommendation to Delete the sponsor's newly proposed wording below:

[

] "

CLINICAL PHARMACOLOGY

Pharmacokinetics and Metabolism

FDA Recommendation to Delete the sponsor's newly proposed wording below:

[

]

FDA Recommendation to Leave In the previous wording:

[

]

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation I (OCPB/DPEI) has reviewed the information provided in NDA 21-392, Amendments dated July 16th, August 1st, September 5th, October 24th, and November 20th 2002 and faxes dated October 17th, 23rd and December 12th, 13th, 2002 for diltiazem extended-release tablets and has the following comments:

1. The sponsor has demonstrated bioequivalence of the 420 mg strength extended-release tablet.

2. The sponsor is reminded that females should not be excluded from bioequivalence studies in the future.

3. The sponsor is reminded that data gathering of timepoints at 6, 12, and 16 hours is not just for information gathering purposes only. The collection of these additional dissolution timepoints is for the purposes of setting final dissolution specifications for the product at a later time. These timepoints have been chosen because the Office of Clinical Pharmacology and Biopharmaceutics considers that dissolution sampling at these new timepoints will provide more appropriate information on the release characteristics of the product. The timepoints chosen by the sponsor at 8, 14, and 24 hours is inappropriate because of almost complete dissolution at earlier timepoints being observed.

4. A biowaiver is granted for the 120, 180, 240 and 360 mg diltiazem extended-release tablets.

5. Dissolution F_2 similarity factor calculations seem to indicate that there should not be any bioavailability issues with the unscored tablet even though clinical trials were performed with a scored version of the 240 and 360 mg diltiazem HCl extended release tablets and a new manufacturing site will be utilized for the unscored (to be marketed) product.

6. Proposed interim dissolution specifications

The sponsor may widen the interim dissolution specification as requested at the 8-hour time point. However, the sponsor's previously accepted dissolution method of USP Apparatus 2 (paddle) at 100 rpm in 900 mL of pH 5.8 phosphate buffer at 37°C is to remain as previously proposed. The new interim dissolution specifications will be:

TIME (HOURS)	NEW INTERIM DISSOLUTION SPECIFICATIONS
2	NMT
8	
14	
24	NLT

We remind the sponsor that future dissolution testing should include timepoints the sponsor has used as well as those listed above. The sponsor has generated dissolution-stability data using 2, 8, 14, and 24 hours and has submitted these in previous supplements to include the original NDA. Therefore, the dissolution timepoints used by the sponsor for dissolution-stability testing are acceptable on an interim basis as well pending submission of further stability and lot-release data on the primary stability lots as well as the first three post-marketing production lots as part of the initial Annual Report. Note that final dissolution specifications will be set at a later time and they will be based on the review of the additional [ ] stability and lot release data that the sponsor provides.

6. Labeling – Agency's Recommendations:

CLINICAL PHARMACOLOGY
FDA Recommendation to Delete the sponsor's newly proposed wording below:

[ ]

CLINICAL PHARMACOLOGY
Pharmacokinetics and Metabolism
FDA Recommendation to Delete the sponsor's newly proposed wording below:

[ ]

FDA Recommendation to Leave In the previous wording:

Please convey the above recommendations to the sponsor.

Lydia Velazquez, Pharm.D.
Division of Pharmaceutical Evaluation I
Primary Reviewer

FT Initialed by Patrick Marroum, Ph.D. _____
CC list: HFD-110: NDA 21-392; HFD-860: (VelazquezL, MehtaM; SahajwallaC; MarroumP);
CDER Central Document Room (Biopharm)

Appendix I
Labeling

15 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Appendix I
Review of BE Study B02-599PK-G99B1 (Issue # 2)

"A two-way, cross-over, single-dose, open-label, fasting, evening administration, comparative bioavailability study of diltiazem hydrochloride extended-release tablets (420 mg) vs diltiazem hydrochloride extended–release capsules (420 mg) in normal, healthy, non-smoking male volunteers"

STUDY **B02-599PK-G99B1** – A TWO-WAY, CROSS-OVER, SINGLE-DOSE, OPEN-LABEL, FASTING, EVENING ADMINISTRATION, COMPARATIVE BIOAVAILABILITY STUDY OF DILTIAZEM HYDROCHLORIDE EXTENDED-RELEASE TABLETS (420 MG) VS DILTIAZEM HYDROCHLORIDE EXTENDED –RELEASE CAPSULES (420 MG) IN NORMAL, HEALTHY, NON-SMOKING MALE VOLUNTEERS.

STUDY INVESTIGATOR AND SITE: [redacted]

REPORT # B02-599PK-G99B1
VOLUME # 1 to 8

OBJECTIVES:
To compare the rate and extent of absorption of diltiazem hydrochloride 420 mg extended-release (ER) tablets (test) versus diltiazem hydrochloride extended-release capsules (administration as a combination of 2 x 120 mg capsules and 1 x 180 mg capsule, total daily dose = 420 mg) (reference) based on evening administration under fasting conditions.

FORMULATIONS:

Test (A) - 1 x 420 mg diltiazem hydrochloride ER tablets, Biovail Corp. Canada (Batch/Lot no. 01M170, Batch size: [redacted] for Treatment A

Reference (B) - 2 x 120 mg diltiazem hydrochloride ER capsules, Biovail Corp. Canada (Batch/Lot no. 01H005, Batch size: [redacted] for Treatment B and
1 x 180 mg diltiazem hydrochloride ER capsules, Biovail Corp. Canada (Batch/Lot no. 01H009, Batch size: [redacted] for Treatment B for a total dose of 420 mg

STUDY DESIGN:
This was a 420 mg single-dose, administered in the evening, single-center, randomized, open-label, fasting, two-way crossover bioequivalence study with a 5-day washout period between the two phases of the study. A total of 36 healthy, non-smoking male volunteers entered the study with 34 completing the study. Demographic data indicates that subjects were of white, black or Hispanic race in the age range of 18 to 60 years. Subjects were confined to the clinical facility from at least 10 hours before dosing until the 48-hour post-dose blood draw in each phase. Subjects abstained from food or drink containing xanthine (e.g., coffee, tea, caffeine-containing sodas, colas, chocolate, or decaffeinated products) from 48 hours prior to drug administration, until the end of sample collection in each period (48-hour post-dose draw), alcohol from 24 hours prior to drug administration, until the end of sample collection in each period, and grapefruit products (e.g., fresh, canned or frozen), natural products (including garlic as a supplement), energy drinks, and

vitamins from 7 days prior to drug administration, until the end of sample collection in each period. Subjects also abstained from food containing poppy seeds for 24 hours prior to admission in each period. Subjects were served a controlled meal at least 3 hours prior to dosing and consumed within one hour with at least a 2 hour fast after their meals before study drug administration. Identical meals were served in the two treatment phases/periods and subjects were requested to consume their meals in entirety. Water was not permitted from 1 hour prior to dosing to 1 hour after dosing except for the water allowed with dosing of medication. All other times water was permitted *ad libitum*. Vigorous physical activity was not permitted throughout confinement.

DRUG ADMINISTRATION:
Subjects were dosed on June 30th, 2002 and on July 5th, 2002 between 22:01 and 23:11. Water restriction was maintained from 1 hour before through one hour post drug administration except for potable, room temperature water (240 mL) given with the dose. After this time, water was permitted *ad lib*.

ANALYTICAL METHODS:
Plasma samples were analyzed for the content of diltiazem, N-desmethyldiltiazem and deacetyldiltiazem by a validated HPLC method.

Linearity
Diltiazem: —
N-desmethyldiltiazem: —
Deacetyldiltiazem: —

Calibration Curve Ranges
Diltiazem: — ng/mL (CV 2.62% for the lower limit of quantitation-LLOQ and 1.76% for the upper limit of quantitation-ULOQ)

N-desmethyldiltiazem: — ng/mL (CV 3.00% for the LLOQ and 2.41% for the ULOQ)

Deacetyldiltiazem: — ng/mL (CV 1.59% for the LLOQ and 1.71% for the ULOQ)

Between Run Accuracy and Precision
Diltiazem: — % (CV 3.68% to 6.27%)

N-desmethyldiltiazem: — (CV 3.93% to 7.21%)

Deacetyldiltiazem: — (CV 4.39% to 5.13%)

Within Run Accuracy and Precision
Diltiazem: — (CV 1.13% to 8.33%)

N-desmethyldiltiazem: — (CV 2.56% to 10.71%)

Deacetyldiltiazem: — (CV 1.23% to 4.07%)

Recovery of Internal Standard
Mean: 82.82%

PK SAMPLE COLLECTION AND EVALUATION CRITERIA:
Blood samples were collected at baseline (pre-dose), then at 2, 3, 4, 6, 8, 10, 11, 12, 13, 14, 15, 16, 18, 20, 24, 30, 36, 42, and 48 hours post dose.

PK Parameters calculated include AUC_{0-t}, AUC_{0-inf} and C_{max}, T_{max}, TLIN (the time point where ln-linear K_{el} calculations begin), LQCT (the sampling time of the last quantifiable concentration used to estimate the K_{el}), K_{el} and $t½_{el}$. To conclude bioequivalence, the 90% geometric confidence interval of the ratio (A/B) of the least-squares means from the ANOVA of the ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} should be within 80% to 125% for diltiazem, desacetyldiltiazem, and N-desmethyldiltiazem.

RESULTS:
Thirty-six subjects were enrolled in the study with two subjects not completing the crossover and one subject vomiting at 19 hours, 57 minutes in period 1 and at 19 hours, 7 minutes in period 2 resulting in 33 subjects completing the study for pharmacokinetic data analysis.

For diltiazem, desacetyldiltiazem, and N-desmethyldiltiazem, ANOVA did not detect any statistically significant difference between treatments for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max}. For diltiazem and desacetyldiltiazem, ANOVA did not detect a statistically significant difference between treatments for untransformed $T_{1/2\ el}$ and K_{el} but did for N-desmethyldiltiazem. Moreover, ANOVA did detect a statistically significant difference between treatments for untransformed T_{max} in all three moieties.

The 90% geometric CI around ratios for AUC_{0-t}, AUC_{0-inf} and C_{max} were within the bioequivalence interval 0.80 to 1.25 for all three moieties when the analysis was performed with and without subject no. 27.

A statistically significant sequence effect was observed for diltiazem and N-desmethyldiltiazem for AUC_{0-t}; but have no impact on the study results regarding establishment of bioequivalence according to the Agency's Guidance. Similar findings were observed in AUC_{0-inf} for the mentioned moieties as well. A significant period effect was detected in C_{max} for diltiazem; but once again, has no impact on the issue of bioequivalence between treatments.

SAFETY:
ECGs, and vital signs were performed prior to drug administration and throughout study. Laboratory tests and a physical exam were performed at the beginning and completion of study to include study withdrawal. A medical sub-investigator was present one hour prior

to drug administration and until 12 hours after drug administration with the last subject in each treatment period. A medical sub-investigator was on call throughout the study. Adverse events were mild to moderate in severity described as 1 hypotensive episode, 2 reports of upper abdominal pain, 5 reports of headache, 4 reports of mild abnormal ECG findings, light-headedness was reported 1 time, 3 reports of nausea, and 2 reports of emesis. A single significant adverse event occurred (subject no. 11) in which a drop in blood pressure, nausea, light-headedness, and abdominal pain was observed in period 1.

Subject no. 35 had a white blood cell count of 3.6 K/UL, hemoglobin of 9.3 GM/DL, hematocrit of 32.7%, MCV of 69.2 FL, MCH of 19.7 FG, and a MCHC of 28.5 G/DL. Attempts were made to contact this subject to return to clinic for repeat tests with no success.

Subject no. 27 had a urobilinogen of 6. However, upon a repeated sample collection 5 days later, a normal result was obtained.

CONCLUSIONS:

A single dose of the test 420 mg extended-release tablets of diltiazem hydrochloride (treatment A) is bioequivalent to a single dose of 420 mg of the reference diltiazem hydrochloride extended-release capsules administered as a combination of two 120 mg capsules plus one 180 mg capsule (treatment B), after evening administration under fasted conditions.

REVIEWER'S COMMENTS:

1. Female gender should not be an exclusion criteria in a bioequivalence study.

2. Batch size for the 120 mg and 180 mg extended release capsules of diltiazem hydrochloride was [ ] respectively. However, a common lot of beads ([ ] size of diltiazem hydrochloride extended release beads) was produced for encapsulation for the capsules since they are compositionally proportional. As a result, the small production sizes of the two strengths should not affect the bioavailability of the final product.

SUMMARY OF RESULTS
DILTIAZEM
N = 33

Pharmacokinetic Parameters

Parameters		Test (Diltiazem HCl ER Tablet (A)) Mean	±	SD	CV (%)	Reference (Diltiazem HCl ER Capsules (B)) Mean	±	SD	CV (%)
AUC_{0-t}	(ng·h/mL)	4095.62	±	1469.55	35.88	4017.21	±	1553.55	38.67
AUC_{0-inf}	(ng·h/mL)	4266.43	±	1572.72	36.86	4196.85	±	1678.13	39.99
C_{max}	(ng/mL)	228.95	±	71.62	31.28	223.36	±	90.91	40.70
T_{max}	(h)	14.7	±	2.0	13.60	12.1	±	2.3	19.21
K_{el}	(h^{-1})	0.0977	±	0.0203	20.79	0.0929	±	0.0232	25.02
$T_{½ el}$	(h)	7.43	±	1.73	23.31	7.97	±	2.15	26.98

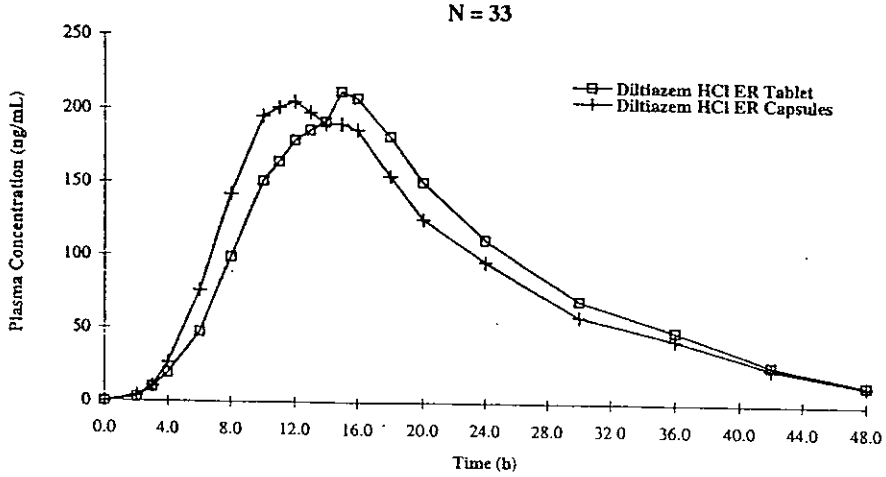
Diltiazem HCl ER Tablet (A) vs Diltiazem HCl ER Capsules (B)

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	103.07%	102.87%	105.19%
90 % Geometric C.I.[2]	95.72 % to 110.99 %	95.57 % to 110.74 %	97.07 % to 113.99 %
Intra-Subject CV	17.87 %	17.79 %	19.41 %

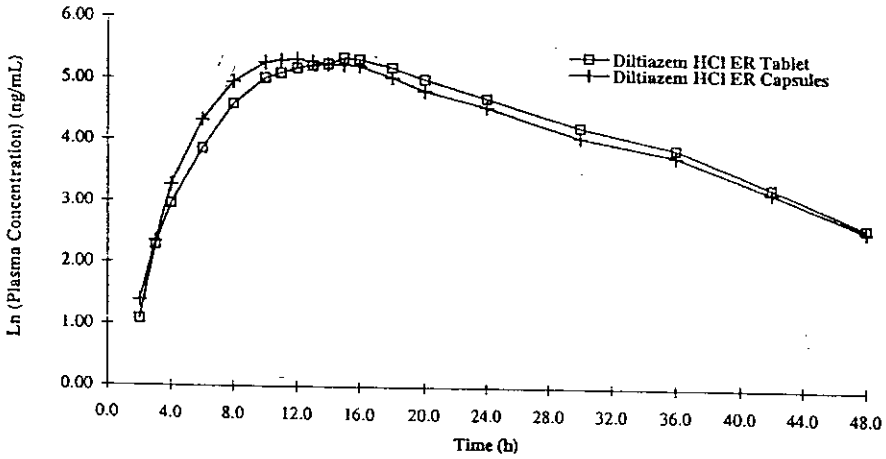
[1] Calculated using least-squares means according to the formula: $e^{(\text{Diltiazem HCl ER Tablet (A) - Diltiazem HCl ER Capsules (B)})} \times 100$

[2] 90% Geometric Confidence Interval using ln-transformed data

Diltiazem Mean Concentration - Time profile
N = 33



Diltiazem Ln (Mean Concentration) - Time profile
N = 33



Appendix II
Issue 4a

Appears This Way
On Original

According to the guidance entitled: "Dissolution Testing of Immediate Release Solid Oral Dosage Forms" only one measurement should be considered after 85% dissolution. Therefore, the last time point for consideration should be 16 hours for F2 similarity factor calculations making the F2 value lower than reported in the tables below. F2 similarity factor calculations for the 240 and 300 mg strength tablets tested in 0.1N HCl using approved dissolution method was recalculated to be 41 and 44, respectively. This slight failure is not expected to have any impact on the bioavailability of the product since the failure is not that large and all other tests passed.

f_2 Calculations Results for the 240 mg Biobatch Lot vs. the 360 mg Biobatch Lot in 0.1 N HCl

Dissolution Testing Results for Diltiazem HCl ER Tablets, 240 mg Biobatch Lot vs. 360 mg Biobatch Lot, in 0.1 N HCl Using Apparatus II at 100 rpm							Calculations		
Time	240 mg (Lot No. 061002)			360 mg (Lot No. 011004)			$R_t - \bar{T}_t$	$(R_t - T_t)^2$	$\sum_{t=1}^{n}(R_t - T_t)^2$
	Mean	Min	Max	Mean	Min	Max			
0	0			0			0	0	3733
1	1			2			-1	1	
2	2			5			-3	9	$(1/n)\sum_{t=1}^{n}(R_t - T_t)^2$
3	4			10			-6	36	155.54167
4	8			17			-11	121	
5	10			26			-16	256	$\{1+(1/n)\sum_{t=1}^{n}(R_t - T_t)^2\}^{-0.5}$
6	18			35			-19	361	0.0799254
7	22			45			-23	529	
8	30			53			-23	629	$50\log\{[1+(1/n)\sum_{t=1}^{n}(R_t - T_t)^2]^{-0.5}\cdot 100\}$
9	38			58			-20	400	f_2 = 45
10	46			07			-21	441	
11	51			68			-17	288	
12	61			77			-16	256	
13	65			78			-13	169	
14	73			84			-11	121	
15	76			84			-8	64	
16	82			89			-7	49	
17	83			89			-6	36	
18	88			92			-4	16	
19	88			92			-4	16	
20	92			94			-2	4	
21	91			94			-3	9	
22	95			96			-1	1	
23	93			95			-2	4	
24	94			98			-4	16	

f_2 Calculations Results for the 300 mg Biobatch Lot vs. the 360 mg Biobatch Lot in 0.1 N HCl

Dissolution Testing Results for Diltiazem HCl ER Tablets, 300 mg Biobatch Lot vs. 360 mg Biobatch Lot, in 0.1 N HCl, (in 0.1 N HCl using Apparatus II at 100 rpm										
Time	300 mg (Lot No. 001005)			360 mg (Lot No. 001004)			Calculations			
	Mean	Min	Max	Mean	Min	Max	$R_t - T_t$	$(R_t - T_t)^2$	$\Sigma_{t=1}^{n} (R_t - T_t)^2$	
0	0			0			0	0	2827	
1	1			2			-1	1		
2	2			5			-3	9	$(1/n) \Sigma_{t=1}^{n} (R_t - T_t)^2$	
3	4			10			-6	36	117.79167	
4	6			17			-11	121		
5	10			26			-16	256	$\{1+(1/n) \Sigma_{t=1}^{n} (R_t - T_t)^2\}^{-0.5}$	
6	16			35			-19	361	0.0917502	
7	23			45			-22	484		
8	32			53			-21	441	$50 \cdot \log(\{1+(1/n) \Sigma_{t=1}^{n} (R_t - T_t)^2\}^{-0.5} \cdot 100)$	
9	40			56			-16	256	f_2	= 48
10	49			67			-18	324		
11	57			68			-11	121		
12	64			77			-13	169		
13	70			78			-8	64		
14	75			84			-9	81		
15	79			84			-5	25		
16	83			89			-6	36		
17	86			89			-3	9		
18	88			92			-4	16		
19	90			92			-2	4		
20	92			94			-2	4		
21	93			94			-1	1		
22	94			96			-2	4		
23	95			95			0	0		
24	96			98			-2	4		

Appendix III
Issue 4b

The sponsor has submitted dissolution data for the 120 and 180 mg versus 360 mg strength tablets in 0.1N HCl, pH 4.2 buffer, pH 5.8 buffer, and pH 6.8 buffer with F2 similarity calculations.

Diltiazem HCl 120 mg extended-release tablets:
For the 120 mg strength comparison to the 360 mg strength tablets, the dissolution profile generated in 0.1N HCl yielded a F2 of 53 indicating that the two dissolution profiles are similar.

For the pH 4.2 medium, the 14 and 16 hour time point of the 120 mg versus the 360 mg tablet was deleted from the Agency's recalculations due to the published guidance entitled: "Dissolution Testing of Immediate Release Solid Oral Dosage Forms" where it is stated that only one measurement should be considered after 85% dissolution. Therefore, the last time point for consideration should be 12 hours for F2 similarity factor calculations. However, the F2 value still remained at 56 after recalculation.

Once again, time point omissions (16 hour time point) leading to recalculations was necessary due to the above mentioned guidance recommended approach to F2 similarity factor calculations. The pH 5.8 medium in which the 120 mg strength dissolution profile was compared to the 360 mg strength tablet dissolution profile yielded the same F2 factor of 53.

All time points submitted for the dissolution profiles of the 120 mg versus the 360 mg strength tablets were acceptable for the F2 calculation in pH 6.8 buffered medium. The F2 similarity factor calculation was 58.

All F2 similarity factor calculations resulted in a value greater than 50 indicating that the 120 mg strength tablet has a similar dissolution profile as the 360 mg strength and that the bioavailability of the 120 mg strength is not expected to be different from the bioavailability of the 360 mg strength.

Diltiazem HCl 180 mg extended-release tablets:
The 180 mg strength compared to the 360 mg strength in 0.1N HCl had a F2 similarity factor of 41. This failure is not expected to have any impact on the bioavailability of the product since it was a slight failure and all other media tested passed.

Time point omission of the 16 hour time point lead to recalculations due to the above mentioned guidance recommended approach to F2 similarity factor calculations. The F2 value was recalculated to be 97 (the same as calculated by the sponsor) in pH 4.2.

When the F2 similarity factor was calculated for pH 5.8, a value of 70 was obtained. Insufficient amounts of data points were submitted for the pH 6.8 dissolution profiles of the 180 versus 360 mg tablet strengths. The deficiency was communicated to the sponsor on November 22nd,26th, and December 9th, 2002 via a telephone message. On December 12th, 2002, new data was submitted. However, they were only summary tables and the F2 calculation was performed incorrectly. This error was communicated to the sponsor on

December 13th, 2002 resulting in further data being submitted. Upon reviewing the newly faxed data, recalculation was required; but resulted in a F2 calculation of 84 instead of the submitted F3 calculation number of 85.

All submitted data seems to indicate that the 120 and 180 mg strength extended-release tablets have the same dissolution profile as the 360 mg strength extended-release tablets and that no bioavailability problems are expected. A biowaiver is therefore granted for both strengths (120 and 180 mg) of diltiazem hydrochloride extended-release tablets.

Appendix IV
Review of Issue 5
(Amendment dated July 16th, 2002)

COMPARATIVE DISSOLUTION PROFILES OF THE 240 MG AND 360 MG STRENGTHS (SCORED VERSUS UNSCORED TABLETS)

SITE LOCATIONS: CLINICAL BATCHES – BIOVAIL TECHNOLOGIES, LTD. (BTL, SCORED)

STABILITY BATCHES – BIOVAIL CORP., MANUF. DIV., STEINBACH, MANITOBA (UNSCORED)

OBJECTIVES:

To establish that the change in manufacturing site between the clinical (BTL site) and stability batches (Manitoba site) does not affect the product for each of the strengths 240 and 360 mg. To establish that the scoring of the clinical batches manufactured at BTL did not affect the product when compared to the stability unscored batches (the to be marketed final product Manufactured in Manitoba) by demonstrating similar f_2 dissolution profiles between the BTL site (scored) batches and the Manitoba site (unscored).

FORMULATIONS:

Clinical (Scored tablets) – BTL site	240 mg – lot number 001002
	360 mg – lot number 001004
Stability (Unscored tablets) – Manitoba site	240 mg – lot number 01A185
	360 mg – lot number 01A176

STUDY DESIGN:

The f_2 similarity factor used below was utilized to establish similarity between dissolution profiles of the products manufactured at both sites in the two mentioned strengths.

$$f_2 = 50 \times \log \left\{ [1 + (1/n) \sum_{t=1}^{n} [(R_t - T_t)^2]^{-0.5}] \times 100 \right\}$$

where:

f_2 = Similarity factor. If f_2 value > 50, then the dissolution profiles are similar.

R_t = Dissolution of reference formulation at time "t"

T_t = Dissolution of test formulation at time "t"

n = number of dissolution points

An f_2 value between 50% and 100% suggests that the two dissolution profiles are similar.

The approved dissolution method the sponsor used for f_2 assessment is 900 mL of pH 5.8 phosphate buffer @ 37°C, using USP apparatus II.

RESULTS:

The dissolution profiles for the 240 mg and the 360 mg strength tablets in both the BTL (clinical batches-scored tablets) and Manitoba (stability batches-unscored tablets) locations are illustrated below. The calculated F_2 values are illustrated as well in a tabulated format.

CONCLUSIONS:

The F_2 values for the 240 mg and the 360 mg tablet strengths are within the range of 50 to 100 suggesting that the two products are similar and the alternative manufacturing site used and scoring of the tablets does not impact upon the quality of the finished product

Diltiazem HCl Extended-Release Bead Tablets
Dissolution Comparison in pH 5.8 Phosphate Buffer

Sampling Time (Hrs)	240 mg Bio (clinical)	240 mg Stability	300 mg Bio (clinical)	300 mg Stability	360 mg Bio (clinical)	360 mg Stability
0						
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
f_2 Comparison	60		87		74	

$$f_2 = 50 \log\{1 + (\frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2)^{-0.5} \times 100\}$$

Appendix V

Review of Study 2547 (justification for widening dissolution specifications) entitled:

"A four-way, crossover, open-label, single-dose, fasting, pharmacokinetic study of three formulations of diltiazem HCl extended-release bead tablets 360 mg (once daily) and one formulation of an oral diltiazem HCl solution 120 mg (once daily) in normal, healthy non-smoking male subjects".

Review of fax dated October 23rd, 2002 and Amendment dated October 24th, 2002

STUDY 2547 – A FOUR-WAY, CROSS-OVER, OPEN-LABEL, SINGLE-DOSE, FASTING, PHARMACOKINETIC STUDY OF THREE FORMULATIONS OF DILTIAZEM HCL EXTENDED-RELEASE BEAD TABLETS 360 MG (ONCE DAILY) AND ONE FORMULATION OF AN ORAL DILTIAZEM HCL SOLUTION 120 MG (ONCE DAILY) IN NORMAL, HEALTHY, NON-SMOKING MALE SUBJECTS.

STUDY INVESTIGATOR AND SITE:

Biovail Contract Research
460 Comstock Road
Toronto, ON, MIL 4S4 Canada
689 Warden Avenue, Units 1&2
Toronto, ON MIL 4R6 Canada

STUDY DATES: November 16, 2001 to December 10, 2001
REPORT # 2547
VOLUME # 1 to 8

NOTE:
This study originally was designed to develop an IVIVC and then submitted retrospectively to justify widening dissolution specifications that were set by the Agency upon reviewing the original NDA. As a result all data pertaining to formulation D [redacted] will not be reviewed. The reviewer's approach to reviewing the submitted study report will be focused on the sponsor's desire to widen the interim dissolution specifications set by the Agency in the approvable letter dated June 11th, 2002 not in assessing the sponsor's approach in attempting to establish an IVIVC (which it did not).

OBJECTIVES:
To generate in-vivo pharmacokinetic data to establish the in-vitro-in-vivo correlation and validate dissolution specifications for diltiazem hydrochloride 360 mg extended-release (ER) bead tablets intended for marketing. The secondary objective was to compare the bioavailability of diltiazem from formulation A (Fast release) relative to formulation B (Target release) and, formulation C (Slow release) relative to formulation B (Target release).

FORMULATIONS:

Fast Release (Treatment A) - diltiazem HCl 360 mg ER bead tablets (potency value = [redacted] of label claim), Biovail Technologies, Ltd. (Lot no. 25061001, manufactured 10/01), an oval, white to off-white tablet with a "B" engraved on one side and with "360" engraved on the other side

Targeted Release (Treatment B) - diltiazem HCl 360mg ER bead tablets (potency value = [redacted] of label claim), Biovail Technologies, Ltd. (Lot no. 001004, manufactured 09/00), a modified oval, half-bisected (scored) light

	blue colored tablet with small pits and fissures present on the surface
Slow Release (Treatment C) -	diltiazem HCl 360mg ER bead tablets (potency value = — of label claim), Biovail Technologies, Ltd. (Lot no. 010207, manufactured 02/01), an oval, blue tablet with a "B" engraved on one side, also with small pits and fissures present on the surface

STUDY DESIGN:

This was a Phase I, four-way crossover, single-dose, randomized, open-label, fasting, pharmacokinetic study with a 7-day washout period between the four treatments. A total of 20 healthy, non-smoking male volunteers entered the study with 18 completing the study. Even though this was an open-label study, the analytical facility was blinded to the randomization code. The code was broken for statistical and reporting purposes after the completion of the analytical portion. Demographic data indicates that subjects were of Caucasian, black or Asian race in the age range of 21 to 46 years. All subjects were informed not to take any prescription or over-the-counter drugs for at least 14 days prior to the study. They were confined to the clinical facility from at least 10 hours before dosing until the 48-hour post-dose blood draw in each phase. Subjects fasted overnight for at least ten hours prior to drug administration. At 4.5, 9.5, 23.5, 28.5, and 33.5 hours post-dose, standardized meals were provided to the subjects with beverages. In addition, standardized snacks were provided at 13.5 and 37.5 hours post-drug administration. All meals and beverages were free from grapefruit products, xanthines, and caffeine and were identical between the study periods. Water was not permitted from 1 hour prior to dosing to 1 hour after dosing except for the water allowed with dosing of medication. Subjects were requested to abstain from alcohol, grapefruit products, xanthine, and caffeine containing foods and fluids for 48 hours prior to the start of each study period.

DRUG ADMINISTRATION:

Medications were administered orally and subjects were dosed at 7:00 am on November 17, 2001 for period 1, November 24, 2001 for period 2, and December 8, 2001 for period three.

ANALYTICAL METHODS:

Plasma samples were analyzed for the content of diltiazem, N-desmethyldiltiazem and desacetyldiltiazem by HPLC method.

Linearity

Diltiazem: —

N-desmethyldiltiazem: —

Desacetyldiltiazem: —

Calibration Curve Ranges

Diltiazem: — ng/mL (CV 5.8% for the lower limit of quantitation-LLOQ and — for the upper limit of quantitation-ULOQ)

N-desmethyldiltiazem: — ng/mL (CV 6.0% for the LLOQ and — for the ULOQ)

Desacetyldiltiazem: — ng/mL (CV 9.8% for the LLOQ and 2 — for the ULOQ)

Intra-Assay Accuracy and Precision

Diltiazem: — (CV 0.7% to 2.9%)

N-desmethyldiltiazem: — (CV 0.6% to 2.8%)

Desacetyldiltiazem: — (CV 2.1% to 11.9%)

Inter-Assay Accuracy and Precision

Diltiazem: — (CV 1.3% to 6.3%)

N-desmethyldiltiazem: — (CV 1.8% to 10.7%)

Desacetyldiltiazem: — (CV 3.3% to 12.3%)

Recovery of Internal Standard

Diltiazem: — CV 2.7%

N-desmethyldiltiazem: — CV 3.4%

Desacetyldiltiazem: — CV 1.9%

PK SAMPLE COLLECTION AND EVALUATION CRITERIA:

Blood samples were collected at baseline (pre-dose) and after dosing at 2, 3, 4, 6, 8, 10, 11, 12, 13, 14, 16, 20, 24, 30, 36, 42, and 48 hours post dose during each treatment period.

PK parameters calculated by standard non-compartmental methods at each sampling time included AUC_{0-t}, AUC_{0-inf} and C_{max}, T_{max}, K_{el}, and t½ for diltiazem, desacetyldiltiazem, and N-desmethyldiltiazem. The intra-subject CV, ratios of means based on the geometric means from ANOVA, and the 90% geometric confidence interval were calculated for the ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max}. The ANOVA model included period, sequence, subjects nested within sequence, and treatment as factors. Treatment differences tested were treatment A versus B and treatment C versus B.

RESULTS:

Twenty subjects were enrolled in the study with two subjects dropping out before finishing all treatment periods resulting in 18 subjects completing the study for pharmacokinetic data analysis.

The 90% geometric confidence intervals on the mean data for AUC_{0-t} and AUC_{0-inf} between the two treatments (A and B) were within 80 to 125% except for C_{max} (79.77 to 111.39%). Formulation A exhibits similar bioavailability to formulation B. However, formulation C did not demonstrate similar bioavailability to formulation B due to the 90% geometric confidence intervals of the mean data for all three parameters being outside the 80 to 125% range. Please refer to Table below for additional information.

SUMMARY OF PHARMACOKINETIC RESULTS:

Pharmacokinetic Parameters	Fast *Diltiazem (A) Lot#: 25061001* *Mean ± SD*	Target *Diltiazem (B) Lot#: 001004* *Mean ± SD*	Slow *Diltiazem (C) Lot#: 010207* *Mean ± SD*	*Diltiazem (D) Lot#: 10000299* *Mean ± SD*
AUC_{0-t} (ng.hr/mL)	3366.51 ± 2070.35	3597.10 ± 2375.03	2997.22 ± 1993.48	1205.65 ± 717.35
AUC_{0-inf} (ng.hr/mL)	3531.55 ± 2291.15	3745.77 ± 2425.14	3381.15 ± 2362.00	1236.15 ± 725.30
C_{max} (ng/mL)	161.02 ± 77.17	185.05 ± 122.71	129.65 ± 81.82	224.04 ± 120.27
T_{max} (hour)	13.11 ± 4.13	14.73 ± 3.29	17.17 ± 4.12	1.06 ± 0.38
$t_{1/2}$ (hour)	7.40 ± 1.69	7.78 ± 2.96	8.26 ± 2.22	5.54 ± 1.68
K_e (hour^{-1})	0.098 ± 0.020	0.097 ± 0.025	0.089 ± 0.023	0.136 ± 0.042

	Fast *Diltiazem (A)* Lot#: 25061001 *vs. Diltiazem (B) Lot#: 001004* Target		
	AUC_{0-t}	AUC_{0-inf}	C_{max}
90% C.I.	83.68% to 112.80%	83.00% to 110.00%	79.77% to 111.39%
Ratio of Means	97.15%	95.55%	94.26%
Intra-Subject CV	26.63%	25.10%	29.76%
	Slow *Diltiazem (C)* Lot#: 010207 *vs. Diltiazem (B) Lot#: 001004* Target		
	AUC_{0-t}	AUC_{0-inf}	C_{max}
90% C.I.	70.79% to 95.34%	75.58% to 100.65%	58.99% to 82.29%
Ratio of Means	82.16%	87.22%	69.67%
Intra-Subject CV	26.63%	25.10%	29.76%

SAFETY:

ECGs, and vital signs were performed prior to drug administration and throughout study for every treatment period.

Ten subjects experienced a total of twenty-eight adverse events during the study consisting of constipation, headache, sore throat, sternal pain during inspiration, primary AV block, protein in urine, elevated ALT, lightheadedness, chest discomfort on the left side of the chest, bradycardia (47 BPM on the ECG tracing), low blood pressure (98/80),

elevated urea, rash on the right torso, dizziness, elevated glucose serum random, and chest pain over left breast.

Subject no. 10 had a primary AV block with treatment D; which has not been reported in this review due to formulation [ ] and not the focus of this analysis. However, the adverse event is believed to be study drug related and occurred during treatment period 2 leading to subject dropping out from the study. The same subject experienced protein in their urine during the same treatment period.

Subject no. 01 also had adverse events while taking formulation D during treatment period 3 consisting of lightheadedness, primary AV block, chest discomfort on left side of chest, bradycardia (47 BPM on the ECG tracing), headache, low blood pressure (98/80), elevated glucose serum random, and elevated ALT. These adverse events lead to the subject dropping out of the study as well.

CONCLUSIONS:

The 90% geometric confidence intervals on the mean data for AUC_{0-t} and AUC_{0-inf} between the two treatments (A and B) were within 80 to 125% except for C_{max} (79.77 to 111.39%). Therefore, formulation A exhibits similar bioavailability to formulation B. However, formulation C did not show similar bioavailability to formulation B due to the 90% geometric confidence intervals of the mean data for all three parameters being outside the 80 to 125% range.

REVIEWER'S COMMENTS:

1. The study describes 3 formulations ("Fast", "Slow", and "Target") studied in order to justify widening of the Agency's interim dissolution specifications in study 2547; but no data was submitted describing the composition of each formulation.
2. Appendices 1.3 and 1.4 (pages 147 to 169) were missing from study 2547. The missing pages are required before a full review can be made of the submitted data.
3. It is unclear whether "Treatment B" used a scored tablet from the description of the three treatments given.

NOTE: On October 21, 2002 the sponsor faxed 41pages with additional data to this amendment addressing the three issues above. However,

Information faxed regarding treatment B confirms that it was a scored tablet. Along with that confirmation, the sponsor sent information on where the data to demonstrate the equivalency of the scored to the unscored tablet could be found. Upon reviewing the faxed data, the sponsor is utilizing 4 different terms to describe whether the formulation is scored or unscored without a reference to go by, making reviewing the information not possible since 8 different terms in total are being used for the scored and unscored tablets. This deficiency was communicated to the sponsor via telecon on October 23, 2002. The sponsor faxed a table cross-referencing all terms used later the same day.

Below is an assessment of the data subsequently submitted and faxed for study 2547.

1. Formulations A (lot no. 25061001-fast), B (lot no.001004-target), C (lot no. 010207-slow) description used for study 2547:

Formulations of Lots Used in Protocol No. 2547

Component	% w/w	Lot No. 010207 (Slow Release) mg/tab	Lot No. 001004 (Target Release) mg/tab	Lot No. 25061001 (Fast Release) mg/tab
Diltiazem HCl Extended Release Coated Beads				
Diltiazem Hydrochloride, USP		360.00	360.0	360.00
Microcrystalline Cellulose, USP				
Povidone K30, USP				
Sucrose Stearate				
Magnesium Stearate, NF				
Talc, USP				
Titanium Dioxide, USP				
Hydroxypropyl Methylcellulose 2910, USP				
Polysorbate 80, NF				
Simethicone C Emulsion, USP				
Eudragit NE30D				
Purified Water, USP*				
Wax Placebo Beads				
Microcrystalline Wax, NF				
Pregelatinized Starch, NF				
Sodium Starch Glycolate, NF				
Croscarmellose Sodium, NF				
Colloidal Silicon Dioxide, NF				
Hydrogenated vegetable oil, Type I, NF				
Opadry Coating				
Carnauba Wax, NF				
Theoretical Total Coated Tablet Weight	100.00	1063.83	1063.83	1063.83

*Water used for the manufacture of the beads is evaporated during the manufacturing process. The water content of the beads is NMT

Note to Reviewer:

All other aspects of the formulation remain identical.

2. The sponsor did verify that "Treatment B" is a scored tablet. As a result, the sponsor has submitted dissolution data for that formulation and the marketed formulation (unscored tablet) demonstrating that the scoring does not influence the dissolution characteristics of treatment B through F2 similarity factor calculations. Please refer to Appendix III for a full review of the submitted data.

3. The Agency tightened the dissolution specifications proposed in the NDA and recommended the following as interim specifications:

Table 1: Recommended Interim Dissolution Specifications.

Time (hours)	Interim Dissolution Specifications
2	NMT %
8	
14	
24	NLT %

During this time period, the sponsor conducted a study in which a discriminatory "fast" and "slow" formulations were created relative to the targeted formulation. The sponsor then conducted the above reviewed study to support the widening of the interim

dissolution specifications. Results of the study demonstrated that the "fast" formulation is bioequivalent to the targeted formulation.

Along with conducting a bioequivalence study, the sponsor generated dissolution profiles for all three formulations. Upon reviewing the dissolution profiles for the fast, targeted, and slow formulations, the 8-hour time point for the fast formulation has % diltiazem dissolved that is higher than the recommended upper limit as illustrated below:

Of Diltiazem HCl ER Tablets, 360 mg.

	% Diltiazem Dissolved		
Time (Hrs)	Fast Release	Target Release	Slow Release
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			

NMT

NLT

However, even though the "fast" formulation dissolves at a faster rate than the recommended Agency interim specifications, the bioequivalence study demonstrates that there are no PK differences between the formulations to cause safety or efficacy concerns. The sponsor concurs with the Agency's recommended tentative dissolution specifications for the lower limit; but believe that the upper limits is too stringent. Specifically, the "fast" formulation exhibits (which is bioequivalent to the target formulation) a mean cumulative % dissolved value of — at the 8-hour time point whereas the recommended specification at this time point is —

The sponsor is proposing the following specifications based on the in-vivo results from the bioequivalence study:

Time (hours)	Interim Dissolution Specifications	Proposed Interim Dissolution Specifications
2	NMT %	NMT %
8	%	%
14	%	%
24	NLT %	NLT %

REVIEWER'S COMMENTS:

Based on the presented data, the sponsor may widen the interim dissolution specification as requested at the 8-hour time point. Since the "fast" formulation is bioequivalent to the "targeted" formulation, safety concerns with the wider 8-hour specification does not seem to be a concern at this time.

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/s/

Lydia Velazquez
12/30/02 06:49:08 PM
PHARMACOLOGIST

Patrick Marroum
1/2/03 08:31:35 AM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-392
SUBMISSION DATES:	Original NDA: June 8, 2001 Supplement: August 22, 2001
TYPE:	3-S
BRAND NAME:	Diltiazem Hydrochloride Extended Release Tablets
GENERIC NAME:	Diltiazem Hydrochloride
DOSAGE STRENGTH:	120, 180, 240, 300, 360 mg and 420-mg extended release tablets
SPONSOR:	Bioavail Technologies Ltd.
PRIMARY REVIEWER:	Gabriel J. Robbie, Ph.D.
TEAM LEADER:	Patrick J. Marroum, Ph.D.

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STUDY 2489 (B01-541PK-DILG99)– A TWO-WAY CROSSOVER, 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 39

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STUDY 2492 (B01-543PK-DILG99)– 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 49

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STUDY 2463 (B01-530PK-DILG99)– A TWO-WAY, CROSSOVER, OPEN-LABEL, MULTIPLE-DOSE, FASTING, COMPARATIVE BIOAVAILABILITY STUDY BETWEEN 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 58

STUDY 2438 (B00-518PK-DILG99)– 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 63

STUDY 2464 (B01-531PK-DILG99)– A TWO-WAY, CROSSOVER, OPEN-LABEL, MULTIPLE-DOSE, FASTING, COMPARATIVE BIOAVAILABILITY STUDY BETWEEN DILTIAZEM HCl EXTENDED RELEASE BEAD TABLETS (360 mg) WITH EVENING DRUG ADMINISTRATION (10:00 P.M.) AND DILTIAZEM HCl EXTENDED RELEASE BEAD TABLETS (360 mg) WITH MORNING (8:00 A.M.) DRUG ADMINISTRATION IN NORMAL HEALTHY NON-SMOKING MALE AND FEMALE SUBJECTS 67

STUDY 2532 (B01-561PK-DILG99)– A TWO-WAY, CROSSOVER, OPEN-LABEL, SINGLE-DOSE, FASTING, COMPARATIVE BIOAVAILABILITY STUDY OF DILTIAZEM HCl EXTENDED RELEASE 360 mg BEAD TABLETS (MANUFACTURED AT STEINBACH, MANITOBA) VERSUS DILTIAZEM HCl EXTENDED RELEASE 360 mg BEAD TABLETS (MANUFACTURED AT CHANTILLY, VIRGINIA) IN NORMAL HEALTHY NON-SMOKING MALE SUBJECTS 71

DISSOLUTION 75

PROPOSED LABEL 83

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 21-392 and its supplement and finds the clinical pharmacology and biopharmaceutics section acceptable. The proposed 360 mg extended release bead tablets of diltiazem hydrochloride were bioequivalent to 2 x 180 mg extended release capsule.

The sponsor proposed dissolution method of USP Apparatus 2 (Paddle) at 100 rpm in 900 ml of pH 5.8 phosphate buffer at 37^0C is acceptable. The dissolution time points of 8, 14 and 24 hours chosen by the sponsor for dissolution specification are inappropriate because of almost complete dissolution at earlier time points. OCPB considers that dissolution sampling at 2, 6, 12 and 16 hours will provide more appropriate information on the release characteristics of the product. Based on the dissolution data provided by the sponsor supporting biowaiver for the lower strengths of diltiazem extended release tablets, OCPB recommends the following dissolution times and specifications.

Time (h)	FDA PROPOSES Dissolution Specifications
2	NMT
6	
12	
16	NLT

However, considering that all the stability data were generated by the sponsor using 2, 8, 14 and 24 hours sampling, OCPB will accept on an interim basis the dissolution time points studied by the sponsor with the following altered specification.

Time (h)	FDA PROPOSES Interim Dissolution Specifications
2	NMT
8	
14	
24	NLT

COMMENTS:

1. The sponsor has amended the NDA to include additional lower tablet strengths such as 120 mg and 180 mg and a higher strength 420 mg.

a. The highest strength was not tested in any of the bioequivalence studies, the 360 mg strength was tested in the bioequivalence studies.
b. Dissolution data supporting the 120 mg and 180 mg strengths were not provided in the NDA. Also, the tablet composition of the new 120 mg and 180 mg strengths were not provided in the NDA. Therefore, bioequivalence study waiver for the 120 mg and 180 mg strengths cannot be granted.

2. The dissolution data supporting the lower strengths 240 mg and 300 mg were inadequate. The sponsor should provide comparative dissolution data in 0.1 N HCl for the lower strengths, i.e. 240 and 300 mg tablets in order to obtain a waiver for in vivo bioequivalence study for the 240 mg and 300 mg strengths. The guidance specifies that comparative dissolution profiles are to be submitted in application/compendial medium and in 3 other media (water, 0.1 N HCl and USP buffer at pH 6.8) to obtain an in vivo bioequivalence study waiver for the lower strengths.

3. In order to obtain an in vivo bioequivalence study waiver for manufacturing site change, the sponsor should provide dissolution profiles in various media (0.1N HCl, Water, Acetate Buffer pH 4.2, Phosphate Buffer pH 5.8, Phosphate Buffer pH 6.8) for the lower strengths - 120, 180, 240 and 300 mg tablets manufactured at the different sites.

OCPB briefing held on Wednesday, May 29, 2002. Attendees were Stockbridge, Mehta, Dorantes, Chen, Chou and Viswanadhan.

Gabriel J. Robbie, Ph.D.
Division of Pharmaceutical Evaluation I

FT Initialed by Patrick J. Marroum, Ph.D._____

cc list: NDA 21-392; HFD-860: (Robbie, Marroum, Mehta); CDER Central Document Room

EXECUTIVE SUMMARY

Diltiazem hydrochloride is a calcium ion cellular influx inhibitor (calcium antagonist) intended for use as an antihypertensive. Diltiazem hydrochloride extended release capsules for oral administration are currently marketed at dose strengths 120, 180, 240, 300, 360 and 420 mg administered as once-a-day extended release capsules, where the sponsor recently obtained approval for marketing of two highest dose strengths, 360 and 420 mg, as extended release capsules.

Bioavail Laboratories proposes to market dose strengths 120 mg, 180 mg, 240 mg, 300 mg, 360 mg and 420 mg as extended release tablets. The basis of approval of this NDA is a double-blind clinical study demonstrating the efficacy of 120, 240, 360 and 540 mg diltiazem when administered at nighttime compared to placebo and 360 mg daytime administration. The clinical study used commercial 120 mg and 180 mg capsules of diltiazem. The highest proposed strength of 420 mg was not tested in any of the bioequivalence studies, the 360 mg strength was tested instead. Bioavail demonstrated bioequivalence of 360 mg tablets and 2 x 180 mg capsules (formulation used in clinical trial) in 2 bioequivalence studies: single-dose fasted/fed study and a multiple dose fasting study.

Two pharmacokinetic studies, a single dose study and a multiple dose study were performed to demonstrate bioequivalence of the new tablet dosage form to the approved capsule dosage form during daytime administration. Both studies demonstrated bioequivalence of the two dosage forms when administered at daytime under fasting conditions.

Bioequivalence studies were also conducted comparing extended release tablets and capsules following night time administration in the fasting state. The nighttime single dose study demonstrated that the tablet was bioequivalent to the capsule. However, the multiple dose study did not result in bioequivalence of the 360mg tablet when compared to the 2 x 180mg capsule. The Cmax and AUC were 12% and 10% lower respectively for diltiazem. Nevertheless, the metabolites met the bioequivalence criteria of 0.8-1.25. The sponsor indicates that bioequivalence was not reached because of inconsistencies in the shapes of plasma concentration versus time curves in two individuals. The multiple dose study was therefore repeated. However, the comparator chosen was 360mg capsules. This study demonstrated bioequivalence of 360mg tablets to the 360mg capsules.

Two studies, a single dose and a multiple dose study were conducted to compare nighttime and daytime pharmacokinetics of the 360 mg bead tablet in the fasted state. In the single dose study, diltiazem systemic and peak exposures were lower for daytime administration relative to nighttime. The Cmax and AUC of diltiazem were lower by 10% and 15% respectively during daytime administration. Therefore, nighttime administration resulted in greater bioavailability relative to daytime.

BIOEQUIVALENCE COMPARISON OF DILTIAZEM AND METABOLITES FOR 360MG TABLETS COMPARED TO 2 X 180 MG CAPSULES (UNLESS OTHERWISE STATED)

	Diltiazem	*DesAcetyl diltiazem*	*Desmethyl Diltiazem*
Fasting – Day Time			
Single Dose (Study 2370)	Bioequivalent	Bioequivalent	Bioequivalent
Multiple Dose (Study 2371)	Bioequivalent	Bioequivalent	Bioequivalent
Fasting – Night Time			
Single Dose (Study 2433)	Bioequivalent	Bioequivalent	Bioequivalent
Multiple Dose (Study 2435)	Not-Bioequivalent Cmax – 12% lower AUC - 10% lower	Bioequivalent	Bioequivalent
Multiple Dose* (Study 2492)	Bioequivalent	Bioequivalent	Bioequivalent
Fed – Day Time			
Single Dose (Study 2370)	Bioequivalent	Bioequivalent	Bioequivalent
Fed - Night time			
Single Dose (Study 2489)	Bioequivalent	**Not Bioequivalent** AUC – 17% higher Cmax – Bioequivalent	Bioequivalent
Fasted - Day vs. Night			
Single Dose (Study 2434)	**Not-Bioequivalent** Cmax – 10% Lower in AM AUC – 15% lower in AM	Bioequivalent	**Not-Bioequivalent** Cmax – Bioequivalent AUC – 16% Lower in AM
360 TABS VS. 360 TABS. Multiple Dose (Study 2464)	**Not-Bioequivalent** Cmax – 16% higher in PM AUC – 22% higher in PM	**Not-Bioequivalent** Cmax – 15% higher in AM AUC –12% higher in AM	**Not-Bioequivalent** Cmax – 12% higher in AM AUC – 18% higher in AM
360 tabs vs. 360 tabs Multiple dose (Study 2463)	Bioequivalent	Bioequivalent	Bioquivalent
Fasting – 2 Manufacturing Sites Capsules vs. capsules			
Single Dose	Bioequivalent	Bioequivalent	Bioequivalent

* This multidose was comparison of 360mg tablets to 360mg capsules

QUESTION BASED REVIEW

I. INTRODUCTION

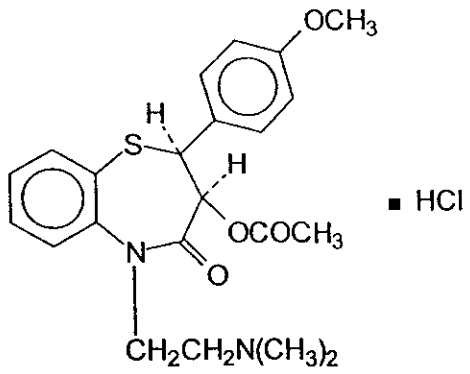
A. WHAT IS THE BASIS OF APPROVAL FOR THIS APPLICATION?

The basis of approval of this NDA is a double-blind clinical study demonstrating the efficacy of 120, 240, 360 and 540 mg diltiazem when administered at nighttime compared to placebo and 360 mg daytime administration. The formulations used in the clinical trial were 120 mg capsule – Lot D000198CL and 180 mg capsule – Lot D000199CL. There are data from 9 pharmacokinetic trials. Bioavailability studies were performed on the 360mg tablets, however, the sponsor has amended the NDA to include 420 mg as the new highest proposed tablet strength to-be-marketed.

B. WHAT ARE THE HIGHLIGHTS OF THE CHEMISTRY, FORMULATION AND PHYSICAL-CHEMICAL PROPERTIES OF THE DRUG AND DRUG PRODUCT?

STRUCTURE

Diltiazem hydrochloride is 1,5-benzothiazepin-4(5H)one,3-(acetyl-oxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxy-phenyl)-monohydrochloride,(+)-cis.



molecular formula: $C_{22}H_{26}N_2O_4S$. HCl
molecular weight: 450.99

FORMULATION AND MANUFACTURING

Diltiazem hydrochloride extended release tablet is formulated as a once-a-day extended release tablet containing either 240 mg, 300 mg or 360 mg diltiazem hydrochloride. Diltiazem hydrochloride is a white to off-white powder with bitter taste. The composition of commercial diltiazem extended release tablets are listed in the following table.

	Quantity (mg)/Tablet		
	240 mg	**300 mg**	**360 mg**
Diltiazem HCl Extended Release Coated Beads			

Diltiazem Hydrochloride, USP	240.00	300.00	360.00
Microcrystalline Cellulose, USP			
Povidone — USP			
Sucrose Stearate			
Magnesium stearate, NF			
Talc, USP			
Titanium Dioxide, USP			
Hydroxypropylmethyl cellulose — USP			
Polysorbate 80, NF			
Simethicone — USP			
Microcrystalline Wax, NF			
Pregelatinized Starch, NF			
Sodium Starch Glycolate, NF			
Croscarmellose Sodium, NF			
Colloidal Silicon Dioxide, NF			
Hydrogenated Vegetable Oil — NF			
Tablet Coating			
Carnuba Wax, NF			

Diltiazem hydrochloride, drug substance is manufactured by [redacted]

Diltiazem hydrochloride immediate release and extended release coated beads are to be manufactured by Bioavail Laboratories, Carolina, Puerto Rico and coated tablets are to be manufactured by Bioavail Corporation, Steinbach, Manitoba, Canada and packaged by [redacted]

SOLUBILITY
Diltiazem hydrochloride is soluble in water, methanol and chloroform.

C. WHAT IS THE PROPOSED MECHANISM OF ACTION AND THERAPEUTIC INDICATION?

Diltiazem hydrochloride is a calcium ion cellular influx inhibitor (slow channel blocker or calcium channel antagonist). It acts to inhibit calcium ions during membrane depolarization of cardiac and vascular smooth muscle and produces its antihypertensive effect by relaxation of vascular smooth muscle and resultant decrease in peripheral vascular resistance.

D. WHAT IS THE PROPOSED DOSAGE AND ADMINISTRATION?

The proposed dose is 120 mg to 540 mg once daily at bedtime and titrated to higher or lower doses as necessary. The proposed starting dose is 240 mg once a day.

II. CLINICAL PHARMACOLOGY

A. WERE THE CORRECT MOIETIES IDENTIFIED AND PROPERLY MEASURED TO ASSESS CLINICAL PHARMACOLOGY?

Yes. diltiazem and its metabolites, desacetyldiltiazem and desmethyldiltiazem, were quantified in plasma.

ASSAY

Analysis of samples were carried out using an analytical technique based on the extraction of diltiazem, desacetyldiltiazem, desmethyldiltiazem and the internal standard, propranolol from human plasma by [ ] The analysis was carried out by HPLC with UV detection.

The standard curve concentrations ranged from — ng/mL to — ng/mL for diltiazem, — ng/mL to — ng/mL for desmethyldiltiazem and — ng/mL to — ng/mL for desacetyldiltiazem.

B. WERE THE FORMULATIONS USED IN THE CLINICAL STUDIES COMPARED TO PROPOSED TABLET STRENGTHS BY A BIOEQUIVALENCE STUDY?

The 120 mg and 180 mg capsules were used in the pivotal clinical study. However, the sponsor has only studied bioequivalence of the 180 mg strength of the capsule. The 120 mg capsule was not tested in any of the bioequivalence studies. Moreover, the new highest proposed tablet strength is 420 mg, however, the 420 mg strength was not studied in any of the bioequivalence studies.

C. WAS BIOEQUIVALENCE DEMONSTRATED FOR THE NEW TABLET DOSAGE FORM WHEN COMPARED TO DILTIAZEM HYDROCHLORIDE CAPSULES DURING DAY TIME ADMINISTRATION?

Yes, 360mg tablet was bioequivalent to 2 x 180mg capsules during daytime administration. However, the highest proposed strength of 420 mg was not tested in any of the bioequivalence studies, the 360 mg strength was tested instead. Two studies were conducted to demonstrate bioequivalence between the tablets and capsules. Study B00-457PK-DILG99 investigated the bioavailability of the tablet dosage form relative to the approved capsule formulation under single dose fasting conditions. Single dose C_{max} and AUC of diltiazem, desacetyldiltiazem and desmethyldiltiazem, of 1 x 360 mg extended release tablet were bioequivalent to 2 x 180 mg extended release capsules in the fasted state with a mean relative bioavailability of 99.2%.

In the second study (BOO-458PK-DILG99), the relative bioavailability of the tablet formulation under steady-state conditions was compared to 2x180 mg capsules. The two formulations, 360 mg diltiazem extended release bead tablets and 2 x 180 mg diltiazem extended release capsules, were bioequivalent at steady-state in the fasted state.

D. DOES FOOD HAVE AN EFFECT ON THE PHARMACOKINETIC CHARACTERISTICS OF THE DILTIAZEM EXTENDED RELEASE TABLET FORMULATION DURING DAY TIME ADMINISTRATION?

No, food did not affect the pharmacokinetic characteristics of diltiazem extended release tablet formulation. The 90% confidence intervals for C_{max} and AUC of diltiazem, desacetyldiltiazem and desmethyldiltiazem were contained within the no food-effect limits of 0.80 and 1.25. Study B00-457PK-DILG99 shows that administration of 360 mg diltiazem extended release tablet 5-min after completion of a high fat meal increased the C_{max} of diltiazem, desacetyldiltiazem and desmethyldiltiazem by 4%, 7% and 13%, respectively, and food increased the AUC of diltiazem, desacetyldiltiazem and desmethyldiltiazem by 9%, 5% and 15%, respectively.

E. DOES FOOD HAVE AN EFFECT ON THE PHARMACOKINETIC CHARACTERISTICS OF THE DILTIAZEM TABLET FORMULATION DURING NIGHT-TIME ADMINISTRATION?

NO, food did not affect the pharmacokinetic parameters of diltiazem. The point estimates and 90% confidence intervals for C_{max} and AUC of diltiazem, and desmethyldiltiazem, comparing 360 mg extended release tablet to 360 mg extended release capsule administered night time in the fed state were contained within the bioequivalence limits of 0.80 and 1.25. However, the AUC of desacetyldiltiazem exceeded the upper limit of bioequivalence of 1.25 by 7%. Mean relative bioavailability of diltiazem, desacetyldiltiazem and desmethyldiltiazem when administered as extended release tablet in the fed state were 112%, 117% and 106%, respectively, compared to extended release capsule. Diltiazem 360 mg extended release tablet is bioequivalent to 360 mg extended release capsule with respect to diltiazem and desmethyldiltiazem, but not with respect to desacetyldiltiazem, when administered night time in the fed state. (Study B01-541PK-DILG99)

F. WERE THE TWO FORMULATIONS (TABLETS AND CAPSULES) BIOEQUIVALENT WHEN ADMINISTERED AT NIGHT TIME?

Yes, diltiazem extended release tablets and capsules were bioequivalent following single dose administration.

However, at steady state, comparison of 360mg tablets to 2 x 180mg capsules did not show bioequivalence. In contrast, a comparison of 360mg tablets to 360mg capsules was bioequivalent at steady state.

Night time single-dose studies were conducted under fasting (B00-514PK-DILG99) and fed (B01-541PK-DILG99). The pharmacokinetic parameters of diltiazem and its metabolites obtained from 1 x 360 mg diltiazem extended release tablet and 2 x 180 mg

extended release capsules administered night time in the fasted state were bioequivalent with a mean relative bioavailability of 98%, 100% and 99%, respectively.

In a steady state, night time study (B00-516K-DILG99), the lower limit of the 90% confidence intervals for C_{max} of diltiazem was not contained within the bioequivalence limits of 0.80 and 1.25. The two formulations, 360 mg diltiazem extended release bead tablets and 2 x 180 mg diltiazem extended release capsules are not bioequivalent with respect to diltiazem but are bioequivalent with respect to its metabolites, desacetyldiltiazem and desmethyldiltiazem at steady-state, administered night time in the fasted state.

However, in another night time steady state study (B01-543PK-DILG99), the mean relative bioavailability of diltiazem at steady-state from the 360 mg extended release tablet was 97.6% compared to 360 mg extended release capsule. The two formulations, 360 mg diltiazem extended release bead tablet and 360 mg diltiazem extended release capsule are bioequivalent with respect to diltiazem and its metabolites, desacetyldiltiazem and desmethyldiltiazem, at steady-state when administered night time in the fasted state.

F. ARE THE PHARMACOKINETICS OF NIGHT TIME DOSING SIMILAR TO DAY TIME DOSING?

Two studies were conducted to compare night time and day time pharmacokinetics of the product. A single dose study (B00-515PK-DILG99) was performed to determine the bioavailability of nightime administration of the bead tablet relative to the daytime administration. Nighttime administration of the product resulted in greater diltiazem bioavailability relative to daytime. Mean C_{max} and AUC of diltiazem from the 360 mg extended release tablet administered in the morning were not bioequivalent to evening administration in the fasted state. Mean C_{max} and AUC of diltiazem from the extended release tablet formulation in the morning were 10% and 15% lower than evening administration. The relative bioavailability of diltiazem following morning administration from the tablet formulation was 85% compared to evening administration. However, mean C_{max} and AUC of desacetyldiltiazem from the 360 mg extended release tablet administered in the morning were bioequivalent to evening administration in the fasted state. Mean C_{max} of desmethyldiltiazem following administration of 360 mg extended release tablet in the morning was bioequivalent to evening administration in the fasted state, but mean AUC of desmethyldiltiazem was not bioequivalent to evening administration. The lower limit of the 90% confidence interval for AUC following morning administration was 0.776, which is below the bioequivalence limit of 0.80.

A steady state study (B01-530PK-DILG99) was performed to compare daytime and nighttime administration of the capsule. Mean steady-state C_{max} and AUC_{0-24} of diltiazem, desacetyldiltiazem and desmethyldiltiazem from 2 x 180 mg extended release capsules administered in the morning were bioequivalent to those administered in the evening in the fasted state.

Mean $C_{ss,6AM-12PM}$ and $AUC_{6AM-12PM}$ of diltiazem were 52% and 54% lower, respectively, and mean $C_{ss,6AM-12PM}$ and $AUC_{6AM-12PM}$ of desmethyldiltiazem were lower by 34% and 35%, respectively, when the capsules were administered in the morning compared to evening administration. However, mean $C_{ss,6AM-12PM}$ of desacetyldiltiazem was similar but $AUC_{6AM-12PM}$ of desacetyldiltiazem was 17% lower when the capsules were administered in the morning compared to evening administration.

III. BIOPHARMACEUTICS

A. ARE THE SPONSOR PROPOSED DISSOLUTION MEDIUM AND SPECIFICATIONS ACCEPTABLE?

Yes, the sponsor proposed dissolution medium and method - 900 ml of pH 5.8 phosphate buffer at 37°C in USP Apparatus 2 (Paddle) at 100 rpm is acceptable.

B. ARE THE SPONSOR PROPOSED DISSOLUTION MEDIUM AND SPECIFICATIONS ACCEPTABLE?

No, the sponsor proposed dissolution specification is not acceptable. The Agency proposes the following changes to the dissolution specifications as follows.

Time (h)	Mean % Dissolved	Range (n=6)	**SPONSOR** Dissolution Specification
2	10	—	NMT —
8	59	—	—
14	80	—	NLT —
24	93	—	NLT —

The sponsor proposed dissolution specification is not acceptable since the specification does not match product performance. Therefore, the Office of Clinical Pharmacology and Biopharmaceutics has proposed changes to the sponsor's dissolution specification that which is presented in the table below.

Time (h)	**FDA PROPOSES Dissolution Specification**
2	NMT —
6	—
12	—
16	NLT —

C. DID THE SPONSOR FULFILL THE DISSOLUTION REQUIREMENTS FOR WAIVER OF IN VIVO BIOEQUIVALENCE STUDY FOR THE LOWER STRENGTHS?

No. The sponsor has amended the NDA to include lower tablet strengths such as 120 mg and 180 mg and a higher strength 420 mg. Dissolution data supporting the 120 mg strength was not provided in the NDA. Also, composition of these new 120 mg strength was not provided in the NDA. Therefore, a bioequivalence study waiver for the 120 mg strength cannot be granted.

For the 240 mg and 300 mg strengths, the sponsor did not provide comparative dissolution data in 0.1 N HCl for the lower strengths. Comparative dissolution profiles are to be submitted in application/compendial medium and in 3 other media (water, 0.1 N HCl and USP buffer at pH 6.8) to obtain an in vivo bioequivalence study waiver for the lower strengths.

For manufacturing site change, the sponsor did not provide dissolution data in various media (0.1N HCl, Water, Acetate Buffer pH 4.2, Phosphate Buffer pH 5.8, Phosphate Buffer pH 6.8) for the proposed lower strengths of 120, 180, 240 and 300 mg tablets manufactured at different sites.

LABELING RECOMMENDATIONS

The sponsor should alter the proposed label to match the class label with the following sentences in the "Pharmacokinetics and Metabolism" Section.

Diltiazem is well absorbed from the gastrointestinal tract and is subject to an extensive first-pass effect when given as an [ ] absolute bioavailability (compared to intravenous administration) is approximately 40%. Diltiazem undergoes extensive metabolism in which only 2% to 4% of the unchanged drug appears in the urine. Drugs that induce or inhibit hepatic microsomal enzymes may alter diltiazem disposition.

In-vitro binding studies show diltiazem is 70% to 80% bound to plasma proteins. Competitive *in-vitro* ligand binding studies have also shown diltiazem hydrochloride binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. The plasma elimination half-life following single or multiple drug administration is approximately 3.0 to 4.5 hours. Desacetyldiltiazem, [ ] is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent as a coronary vasodilator as diltiazem. Minimum therapeutic plasma diltiazem concentrations appear to be in the range of 50 to 200 ng/mL. There is a departure from linearity when dose strengths are increased; the half-life is slightly increased with dose. A study that compared patients with normal hepatic function to patients with cirrhosis found an increase in half-life and a 69% increase in bioavailability in the hepatically impaired patients. A single study in patients with severely impaired renal function showed no difference in the pharmacokinetic profile of diltiazem compared to patients with normal renal function.

Cardizem — A single 360 mg dose of Cardizem — results in detectable diltiazem plasma levels after 3 to 4 hours and peak plasma levels between 11 and — hours. The apparent elimination half-life for Cardizem — after single or multiple dosing is 6 to 9 hours. When Cardizem — was coadministered with a high fat content breakfast, diltiazem peak and systemic exposures were not affected indicating that the tablet can be administered without regard to food. [

Delete

As the dose of the diltiazem hydrochloride [redacted] is increased from 120 mg to 240 mg, [redacted] increase in the area-under-the curve of 2.5

[redacted]

Appears This Way
On Original

SUMMARY OF STUDIES:

Detailed description of the individual studies and their results are attached in Appendix I.

STUDY 2370

This was a single-dose crossover study comparing 1 x 360 mg diltiazem hydrochloride extended release bead tablet to 2 x 180 mg diltiazem hydrochloride extended release capsules in the fasted state and the effect of food on 1 x 360 mg diltiazem hydrochloride extended release bead tablet . The single-dose point estimates and 90% confidence intervals for C_{max} and AUC of diltiazem, desacetyldiltiazem and desmethyldiltiazem, comparing 1 x 360 mg extended release tablet to 2 x 180 mg extended release capsules were contained within the bioequivalence limits of 0.80 and 1.25 with a mean relative bioavailability of 99.2% in the fasted state. The single dose pharmacokinetic parameters of diltiazem and its metabolites obtained from 1 x 360 mg diltiazem extended release tablet and 2 x 180 mg extended release capsules were bioequivalent in the fasted state.

Following administration of 360 mg diltiazem extended release tablet after an high fat meal diltiazem, desacetyldiltiazem and desmethyldiltiazem C_{max} increased by 4%, 7% and 13%, respectively, and AUC increased by 9%, 5% and 15%, respectively. The 90% confidence intervals for C_{max} and AUC of diltiazem, desacetyldiltiazem and desmethyldiltiazem were contained within the no food-effect limits of 0.80 and 1.25. The label should incorporate information regarding the lack of effect of food on the pharmacokinetics of diltiazem and that diltiazem can be administered with or without food.

STUDY 2371

This was a multiple-dose, crossover study comparing 360 mg diltiazem extended release bead tablet and 2 x 180 mg diltiazem extended release capsules in the fasted state. The two formulations, 360 mg diltiazem extended release bead tablets and 2 x 180 mg diltiazem extended release capsules, were bioequivalent at steady-state. The steady state C_{max}, AUC, $C_{average}$ of diltiazem were lower by 10%, 5% and 4%, respectively, when administered as 360 mg extended release tablet compared to administration of 2 x 180 mg extended release capsules in the fasted state. The mean relative bioavailability of diltiazem at steady-state from the 360 mg extended release tablet formulation was 95% compared to 2 x 180 mg extended release capsule formulation. Mean fluctuation of peak-to-trough concentrations of diltiazem was lower by 22% when diltiazem was administered as 360 mg extended release bead tablet compared to 2 x 180 mg extended release capsules.

STUDY 2433

This was a single-dose, crossover study comparing 1 x 360 mg diltiazem hydrochloride extended release bead tablet to 2 x 180 mg diltiazem hydrochloride extended release capsules at 10:00 PM following a fast of at least 2 hours. The 2 formulations, 1 x 360 mg extended release tablet to 2 x 180 mg extended release capsules were bioequivalent when

administered night time in the fasted state with a mean relative bioavailability of 98%, 100% and 99% or diltiazem, desacetyldiltiazem and desmethyldiltiazem, respectively.

STUDY 2489

This was a single dose, crossover study comparing 360 mg diltiazem hydrochloride extended release bead tablet and 360 mg diltiazem hydrochloride extended release capsule administered at 10:00 PM under fed conditions. Mean C_{max} and AUC of diltiazem, and desmethyldiltiazem from 360 mg extended release tablet were bioequivalent to 360 mg extended release capsule administered night time in the fed state. However, the AUC of desacetyldiltiazem exceeded the upper limit of bioequivalence of 1.25 by 7%. Mean relative bioavailability of diltiazem, desacetyldiltiazem and desmethyldiltiazem when administered as extended release tablet in the fed state were 112%, 117% and 106%, respectively, compared to extended release capsule.

STUDY 2435

This was a multiple-dose, crossover study comparing 360 mg diltiazem hydrochloride extended release bead tablet and 2 x 180 mg diltiazem hydrochloride extended release capsules at 10:00 PM following a fast of at least 2 hours. Steady-state C_{max}, AUC_{0-24}, $C_{average}$ of diltiazem and desmethyldiltiazem were bioequivalent but lower by 12%, 10% and 10%, respectively, when administered as 360 mg extended release tablet compared to administration of 2 x 180 mg extended release capsules administered night time in the fasted state. However, C_{max}, AUC_{0-24}, $C_{average}$ of desacetyldiltiazem were lower by only 7%, 3% and 6%, respectively, when administered as a tablet compared to capsule.

STUDY 2492

This was a multiple-dose, crossover study comparing 360 mg diltiazem hydrochloride extended release bead tablet and 1x360 mg diltiazem hydrochloride extended release capsule at 10:00 PM following a fast of at least 2 hours. Mean steady-state C_{max}, AUC_{0-24}, $C_{average}$ of diltiazem, desacetyldiltiazem and desmethyldiltiazem were similar and bioequivalent with mean relative bioavailability of diltiazem at steady-state of 97.6% when administered as 360 mg extended release tablet or 360 mg extended release capsule administered night time in the fasted state.

STUDY 2434

This was a single-dose, morning and evening administration, crossover study comparing 1x360 mg diltiazem hydrochloride extended release bead tablet administered at 7:00 AM following an overnight fast to 360 mg diltiazem hydrochloride extended release bead tablet administered at 10:00 PM following a fast of at least 2 hours. Mean single dose C_{max} and AUC of diltiazem from the 360 mg extended release tablet administered in the morning were not bioequivalent to evening administration in the fasted state. Mean C_{max} and AUC of diltiazem from the extended release tablet formulation in the morning were 10% and 15% lower than evening administration. The relative bioavailability of diltiazem was 85% following morning administration from the tablet formulation compared to evening administration in the fasted state. Contrary to diltiazem, mean C_{max} and AUC of desacetyldiltiazem from the 360 mg extended release tablet administered in the morning

were bioequivalent to evening administration in the fasted state. Mean C_{max} of desmethyldiltiazem following administration of 360 mg extended release tablet in the morning was bioequivalent to evening administration in the fasted state, however, mean AUC of desmethyldiltiazem was not bioequivalent to evening administration. The lower limit of the 90% confidence interval for AUC following morning administration was 0.776, which is below the bioequivalence limit of 0.80.

STUDY 2463

This was a multiple-dose, crossover study comparing 2 x 180 mg diltiazem hydrochloride extended release capsules administered at 8:00 AM following an overnight fast to 2 x 180 mg diltiazem hydrochloride extended release capsules administered at 10:00 PM following a fast of at least 2 hours. Mean steady-state C_{max} and AUC_{0-24} of diltiazem, desacetyldiltiazem and desmethyldiltiazem from 2 x 180 mg extended release capsules administered in the morning were bioequivalent to those administered in the evening in the fasted state.

Mean $C_{ss,6AM-12PM}$ and $AUC_{6AM-12PM}$ of diltiazem were 52% and 54% lower, respectively, and mean $C_{ss,6AM-12PM}$ and $AUC_{6AM-12PM}$ of desmethyldiltiazem were lower by 34% and 35%, respectively, when the capsules were administered in the morning compared to evening administration. However, mean $C_{ss,6AM-12PM}$ of desacetyldiltiazem was similar but $AUC_{6AM-12PM}$ of desacetyldiltiazem was 17% lower when the capsules were administered in the morning compared to evening administration.

STUDY 2438

This was a four-way, single-dose, crossover study designed to construct an in vivo-in vitro correlation using 3 formulations of diltiazem with different release rates- 1x360 mg diltiazem hydrochloride extended release bead tablet, Lot # 010309, Lot # 001014, and Lot # 010207 and 120 mg diltiazem hydrochloride as 50 ml solution administered in the morning following an overnight fast. The sponsor was unable to obtain an in vivo-in vitro correlation.

STUDY 2464

This was a multiple-dose, crossover study comparing 360 mg diltiazem hydrochloride extended release bead tablet administered at 8:00 AM following an overnight fast (reference) to 360 mg diltiazem hydrochloride extended release bead tablet administered at 10:00 PM following a fast of at least 2 hours (test). The steady state pharmacokinetics of diltiazem and its metabolites administered in the morning (8 AM) were **not** bioequivalent to night time (10 PM) administration. Following night time administration of 360 mg extended release bead tablet mean steady-state C_{max} of diltiazem, desacetyldiltiazem and desmethyldiltiazem were higher by 16%, 15% and 12%, respectively, and AUC_{0-24} was higher by 22%, 12% and 18%, respectively, compared to morning (8:00 AM) administration in the fasted state. Similarly, mean $AUC_{6AM-12PM}$ of diltiazem, desacetyldiltiazem and desmethyldiltiazem was higher by 142%, 20% and 66%, respectively, following evening administration compared to morning administration.

STUDY 2532

This was a single-dose, crossover study comparing 360 mg diltiazem hydrochloride extended release bead tablet (manufactured in Steinbach, Canada) to 360 mg diltiazem hydrochloride extended release bead tablet (manufactured in Chantilly, Virginia) following an overnight fast of at least 10 hours. The pharmacokinetics of diltiazem and its metabolites, desacetyldiltiazem and desmethyldiltiazem, following administration of a single dose of 360mg extended release bead tablet manufactured at the proposed site, Steinbach, Canada was bioequivalent to the diltiazem reference site, Chantilly, Virginia under fasting conditions. Mean Cmax and AUC of diltiazem manufactured at the proposed site was on average 10% higher compared to the reference site.

APPENDIX I

STUDY 2370 (B00-457PK-DILG99)– A THREE-WAY CROSSOVER OPEN-LABEL SINGLE-DOSE FASTING AND FED COMPARATIVE BIOAVAILABILITY STUDY OF DILTIAZEM HYDROCHLORIDE 360 mg EXTENDED RELEASE BEAD TABLETS VERSUS DILTIAZEM HYDROCHLORIDE 2 X 180 mg EXTENDED RELEASE CAPSULES IN HEALTHY NON-SMOKING MALE AND FEMALE SUBJECTS

STUDY INVESTIGATOR AND SITE:

Bioavail Contract Research
Bioavail Corporation
Toronto, Ontario
CANADA

Volumes: 15 to 26

OBJECTIVE:

To compare the rate and extent of absorption of the diltiazem hydrochloride 360 mg extended release bead tablets (test) to diltiazem hydrochloride 2 x 180 mg extended release capsules (reference) under fasting and fed conditions.

FORMULATIONS:

A. **Test** - Diltiazem hydrochloride extended release bead tablets –360 mg (Lot #: 001004) manufactured by Bioavail Technologies, Ltd. Batch size: [redacted] tablets

B. **Reference** - Diltiazem hydrochloride extended release capsules –180 mg (Lot #: D000199CL manufactured by Bioavail Corporation. Batch size: [redacted] capsules

STUDY DESIGN:

This was a randomized, open-label, three-treatment, three-period, single-dose crossover study with a 1-week washout interval between consecutive treatments. This study was conducted in 36 healthy non-smoking, male (n=18) and female (n=18), volunteers between 21 and 44 years of age (mean: 30 yr) weighing between 113 and 210 lbs (mean: 157 lbs). On Day 1 subjects were randomized to receive, **Treatment A:** 1 x 360 mg diltiazem hydrochloride extended release bead tablet following an overnight (10-h) fast, or **Treatment B:** 2 x 180 mg diltiazem hydrochloride extended release capsules following an overnight (10-h) fast, or **Treatment C:** 1 x 360 mg diltiazem hydrochloride extended release bead tablet 5-min after completion of a high fat content breakfast. Thereafter, subjects crossed over to receive alternate treatments in subsequent periods following a 1-week washout interval.

ASSAY:

Compound	Matrix	Method	Range (ng/ml)	Linearity	LOQ (ng/ml)	QC (ng/ml)	CV%	Accuracy (% Bias)
Diltiazem	Plasma	HPLC/UV	\		\	/	7.2 4.3	\

					3.6 3.0
Desacetyl diltiazem	Plasma	HPLC/UV			13.5 7.1 4 2 2.8
Desmethyl diltiazem	Plasma	HPLC/UV			6.8 4.2 2.9 2.2

Sample Collection:

Blood samples were taken for assessment of pharmacokinetic parameters of diltiazem, desacetyldiltiazem and desmethyldiltiazem, predose and at 2, 3, 4, 6, 8, 10, 11, 12, 13, 14, 15, 16, 18, 20, 24, 30, 36, 42 and 48 hours post dose in each period.

RESULTS

The mean pharmacokinetic parameters of diltiazem and its metabolites-desacetyldiltiazem and desmethyldiltiazem, obtained following administration of a 1 x 360-mg diltiazem extended release bead tablet in fed and fasted states, or 2 x 180 mg diltiazem extended release capsule in the fasted state are presented in the following table.

Table 1: Mean (SD) Pharmacokinetic Parameters of Diltiazem, Desacetyldiltiazem and Desmethyldiltiazem

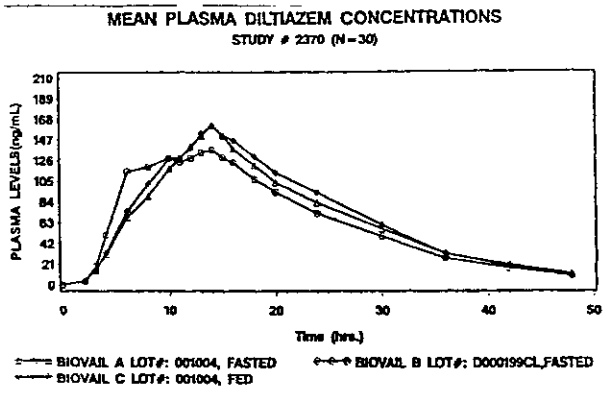
	DILTIAZEM			POINT ESTIMATE (90% CI)	
Parameter	1 x 360 mg TABLET FASTING	2 x 180 mg CAPSULES FASTING	1 x 360 mg TABLET FED	TABLET vs. CAPSULE	FED vs. FASTED
C_{max} (ng/ml)	171.83 (99.25)	151.28 (56.14)	166.21 (57.89)	1.07 (0.954, 1.20)	1.04 (0.929, 1.17)
$AUC_{0\text{-}last}$ (ng.h/ml)	3155.35 (1558.32)	3046.37 (1135.98)	3335.68 (1245.04)	0.975 (0.877, 1.08)	1.12 (1.02, 1.25)
$AUC_{0\text{-}inf}$ (ng.h/ml)	3336.19 (1635.64)	3170.60 (1173.80)	3450.40 (1324.53)	0.992 (0.899, 1.09)	1.09 (0.991, 1.21)
T_{max} (h)	13.30 (3.37)	10.47 (3.38)	13.70 (2014)		
$T_{1/2}$ (h)	8.09 (2.68)	7.94 (1.97)	6.94 (1.41)		
	DESACETYLDILTIAZEM			**POINT ESTIMATE (90% CI)**	
Parameter	**1 x 360 mg TABLET FASTING**	**2 x 180 mg CAPSULES FASTING**	**1 x 360 mg TABLET FED**	**TABLET vs. CAPSULE**	**FED vs. FASTED**
C_{max} (ng/ml)	15.98 (10.74)	16.72 (13.70)	16.56 (10.69)	0.989 (0.904, 1.08)	1.07 (0.982, 1.18)
$AUC_{0\text{-}last}$ (ng.h/ml)	401.07 (286.42)	451.53 (366.82)	449.04 (324.11)	0.893 (0.804, 0.991)	1.16 (1.05, 1.29)
$AUC_{0\text{-}inf}$ (ng.h/ml)	541.32 (420.34)	585.58 (453.12)	560.81 (460.63)	0.955 (0.868, 1.05)	1.05 (0.958, 1.16)
T_{max} (h)	18.77 (5.14)	18.53 (4.64)	20.64 (4.50)		

$T_{1/2}$ (h)	12.19 (6.23)	12.73 (4.87)	10.77 (3.29)		
	DESMETHYLDILTIAZEM			POINT ESTIMATE (90% CI)	
Parameter	1 x 360 mg TABLET FASTING	2 x 180 mg CAPSULES FASTING	1 x 360 mg TABLET FED	TABLET vs. CAPSULE	FED vs. FASTED
C_{max} (ng/ml)	49.61 (18.85)	48.13 (12.21)	53.58 (12.15)	0.990 (0.907, 1.08)	1.13 (1.04, 1.24)
$AUC_{0\text{-last}}$ (ng.h/ml)	1161.87 (431.34)	1200.06 (315.71)	1320.74 (374.99)	0.924 (0.845, 1.01)	1.19 (1.08, 1.30)
$AUC_{0\text{-inf}}$ (ng.h/ml)	1310.66 (502.82)	1325.67 (366.65)	1442.81 (439.59)	0.942 (0.865, 1.03)	1.15 (1.05, 1.25)
T_{max} (h)	15.33 (3.02)	13.87 (2.64)	14.71 (1.89)		
$T_{1/2}$ (h)	10.96 (3.49)	11.0 (2.80)	9.85 (1.75)		

Comparison of Extended Release Tablet and Capsule:

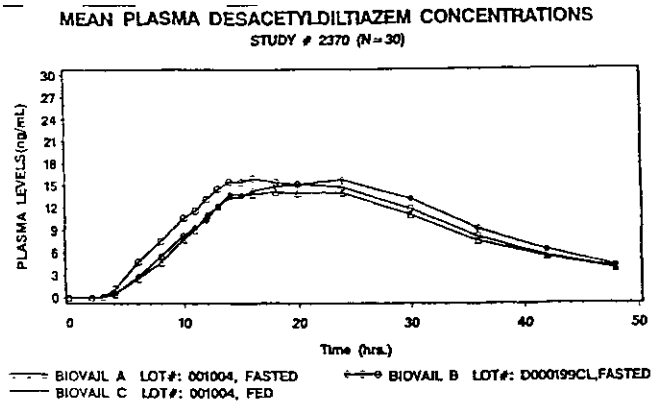
Diltiazem:

Mean Cmax and AUC of diltiazem from the 1 x 360 mg extended release tablet were bioequivalent to 2 x 180 mg capsules. Mean C_{max} of diltiazem from the extended tablet formulation was slightly higher (7%) than the mean C_{max} obtained with 2 x 180-mg capsules. Mean AUC_{inf} and $T_{1/2}$ of diltiazem from the extended tablet formulation was similar to that obtained from 2 x 180-mg capsules. The relative bioavailability was 99.2% from the tablet formulation compared to 2 x 180 mg capsules. The T_{max} of diltiazem from the tablet formulation occurred about 3 hours later compared to the capsule formulation.



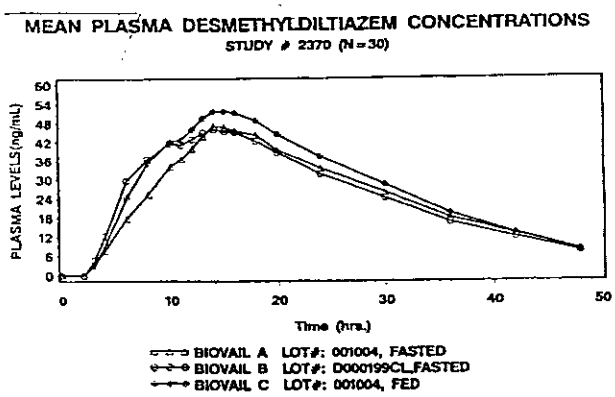
Desacetyldiltiazem:

Mean C_{max} and AUC of desacetyldiltiazem from the 1 x 360 mg extended release tablet were bioequivalent to 2 x 180 mg capsules. Mean C_{max}, T_{max} and $T_{1/2}$ of desacetyldiltiazem from the extended tablet formulation were similar to those obtained with 2 x 180-mg capsules. Mean AUC_{inf} of desacetyldiltiazem from the extended tablet formulation was slightly lower (5%) compared 2 x 180-mg capsules.



Desmethyldiltiazem:

Mean C_{max} and AUC of desmethyldiltiazem from the 1 x 360 mg extended release tablet were bioequivalent to 2 x 180 mg capsules. Mean C_{max} and $T_{1/2}$ of desmethyldiltiazem from the extended tablet formulation were similar to those obtained with 2 x 180-mg capsules. Mean AUC_{inf} of desmethyldiltiazem from the extended tablet formulation was slightly lower (6%) compared to 2 x 180-mg capsules.



Effect of Food on the Pharmacokinetics of Diltiazem and its Metabolites When Administered as 360 mg Extended Release Tablet:

Diltiazem:

Food did not affect C_{max} or AUC of diltiazem. Mean C_{max} and AUC of diltiazem increased slightly, 4% and 9%, respectively, in the presence of food. Food delayed T_{max} of diltiazem by 3 h and decreased $T_{1/2}$ of diltiazem by 1 hour.

Desacetyldiltiazem:

Food did not affect C_{max} or AUC of desacetyldiltiazem. Mean C_{max} and AUC of desacetyldiltiazem increased slightly, 7% and 5%, respectively, in the presence of food. Food delayed T_{max} of desacetyldiltiazem by 2 h and decreased $T_{1/2}$ of desacetyldiltiazem by 2 hour.

Desmethyldiltiazem:

Food had a larger effect on C_{max} and AUC of desmethyldiltiazem compared to diltiazem or desacetyldiltiazem. Mean Cmax and AUC of desmethyldiltiazem increased 13% and 15%, respectively, in the presence of food. Food delayed T_{max} of desmethyldiltiazem by 1 h and decreased $T_{1/2}$ of desmethyldiltiazem by 1 hour.

Effect of Gender on Diltiazem Pharmacokinetics:

Males:

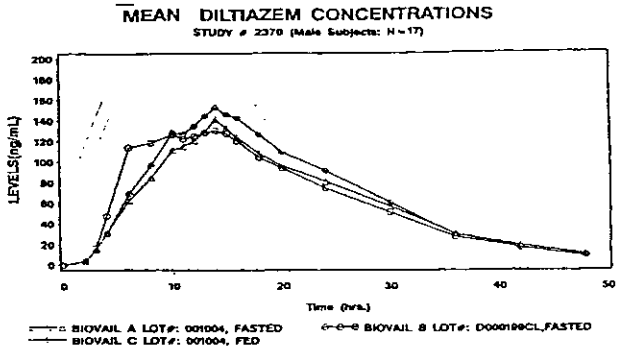
Table 2: Mean (SD) Pharmacokinetic Parameters of Diltiazem, Desacetyldiltiazem and Desmethyldiltiazem in Males (n=17)

	DILTIAZEM			POINT ESTIMATE (90% CI)	
Parameter	1 x 360 mg TABLET FASTING	2 x 180 mg CAPSULES FASTING	1 x 360 mg TABLET FED	TABLET vs. CAPSULE	FED vs. FASTED
C_{max} (ng/ml)	147.24 (62.22)	145.15 (49.72)	157.14 (44.77)	0.966 (0.821, 1.14)	1.14 (0.970, 1.34)
$AUC_{0\text{-}last}$ (ng.h/ml)	2915.40 (1389.69)	3010.85 (1054.0)	3211.60 (1043.91)	0.878 (0.741, 1.04)	1.23 (1.03, 1.45)
$AUC_{0\text{-}inf}$ (ng.h/ml)	3077.17 (1482.10)	3125.06 (1084.75)	3295.98 (1083.69)	0.896 (0.768, 1.05)	1.19 (1.02, 1.38)
T_{max} (h)	14.06 (3.40)	9.65 (3.60)	14.0 (1.94)		
$T_{1/2}$ (h)	7.55 (2.29)	7.64 (2.01)	6.50 (0.91)		
	DESACETYLDILTIAZEM			**POINT ESTIMATE (90% CI)**	
Parameter	**1 x 360 mg TABLET FASTING**	**2 x 180 mg CAPSULES FASTING**	**1 x 360 mg TABLET FED**	**TABLET vs. CAPSULE**	**FED vs. FASTED**
C_{max} (ng/ml)	13.26 (7.36)	14.46 (10.78)	15.64 (9.14)	0.916 (0.810, 1.04)	1.24 (1.09, 1.40)
$AUC_{0\text{-}last}$ (ng.h/ml)	325.10 (175.93)	395.74 (300.23)	410.42 (268.02)	0.802 (0.677, 0.949)	1.32 (1.12, 1.57)
$AUC_{0\text{-}inf}$ (ng.h/ml)	414.35 (183.62)	483.05 (347.71)	476.04 (315.12)	0.910 (0.796, 1.04)	1.15 (1.07, 1.31)
T_{max} (h)	19.47 (5.36)	18.71 (4.59)	21.29 (4.31)		
$T_{1/2}$ (h)	10.12 (3.36)	11.66 (3.41)	9.60 (2.00)		
	DESMETHYLDILTIAZEM			**POINT ESTIMATE (90% CI)**	
Parameter	**1 x 360 mg TABLET FASTING**	**2 x 180 mg CAPSULES FASTING**	**1 x 360 mg TABLET FED**	**TABLET vs. CAPSULE**	**FED vs. FASTED**

C_{max} (ng/ml)	42.82 (12.70)	46.04 (10.11)	50.01 (9.87)	0.888 (0.791, 1.09)	1.22 (1.08, 1.39)
$AUC_{0\text{-}last}$ (ng.h/ml)	1070.56 (386.98)	1188.88 (289.71)	1269.02 (335.10)	0.835 (0.720, 0.968)	1.27 (1.09, 1.47)
$AUC_{0\text{-}inf}$ (ng.h/ml)	1223.60 (485.86)	1325.19 (345.55)	1390.13 (386.96)	0.854 (0.741, 0.983)	1.22 (1.06, 1.40)
T_{max} (h)	16.06 (3.11)	13.88 (2.76)	15.30 (1.31)		
$T_{1/2}$ (h)	11.08 (3.59)	11.30 (3.35)	10.09 (1.60)		

Diltiazem:

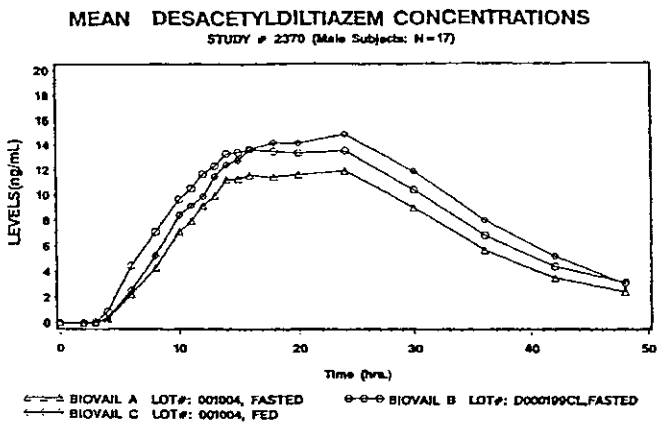
In males, mean AUC of diltiazem was lower by 10% and the lower limit of the 90% confidence interval of 0.768 was below the bioequivalence criteria of 0.80. However, C_{max} of diltiazem from 360-mg tablet and 2 x 180 mg capsules was bioequivalent. In males, T_{max} of diltiazem occurred 4 h later when administered as 360-mg tablet compared to 2 x 180 mg capsules and the $T_{1/2}$ was similar between formulations.



In males, food increased both C_{max} and AUC of diltiazem by 14% and 19%, respectively and the upper limit of the 90% confidence intervals were 1.34 and 1.38, respectively. Food did not affect the T_{max} of diltiazem in males but decreased $T_{1/2}$ by 1 h in the fed state.

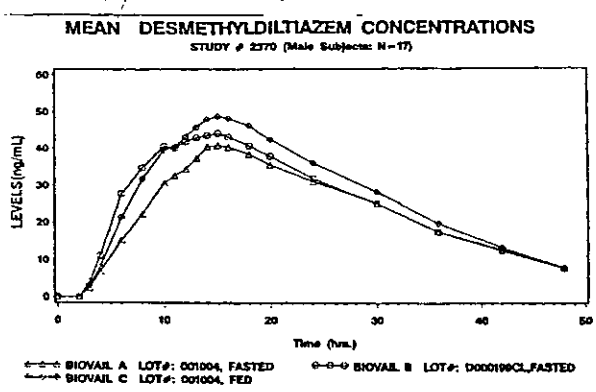
Desacetyldiltiazem:

In males, mean AUC of desacetyldiltiazem was lower by 9% and the lower limit of the 90% confidence interval of 0.796 was just below the bioequivalence criteria of 0.80. Mean C_{max} of desacetyldiltiazem was lower by 8% when administered as a 360 mg tablet but was bioequivalent to 2 x 180 mg capsules. In males, T_{max} of desacetyldiltiazem occurred slightly later when administered as 360-mg tablet compared to 2 x 180 mg capsules and the $T_{1/2}$ was lower by 1 hour when administered as a 360 mg tablet in males. In males, food increased both C_{max} and AUC of desacetyldiltiazem by 24% and 15%, respectively and the upper limit of the 90% confidence intervals were 1.40 and 1.31, respectively. In males, food increased the T_{max} of desacetyldiltiazem by 2 h but $T_{1/2}$ was similar.



Desmethyldiltiazem:

In males, mean C_{max} and AUC of desmethyldiltiazem were lower by 11% and 15%, respectively, the lower limit of the 90% confidence interval for both C_{max} and AUC of desmethyldiltiazem were below the bioequivalence criteria of 0.80 (0.791 and 0.741, respectively). In males, T_{max} of desacetyldiltiazem occurred 2 h later when administered as 360-mg tablet compared to 2 x 180 mg capsules but the $T_{1/2}$ was similar between the formulations.



In males, food increased both C_{max} and AUC of desmethyldiltiazem by 22% and the upper limit of the 90% confidence intervals were 1.39 and 1.40, respectively. In males, food decreased the $T_{1/2}$ desmethyldiltiazem by 1 h but the T_{max} was similar.

Females:

Table 3: Mean (SD) Pharmacokinetic Parameters of Diltiazem, Desacetyldiltiazem and Desmethyldiltiazem in Females (n=13)

	DILTIAZEM			POINT ESTIMATE (90% CI)	
Parameter	1 x 360 mg TABLET FASTING	2 x 180 mg CAPSULES FASTING	1 x 360 mg TABLET FED	TABLET vs. CAPSULE	FED vs. FASTED

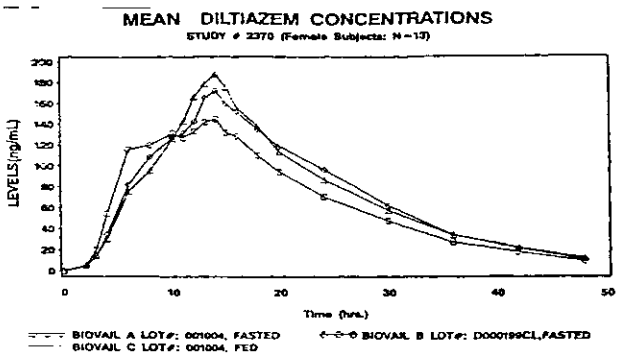
C_{max} (ng/ml)	203.99 (129.10)	159.30 (64.79)	178.08 (71.81)	1.26 (1.07, 1.48)	0.911 (0.772, 1.07)
AUC_{0-last} (ng.h/ml)	3469.12 (1762.20)	3092.82 (1277.99)	3497.93 (1497.60)	1.13 (1.00, 1.27)	1.01 (0.894, 1.13)
AUC_{0-inf} (ng.h/ml)	3674.92 (1821.31)	3230.15 (1324.38)	3652.32 (1611.21)	1.14 (1.02, 1.28)	0.986 (0.878, 1.11)
T_{max} (h)	12.31 (3.18)	11.54 (2.84)	13.31 (2.39)		
$T_{1/2}$ (h)	8.79 (3.06)	8.32 (1.92)	7.51 (1.76)		

	DESACETYLDILTIAZEM			**POINT ESTIMATE (90% CI)**	
Parameter	**1 x 360 mg TABLET FASTING**	**2 x 180 mg CAPSULES FASTING**	**1 x 360 mg TABLET FED**	**TABLET vs. CAPSULE**	**FED vs. FASTED**
C_{max} (ng/ml)	19.55 (13.51)	19.66 (16.80)	17.76 (12.72)	1.07 (0.944, 1.22)	0.902 (0.793, 1.03)
AUC_{0-last} (ng.h/ml)	500.42 (371.64)	524.49 (441.38)	499.54 (391.48)	0.995 (0.894, 1.11)	0.999 (0.897, 1.11)
AUC_{0-inf} (ng.h/ml)	689.44 (563.25)	716.07 (549.68)	673.83 (600.85)	0.998 (0.852, 1.17)	0.963 (0.829, 1.12)
T_{max} (h)	17.85 (4.88)	18.31 (4.89)	19.78 (4.76)		
$T_{1/2}$ (h)	14.62 (7.94)	14.10 (6.18)	12.32 (4.07)		

	DESMETHYLDILTIAZEM			**POINT ESTIMATE (90% CI)**	
Parameter	**1 x 360 mg TABLET FASTING**	**2 x 180 mg CAPSULES FASTING**	**1 x 360 mg TABLET FED**	**TABLET vs. CAPSULE**	**FED vs. FASTED**
C_{max} (ng/ml)	58.50 (22.20)	50.86 (14.49)	58.26 (13.61)	1.14 (1.00, 1.29)	1.04 (0.914, 1.17)
AUC_{0-last} (ng.h/ml)	1281.26 (471.92)	1214.67 (358.55)	1388.37 (425.85)	1.05 (0.957, 1.15)	1.10 (1.00, 1.20)
AUC_{0-inf} (ng.h/ml)	1424.51 (521.03)	1326.31 (407.03)	1511.69 (508.20)	1.06 (0.981, 1.15)	1.07 (0.984, 1.16)
T_{max} (h)	14.38 (2.73)	13.85 (2.58)	13.94 (2.28)		
$T_{1/2}$ (h)	10.80 (3.50)	10.61 (1.91)	9.54 (1.95)		

Diltiazem:

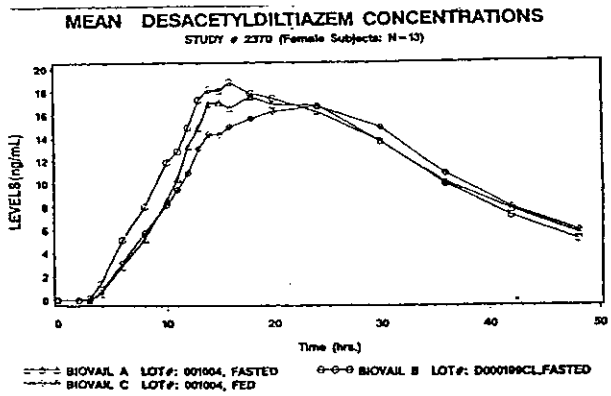
In females, mean C_{max} and AUC of diltiazem were higher by 26% and 14%, respectively, and the upper limit of the 90% confidence interval of 1.48 and 1.28, respectively, which were above the bioequivalence criteria of 1.25. This is in contrast to males where the mean AUC was 10% lower when 360 mg tablet was administered compared to capsules. In females, T_{max} of diltiazem occurred 1 h later when administered as 360-mg tablet compared to 2 x 180 mg capsules and the $T_{1/2}$ was similar between formulations.



In contrast to males, where food increased C_{max} and AUC of diltiazem, in females, food decreased C_{max} by 9% and there was no effect on AUC of diltiazem. Food decreased both T_{max} and $T_{1/2}$ by 1 h in females.

Desacetyldiltiazem:

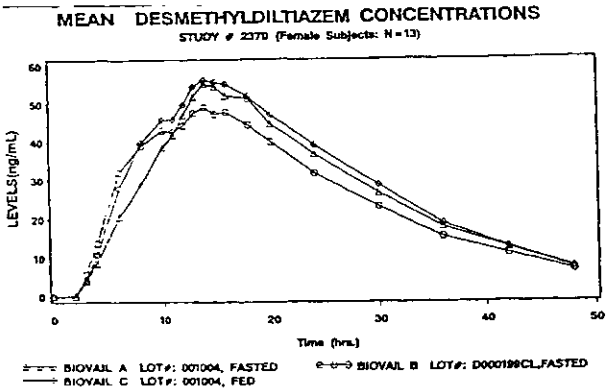
In females, both C_{max} and AUC of desacetyldiltiazem were bioequivalent and the T_{max} and $T_{1/2}$ of desacetyldiltiazem were similar between formulations. This is in contrast to the lower Cmax (8%) and AUC (9%) seen in males.



The lower limit of the 90% confidence interval for C_{max} was 0.793 that is slightly below the no food effect criteria of 0.80. Food increased the T_{max} of desacetyldiltiazem by 2 h and decreased $T_{1/2}$ by 2 h.

Desmethyldiltiazem:

In females, mean C_{max} of desmethyldiltiazem were higher by 14% and the upper limit of the 90% confidence interval of 1.29 was above the bioequivalence criteria of 1.25. The AUC, however, was slightly higher (6%) but was bioequivalent to the capsule formulation. Both T_{max} and $T_{1/2}$ of desmethyldiltiazem were similar between the formulations.



In females, food increased both C_{max} and AUC of desmethyldiltiazem by 4% and 7%, respectively, compared to a 22% increase in both Cmax and AUC in males. As seen in males, food decreased the $T_{1/2}$ by 1 h but the T_{max} was similar in females.

CONCLUSIONS:

The point estimates and 90% confidence intervals for C_{max} and AUC of diltiazem, desacetyldiltiazem and desmethyldiltiazem, comparing 1 x 360 mg extended release tablet to 2 x 180 mg extended release capsules were contained within the bioequivalence limits of 0.80 and 1.25 with a mean relative bioavailability of 99.2%. The pharmacokinetic parameters of diltiazem and its metabolites obtained from 1 x 360 mg diltiazem extended release tablet and 2 x 180 mg extended release capsules were bioequivalent.

Administration of 360 mg diltiazem extended release tablet 5-min after completion of a high fat meal increased the C_{max} of diltiazem, desacetyldiltiazem and desmethyldiltiazem by 4%, 7% and 13%, respectively, and food increased the AUC of diltiazem, desacetyldiltiazem and desmethyldiltiazem by 9%, 5% and 15%, respectively. The 90% confidence intervals for C_{max} and AUC of diltiazem, desacetyldiltiazem and desmethyldiltiazem were contained within the no food-effect limits of 0.80 and 1.25. The label should incorporate information regarding the lack of effect of food on the pharmacokinetics of diltiazem and that diltiazem can be administered with or without food.

There was clear evidence of subject by formulation interaction on the pharmacokinetics of diltiazem and desacetyldiltiazem. In males AUC of diltiazem was 10% lower while in females diltiazem AUC was higher by 14% when a 360 mg tablet was administered compared to 2 x 180 mg capsules. In females food decreased C_{max} by 9% while in males food increased C_{max} and AUC by 14% and 19%, respectively. Similarly, in males C_{max} and AUC of desacetyldiltiazem were lower by 8% ad 9%, respectively, while in females both C_{max} and AUC of diltiazem were similar when a 360 mg tablet was administered compared to 2 x 180 mg capsules. In contrast to males where food increased both C_{max} and AUC of desacetyldiltiazem by 24% and 15%, respectively, in females food decreased C_{max} by 10% and AUC by 4%.

STUDY 2371 (B00-458PK-DILG99)– A TWO-WAY, CROSSOVER, OPEN-LABEL, MULTIPLE-DOSE, FASTING, COMPARATIVE BIOAVAILABILITY STUDY OF DILTIAZEM HYDROCHLORIDE 360 mg EXTENDED RELEASE TABLETS VERSUS DILTIAZEM HYDROCHLORIDE 2 x 180 mg EXTENDED RELEASE CAPSULES IN HEALTHY NON-SMOKING MALE VOLUNTEERS

STUDY INVESTIGATOR AND SITE:

Bioavail Contract Research
460 Comstock Road
Toronto, Ontario
Canada M1L 4R6

Volumes: 27 to 47

OBJECTIVE:

To evaluate the relative bioavailability of diltiazem hydrochloride 360 mg extended release bead tablets relative to diltiazem hydrochloride 2 x 180 mg extended release bead capsules under steady state fasting conditions.

FORMULATIONS:

A. Test - Diltiazem hydrochloride extended release bead tablets –360 mg (Lot #: 001004) manufactured by Bioavail Technologies, Ltd. Batch size: —

B. Reference - Diltiazem hydrochloride extended release capsules –180 mg (Lot #: D000199CL manufactured by Bioavail Corporation. Batch size: —

STUDY DESIGN:

This was a randomized, open-label, two-treatment, multiple-dose, crossover, single center study in 30 normal, healthy, non-smoking male volunteers and 4 alternates under fasting conditions. The volunteers were between 20 and 44 years of age (mean: 30 yr) and weighed between 130 and 229 lb (mean: 171 lb). On Day 1 of Period I, subjects were randomized to receive either 360 mg diltiazem extended release bead tablet or 2 x 180 mg diltiazem extended release capsules for 7 days. Each formulation was administered orally on the morning of Days 1, 2, 3, 4, 5, 6 and 7 following an overnight 10 hour fast. Following a washout interval of 1 week between treatments all subjects received alternate formulation in Period II.

ASSAY:

Compound	Matrix	Method	Range (ng/ml)	Linearity	LOQ (ng/ml)	QC (ng/ml)	CV%	Accuracy (% Bias)
Diltiazem	Plasma	HPLC/UV					6.7 3.2 3.2 2.5	

Desacetyl diltiazem	Plasma	HPLC/UV		8.9 5.2 3.2 5.5
Desmethyl diltiazem	Plasma	HPLC/UV		5.2 3.8 2.1 1.5

Sample Collection:
Blood samples were taken for assessment of pharmacokinetic parameters of diltiazem, desacetyldiltiazem and desmethyldiltiazem predose on Days 1, 4, 5, 6, 7 and after dosing at 2, 3, 4, 6, 8, 10, 11, 12, 13, 14, 15, 16, 18, 20 and 24 hours on Day 7 in each period.

RESULTS

The following table lists the mean steady-state pharmacokinetic parameters of diltiazem, desacetyldiltiazem and desmethyldiltiazem obtained following multiple oral administration of a 360 mg diltiazem extended release tablet or 2 x 180 mg diltiazem extended release capsules in the fasted state.

Table 1: Mean (SD) Steady-state Pharmacokinetic Parameters of Diltiazem & Metabolites

	Diltiazem		Desacetyldiltiazem		Desmethyldiltiazem	
Parameter	360 mg Tablet	2 x 180 mg Capsule	360 mg Tablet	2 x 180 mg Capsule	360 mg Tablet	2 x 180 mg Capsule
C_{max} (ng/ml)	216.88 (75.92)	236.51 (71.0)	28.42 (42.37)	31.22 (48.70)	64.76 (19.02)	69.63 (17.21)
AUC_{0-24} (ng.h/ml)	3658.42 (1327.24)	3820.39 (1257.70)	550.89 (774.72)	631.94 (1090.19)	1245.33 (381.60)	1318.56 (334.72)
C_{min} (ng/ml)	111.38 (48.74)	97.07 (41.93)	21.77 (29.58)	24.06 (44.22)	43.88 (14.49)	41.38 (12.12)
T_{max} (h)	11.82 (4.44)	8.08 (2.57)	11.71 (6.94)	12.96 (4.38)	12.26 (4.16)	11.11 (2.71)
$C_{average}$ (ng/ml)	152.43 (55.30)	159.18 (52.40)	22.95 (32.28)	26.33 (45.42)	51.89 (15.90)	54.94 (13.95)
Fluctuation (%)	70.27 (35.49)	90.05 (30.70)	25.98 (23.90)	34.03 (32.46)	40.87 (18.72)	51.84 (16.93)

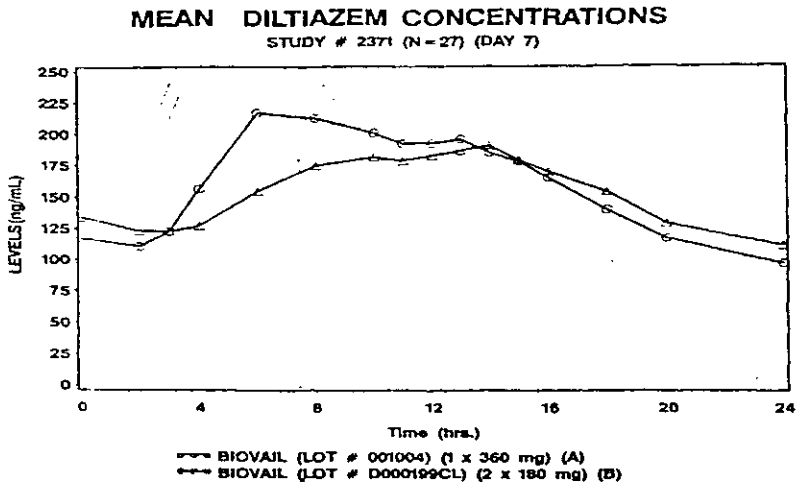
The C_{max}, AUC, $C_{average}$ of diltiazem and its metabolites - desacetyldiltiazem and desmethyldiltiazem were lower when administered as 360 mg extended release tablet compared to administration of 2 x 180 mg extended release capsules. Mean C_{max} of diltiazem, desacetyldiltiazem and desmethyldiltiazem were lower by 10%, 5% and 8%, respectively, mean steady-state AUC of diltiazem, desacetyldiltiazem and desmethyldiltiazem were lower by 5%, 5% and 7%, respectively, when administered as 360 mg extended release tablet compared to administration of 2 x 180 mg extended release capsules. The relative bioavailability of diltiazem at steady-state was 94.7% from

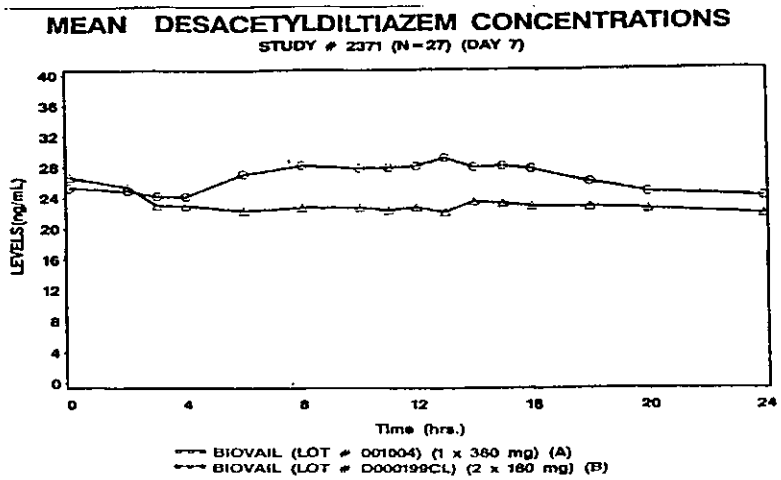
the 360 mg extended release tablet compared to 2 x 180 mg extended release capsules. Mean C_{min} of diltiazem at the end of the dosing interval, however, was slightly higher when administered as 360 mg extended release tablet compared to administration of 2 x 180 mg extended release capsules. Mean fluctuation of peak-to-trough concentrations of diltiazem was lower by 22% when diltiazem was administered as 360 mg extended release bead tablet compared to 2 x 180 mg extended release capsules.

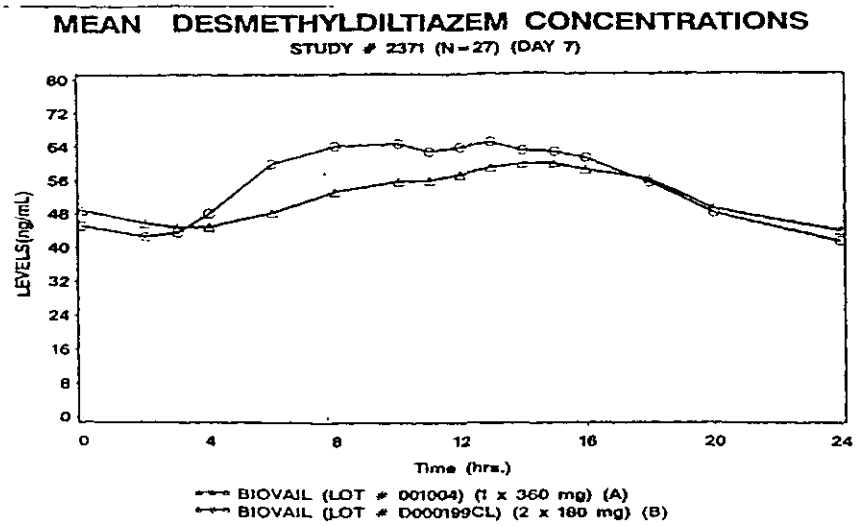
Table 2: Mean Ratios and 90% Confidence Intervals for Diltiazem and Metabolites

	Diltiazem		Desacetyldiltiazem		Desmethyldiltiazem	
Parameter	Ratio Tab/Capsule	90% CI	Ratio Tab/Capsule	90% CI	Ratio Tab/Capsule	90% CI
C_{max}	0.901	0.822 – 0.987	0.947	0.881 – 1.02	0.920	0.868 – 0.974
AUC_{0-24}	0.947	0.879 – 1.02	0.948	0.896 – 1.00	0.933	0.885 – 0.984

As listed in the table above, the point estimate for the ratio and 90% confidence intervals for C_{max} and AUC of diltiazem, desacetyldiltiazem and desmethyldiltiazem were contained within the bioequivalence limits of 0.80 and 1.25.







CONCLUSIONS:

The C_{max}, AUC, $C_{average}$ of diltiazem were lower by 10%, 5% and 4%, respectively when administered as 360 mg extended release tablet compared to administration of 2 x 180 mg extended release capsules. The C_{max}, AUC, $C_{average}$ of desacetyldiltiazem and desmethyldiltiazem were lower by a similar degree as diltiazem when administered as 360 mg extended release tablet compared to administration of 2 x 180 mg extended release capsules. The mean relative bioavailability of diltiazem at steady-state from the 360 mg extended release tablet formulation was 94.7% compared to 2 x 180 mg extended release capsule formulation. Mean fluctuation of peak-to-trough concentrations of diltiazem was lower by 22% when diltiazem was administered as 360 mg extended release bead tablet compared to 2 x 180 mg extended release capsules.

The point estimate for the ratio and 90% confidence intervals for C_{max} and AUC of diltiazem, desacetyldiltiazem and desmethyldiltiazem were contained within the bioequivalence limits of 0.80 and 1.25. The two formulations, 360 mg diltiazem extended release bead tablets and 2 x 180 mg diltiazem extended release capsules, were bioequivalent at steady-state.

STUDY 2433 (B00-514PK-DILG99)– 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 INVESTIGATOR AND SITE:

Bioavail Contract Research
Bioavail Corporation
Toronto, Ontario
CANADA

Volumes: 16 to 21

OBJECTIVE:

To compare the rate and extent of absorption of the diltiazem hydrochloride 360 mg extended release bead tablets (test) to diltiazem hydrochloride 2 x 180 mg extended release capsules (reference) following night time administration.

FORMULATIONS:

C. **Test** - Diltiazem hydrochloride extended release bead tablets –360 mg (Lot #: 001004) manufactured by Bioavail Technologies, Ltd. Batch size: — tablets

D. **Reference** - Diltiazem hydrochloride extended release capsules –180 mg (Lot #: D000199CL manufactured by Bioavail Corporation. Batch size: — capsules

STUDY DESIGN:

This was a randomized, open-label, two-treatment, two-period, single-dose, night time administration, crossover study conducted under fasting conditions in 24 healthy non-smoking, male (n=21) and female (n=3), volunteers between 18 and 38 years of age (mean: 29 yr) weighing between 114 and 209 lbs (mean: 167 lbs). Subject # 12, 16, 18 and 21 withdrew from the study. Pharmacokinetic and statistical analyses were conducted on 20 evaluable subjects. On Day 1 subjects were randomized to receive, **Treatment A:** 1 x 360 mg diltiazem hydrochloride extended release bead tablet at 10:00 PM following a fast of at least 2 hours, or **Treatment B:** 2 x 180 mg diltiazem hydrochloride extended release capsules at 10:00 PM following a fast of at least 2 hours. In Period 2, subjects crossed over to receive alternate treatment following a 1-week washout interval.

ASSAY:

Compound	Matrix	Method	Range (ng/ml)	Linearity	LOQ (ng/ml)	QC (ng/ml)	CV%	Accuracy (% Bias)
Diltiazem	Plasma	HPLC/UV	\	\	\	\	6.7 4.6 3.7 3.2	\

Desacetyl diltiazem	Plasma	HPLC/UV			9.9 4.7 3.6 3.5
Desmethyl diltiazem	Plasma	HPLC/UV			7.2 4.4 2.7 2.3

Sample Collection:

Blood samples were taken for assessment of pharmacokinetic parameters of diltiazem, desacetyldiltiazem and desmethyldiltiazem, predose and at 2, 3, 4, 6, 8, 10, 11, 12, 13, 14, 15, 16, 18, 20, 24, 30, 36, 42 and 48 hours post dose in each period.

RESULTS

The mean pharmacokinetic parameters of diltiazem and its metabolites-desacetyldiltiazem and desmethyldiltiazem, obtained following administration of a 1 x 360-mg diltiazem extended release bead tablet and 2 x 180 mg diltiazem extended release capsules administered at night time in the fasted state are presented in the following table.

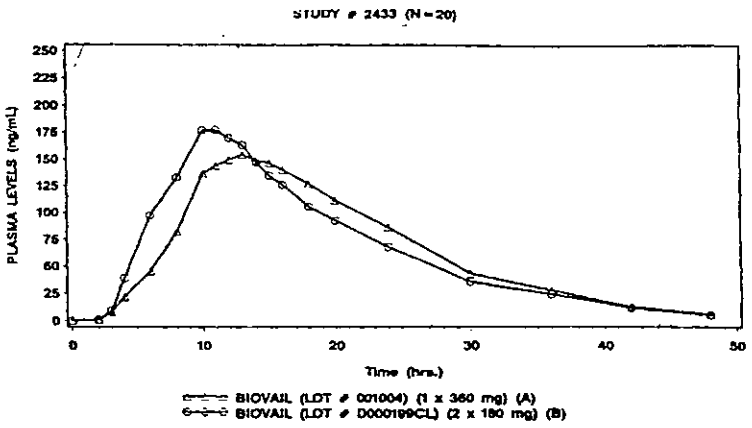
Table 1: Mean (SD) Pharmacokinetic Parameters of Diltiazem, Desacetyldiltiazem and Desmethyldiltiazem

	DILTIAZEM			
Parameter	**1 x 360 mg TABLET NIGHT TIME FASTING**	**2 x 180 mg CAPSULES NIGHT TIME FASTING**	**POINT ESTIMATE**	**90% CI**
C_{max} (ng/ml)	167.87 (58.37)	192.15 (89.68)	0.892	0.823 – 0.967
AUC_{0-last} (ng.h/ml)	2983.95 (1248.0)	3036.25 (1309.30)	0.978	0.913 – 1.05
AUC_{0-inf} (ng.h/ml)	3060.76 (1280.04)	3120.57 (1351.50)	0.977	0.913 – 1.05
T_{max} (h)	13.40 (2.72)	11.00 (1.81)		
$T_{1/2}$ (h)	6.58 (1.26)	7.03 (1.30)		
	DESACETYLDILTIAZEM			
Parameter	**1 x 360 mg TABLET NIGHT TIME FASTING**	**2 x 180 mg CAPSULES NIGHT TIME FASTING**	**POINT ESTIMATE**	**90% CI**
C_{max} (ng/ml)	11.63 (4.79)	11.32 (4.29)	1.01	0.937 – 1.09
AUC_{0-last} (ng.h/ml)	257.95 (123.41)	244.81 (111.29)	1.03	0.938 – 1.13
AUC_{0-inf} (ng.h/ml)	277.37 (124.17)	270.32 (112.99)	1.00	0.916 – 1.09
T_{max} (h)	17.70 (4.10)	15.00 (2.62)		
$T_{1/2}$ (h)	8.13 (1.98)	9.61 (2.99)		
	DESMETHYLDILTIAZEM			
Parameter	**1 x 360 mg TABLET NIGHT TIME**	**2 x 180 mg CAPSULES NIGHT TIME**	**POINT ESTIMATE**	**90% CI**

	FASTING	FASTING		
C_{max} (ng/ml)	56.94 (16.36)	60.87 (21.62)	0.943	0.887 – 1.00
AUC_{0-last} (ng.h/ml)	1265.66 (461.37)	1275.19 (475.83)	0.987	0.931 – 1.05
AUC_{0-inf} (ng.h/ml)	1359.54 (498.86)	1369.20 (517.74)	0.989	0.934 – 1.05
T_{max} (h)	14.60 (2.74)	12.20 (1.77)		
$T_{1/2}$ (h)	9.25 (1.71)	9.65 (1.79)		

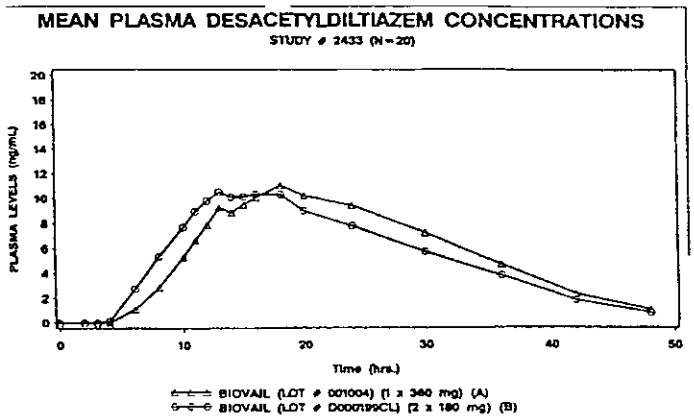
Diltiazem:

Mean Cmax and AUC of diltiazem from the 1 x 360 mg extended release tablet were bioequivalent to 2 x 180 mg capsules administered at night time. Mean C_{max} of diltiazem from the extended release tablet formulation was lower (10%) than the mean C_{max} obtained with 2 x 180-mg capsules. Mean AUC_{inf} and $T_{1/2}$ of diltiazem from the extended tablet formulation were similar to that obtained from 2 x 180-mg capsules. The relative bioavailability was 97.7% from the tablet formulation compared to 2 x 180 mg capsules. The intra-subject variability in C_{max} and AUC_{inf} were 14.70% and 12.44%, respectively. The T_{max} of diltiazem from the tablet formulation occurred about 2 hours later compared to the capsule formulation.



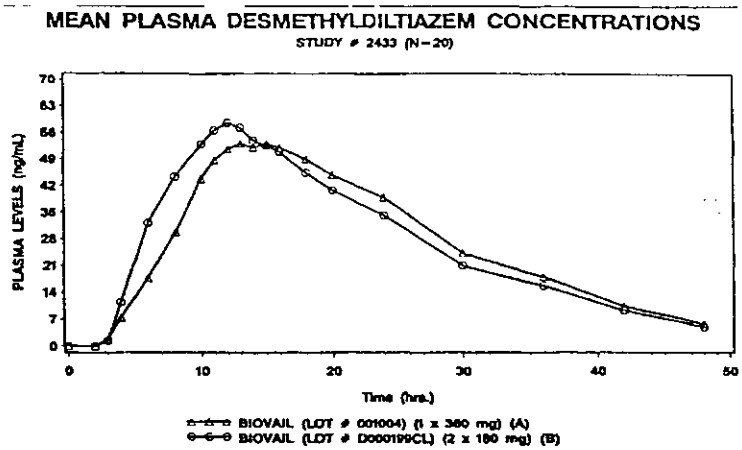
Desacetyldiltiazem:

Mean C_{max} and AUC of desacetyldiltiazem from the 1 x 360 mg extended release tablet were bioequivalent to 2 x 180 mg capsules. Ratio of mean C_{max} and AUC_{inf} of desacetyldiltiazem from the extended tablet formulation to those obtained with 2 x 180-mg capsules was equal to 1.0. The T_{max} of desacetyldiltiazem from the tablet formulation occurred about 2 hours later compared to the capsule formulation. The intra-subject variability in C_{max} and AUC_{inf} were 13.69% and 16.04%, respectively.



Desmethyldiltiazem:

Mean C_{max} and AUC of desmethyldiltiazem from the 1 x 360 mg extended release tablet were bioequivalent to 2 x 180 mg capsules. Mean C_{max} of desmethyldiltiazem from the extended tablet formulation was slightly lower (6%) compared to 2 x 180-mg capsules. Mean AUC_{inf} and $T_{1/2}$ of desmethyldiltiazem from the extended tablet formulation were almost identical to 2 x 180-mg capsules. The intra-subject variability in C_{max} and AUC_{inf} were 11.26% and 10.37%, respectively. The T_{max} of desmethyldiltiazem from the tablet formulation occurred about 2 hours later compared to the capsule formulation.



CONCLUSIONS:

The point estimates and 90% confidence intervals for C_{max} and AUC of diltiazem, desacetyldiltiazem and desmethyldiltiazem, comparing 1 x 360 mg extended release tablet to 2 x 180 mg extended release capsules administered night time were contained within the bioequivalence limits of 0.80 and 1.25 with a mean relative bioavailability of 98%, 100% and 99%, respectively. The pharmacokinetic parameters of diltiazem and its metabolites obtained from 1 x 360 mg diltiazem extended release tablet and 2 x 180 mg extended release capsules administered night time in the fasted state were bioequivalent.

STUDY 2489 (B01-541PK-DILG99)– A TWO-WAY CROSSOVER, 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 INVESTIGATOR AND SITE:

Bioavail Contract Research
Bioavail Corporation
Toronto, Ontario
CANADA

Volumes: 22-27

OBJECTIVE:

To compare the rate and extent of absorption of the diltiazem hydrochloride 360 mg extended release bead tablets (test) to diltiazem hydrochloride 360 mg extended release capsules (reference) following night time administration under fed conditions.

FORMULATIONS:

A. Test - Diltiazem hydrochloride extended release bead tablets –360 mg (Lot #: 001004) manufactured by Bioavail Technologies, Ltd. Batch size: — tablets

B. Reference - Diltiazem hydrochloride extended release capsules –360 mg (Lot #: T990805CL manufactured by Bioavail Laboratories Inc. Batch size: capsules

STUDY DESIGN:

This was a randomized, open-label, two-treatment, two-period, single-dose, night time administration, crossover study conducted under fed conditions in 25 healthy non-smoking, male (n=13) and female (n=12), volunteers between 19 and 40 years of age (mean: 29 yr) weighing between 107 and 193 lbs (mean: 147 lbs). Subject # 2, 10, 12 and 17 withdrew from the study, Subject # 18 was not analyzed because of vomiting during dosing interval. Pharmacokinetic and statistical analyses were conducted on 20 evaluable subjects. On Day 1 subjects were randomized to receive, **Treatment A:** 360 mg diltiazem hydrochloride extended release bead tablet at 10:00 PM following ingestion of a high fat meal 30 minutes prior to drug administration, or **Treatment B:** 360 mg diltiazem hydrochloride extended release capsule at 10:00 PM following ingestion of a high fat meal 30 minutes prior to drug administration. The standard high-fat content meal consisted of the following: one (1) egg (fried), one (1) buttered english muffin, one (1) slice of American cheese, one (1) slice of candian bacon, one (1) serving of hash brown potatoes, eight (8) fluid ounces (240mL) of whole milk and six (6) fluid ounces of orange juice. In Period 2, subjects crossed over to receive alternate treatment following a 1-week washout interval.

ASSAY:

Compound	Matrix	Method	Range (ng/ml)	Linearity	LOQ (ng/ml)	QC (ng/ml)	CV%	Accuracy (% Bias)
Diltiazem	Plasma	HPLC/UV					6.0 9.6 5.2 4.9	
Desacetyl diltiazem	Plasma	HPLC/UV					8.4 7.9 4.7 4.5	
Desmethyl diltiazem	Plasma	HPLC/UV					11.1 4.8 1.8 2.5	

Sample Collection:

Blood samples were taken for assessment of pharmacokinetic parameters of diltiazem, desacetyldiltiazem and desmethyldiltiazem, predose and at 2, 3, 4, 6, 8, 10, 11, 12, 13, 14, 15, 16, 18, 20, 24, 30, 36, 42 and 48 hours post dose in each period.

RESULTS

The mean pharmacokinetic parameters of diltiazem and its metabolites-desacetyldiltiazem and desmethyldiltiazem, obtained following administration of a 360-mg diltiazem extended release bead tablet and 360 mg diltiazem extended release capsule administered at night time in the fed state are presented in the following table.

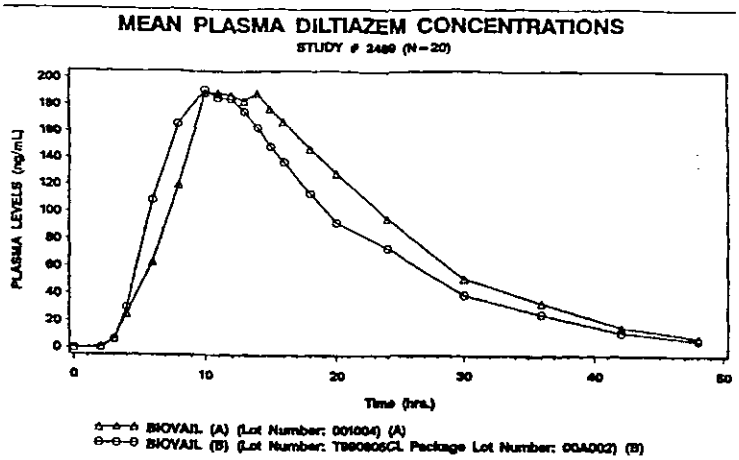
Table 1: Mean (SD) Pharmacokinetic Parameters of Diltiazem, Desacetyldiltiazem and Desmethyldiltiazem

	DILTIAZEM			
Parameter	**360 mg TABLET NIGHT TIME FED**	**360 mg CAPSULE NIGHT TIME FED**	**POINT ESTIMATE**	**90% CI**
C_{max} (ng/ml)	207.10 (67.03)	202.94 (69.41)	1.03	0.908 – 1.18
AUC_{0-last} (ng.h/ml)	3658.55 (1128.87)	3293.26 (1141.81)	1.13	1.02 – 1.25
AUC_{0-inf} (ng.h/ml)	3749.13 (1172.73)	3295.72 (1141.81)	1.12	1.01 – 1.25
T_{max} (h)	11.75 (1.48)	10.81 (1.77)		
$T_{1/2}$ (h)	6.86 (1.07)	7.01 (1.44)		
	DESACETYLDILTIAZEM			
Parameter	**360 mg TABLET NIGHT TIME FED**	**360 mg CAPSULE NIGHT TIME FED**	**POINT ESTIMATE**	**90% CI**
C_{max} (ng/ml)	18.25 (9.09)	16.23 (7.93)	1.12	1.02 – 1.22
AUC_{0-last} (ng.h/ml)	457.67 (253.34)	378.58 (184.56)	1.17	1.06 – 1.29
AUC_{0-inf} (ng.h/ml)	504.37 (287.16)	399.02 (175.55)	1.17	1.04 – 1.32

T_{max} (h)	18.90 (2.79)	14.51 (2.34)		
$T_{1/2}$ (h)	9.10 (2.38)	9.37 (2.79)		
	DESMETHYLDILTIAZEM			
Parameter	360 mg TABLET NIGHT TIME FED	360 mg CAPSULE NIGHT TIME FED	POINT ESTIMATE	90% CI
C_{max} (ng/ml)	62.44 (17.86)	65.16 (17.28)	0.953	0.885 – 1.03
$AUC_{0\text{-}last}$ (ng.h/ml)	1428.99 (402.13)	1339.38 (379.74)	1.07	1.00 – 1.13
$AUC_{0\text{-}inf}$ (ng.h/ml)	1522.35 (431.86)	1380.58 (399.88)	1.06	0.991 – 1.14
T_{max} (h)	12.95 (1.85)	12.06 (1.53)		
$T_{1/2}$ (h)	9.25 (1.25)	9.08 (1.31)		

Diltiazem:

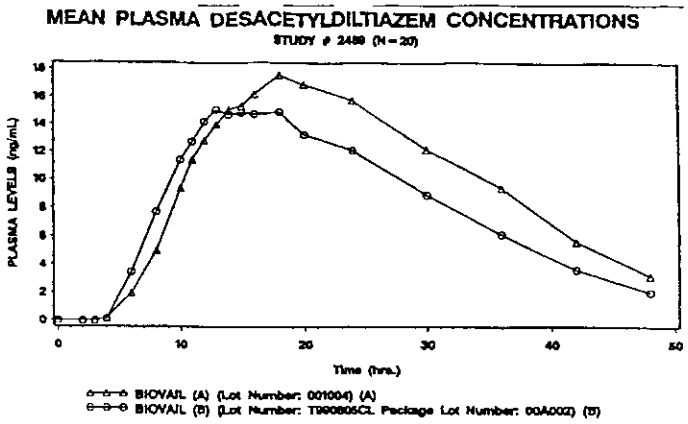
Mean C_{max} and AUC of diltiazem from the 360 mg extended release tablet were bioequivalent to the 360 mg extended release capsule administered at night time in the fed state. Mean AUC of diltiazem from the extended release tablet formulation was 12% higher than the mean AUC obtained with 360 mg extended release capsule. Mean C_{max} and $T_{1/2}$ of diltiazem from the tablet formulation were similar to capsule. The relative bioavailability was 112% from the tablet formulation compared to capsule. The intra-subject variability in C_{max} and AUC_{inf} were 23.5% and 18.9%, respectively. The T_{max} of diltiazem from the tablet occurred about 1 hour later compared to the capsule.



Desacetyldiltiazem:

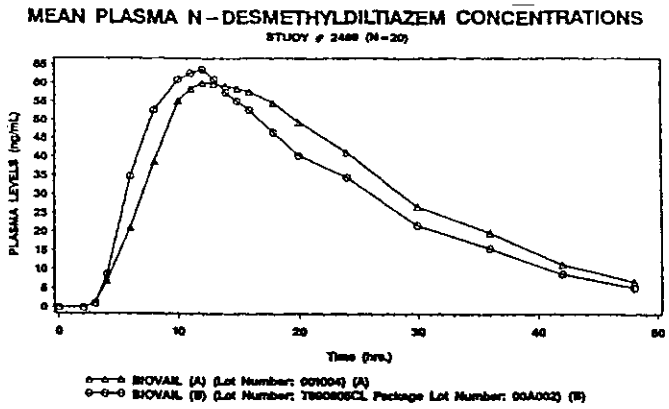
Mean C_{max} of desacetyldiltiazem from the 360 mg extended release tablet was bioequivalent to 360 mg extended release capsule administered at night time following a meal. However, mean AUC of desacetyldiltiazem from the tablet was not bioequivalent to the capsule. Mean AUC from the tablet was 17% higher when administered as tablet compared to capsule, consequently, the upper limit of the 90% confidence interval was above the bioequivalence limit of 1.25. Mean desacetyldiltiazem C_{max} from the extended tablet formulation was 12% higher and desacetyldiltiazem T_{max} occurred about 4 hours

later when administered as tablet compared to the capsule. The intra-subject variability in C_{max} and AUC_{inf} were 16.1% and 19.9%, respectively. The $T_{1/2}$ of desacetyldiltiazem was similar when administered as either tablet or capsule.



Desmethyldiltiazem:

Mean C_{max} and AUC of desmethyldiltiazem from the 360 mg extended release tablet were bioequivalent to 360 mg capsule administered at night time in the fed state. Mean C_{max} of desmethyldiltiazem from the extended tablet was slightly lower (5%), while mean AUC_{inf} was slightly higher (6%) compared to capsule. The intra-subject variability in C_{max} and AUC_{inf} were 13.4% and 11.8%, respectively. Mean T_{max} and $T_{1/2}$ of desmethyldiltiazem from the tablet formulation were similar to capsule.



CONCLUSIONS:

The point estimates and 90% confidence intervals for C_{max} and AUC of diltiazem, and desmethyldiltiazem, comparing 360 mg extended release tablet to 360 mg extended release capsule administered night time in the fed state were contained within the bioequivalence limits of 0.80 and 1.25. However, the AUC of desacetyldiltiazem exceeded the upper limit of bioequivalence of 1.25 by 7%. Mean relative bioavailability of diltiazem, desacetyldiltiazem and desmethyldiltiazem when administered as extended

release tablet in the fed state were 112%, 117% and 106%, respectively, compared to the extended release capsule. Diltiazem 360 mg extended release tablet is bioequivalent to 360 mg extended release capsule with respect to diltiazem and desmethyldiltiazem, but not with respect to desacetyldiltiazem, when administered night time in the fed state.

STUDY 2435 (B00-516PK-DILG99)– 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 INVESTIGATOR AND SITE:

Bioavail Contract Research
460 Comstock Road
Toronto, Ontario
Canada M1L 4R6

Volumes: 28 to 38

OBJECTIVE:

To evaluate the relative bioavailability of diltiazem hydrochloride 360 mg extended release bead tablets relative to diltiazem hydrochloride 2 x 180 mg extended release bead capsules administered night time under steady state fasting conditions.

FORMULATIONS:

A. **Test** - Diltiazem hydrochloride extended release bead tablets –360 mg (Lot #: 001004) manufactured by Bioavail Technologies, Ltd. Batch size: —
B. **Reference** - Diltiazem hydrochloride extended release capsules –180 mg (Lot #: D000199CL manufactured by Bioavail Corporation. Batch size: —

STUDY DESIGN:

This was a randomized, open-label, two-treatment, multiple-dose, night time administration, crossover, single center study in 30 normal, healthy, non-smoking male (n=15) and female (n=15) volunteers under fasting conditions. The volunteers were between 19 and 45 years of age (mean: 32 yr) and weighed between 113 and 208 lbs (mean: 163 lbs). Subject # 17, 21, 22 and 28 were either dismissed or withdrew from the study. Pharmacokinetic and statistical analyses were conducted on 26 evaluable subjects. On Day 1 of Period I, subjects were randomized to receive either, **Treatment A:** 1 x 360 mg diltiazem hydrochloride extended release bead tablet at 10:00 PM following a fast of at least 2 hours, or **Treatment B:** 2 x 180 mg diltiazem hydrochloride extended release capsules at 10:00 PM following a fast of at least 2 hours. Each formulation was administered once-daily orally at 10:00 PM following a fast of at least 2 hours on Days 1, 2, 3, 4, 5, 6 and 7. Following a washout interval of 1 week between treatments all subjects received alternate formulation in Period II.

ASSAY:

Compound	Matrix	Method	Range	Linearity	LOQ	QC	CV%	Accuracy

			(ng/ml)	(ng/ml)	(ng/ml)	(% Bias)
Diltiazem	Plasma	HPLC/UV			4.9 3.9 3.4 3.0	
Desacetyl diltiazem	Plasma	HPLC/UV			8.9 9.3 3.3 2.8	
Desmethyl diltiazem	Plasma	HPLC/UV			5.8 2.8 2.4 1.9	

Sample Collection:

Blood samples were taken for assessment of pharmacokinetic parameters of diltiazem, desacetyldiltiazem and desmethyldiltiazem predose on Days 1, 4, 5, 6, 7 and after dosing at 2, 3, 4, 6, 8, 10, 11, 12, 13, 14, 15, 16, 18, 20 and 24 hours on Day 7 in each period.

RESULTS

The following table lists the mean steady-state pharmacokinetic parameters of diltiazem, desacetyldiltiazem and desmethyldiltiazem obtained following multiple oral administration of a 360 mg diltiazem extended release tablet or 2 x 180 mg diltiazem extended release capsules following night time administration in the fasted state.

Table 1: Mean (SD) Steady-state Pharmacokinetic Parameters of Diltiazem & Metabolites

	Diltiazem		Desacetyldiltiazem		Desmethyldiltiazem	
Parameter	360 mg Tablet	2 x 180 mg Capsule	360 mg Tablet	2 x 180 mg Capsule	360 mg Tablet	2 x 180 mg Capsule
C_{max} (ng/ml)	211.56 (65.75)	242.95 (85.73)	27.59 (22.54)	30.60 (2.49)	62.56 (15.93)	70.57 (16.11)
AUC_{0-24} (ng.h/ml)	3243.37 (996.41)	3600.61 (1095.85)	544.12 (497.68)	576.79 (542.30)	1123.63 (292.98)	1241.52 (289.81)
C_{min} (ng/ml)	91.83 (30.24)	86.31 (36.27)	22.26 (20.63)	22.63 (23.40)	40.12 (10.44)	39.08 (11.19)
T_{max} (h)	11.93 (2.12)	10.58 (1.88)	16.29 (3.86)	13.93 (2.56)	12.85 (2.19)	11.66 (1.34)
$C_{average}$ (ng/ml)	135.14 (41.52)	150.03 (45.66)	22.67 (20.74)	24.03 (22.60)	46.82 (12.21)	51.73 (12.08)
Fluctuation (ng/ml)	89.57 (27.72)	101.43 (29.91)	31.44 (20.08)	40.92 (19.80)	47.74 (16.55)	60.05 (20.34)

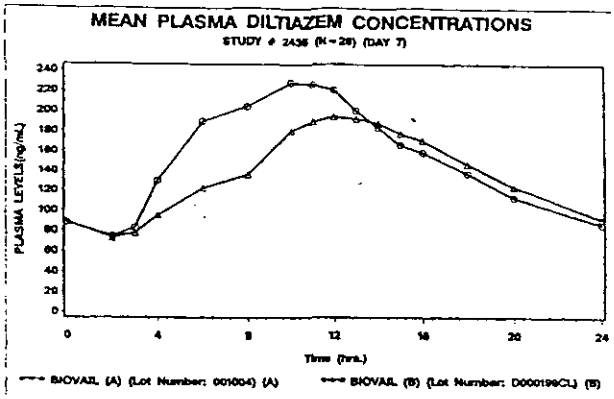
Table 2: Mean Ratios and 90% Confidence Intervals for Diltiazem and Metabolites

	Diltiazem		Desacetyldiltiazem		Desmethyldiltiazem	
Parameter	Ratio Tab/Capsule	90% CI	Ratio Tab/Capsule	90% CI	Ratio Tab/Capsule	90% CI
C_{max}	0.881	0.792 – 0.980	0.930	0.858 – 1.01	0.884	0.829 – 0.944

AUC_{0-24}	0.902	0.837 – 0.972	0.966	0.901 – 1.03	0.902	0.855 – 0.952

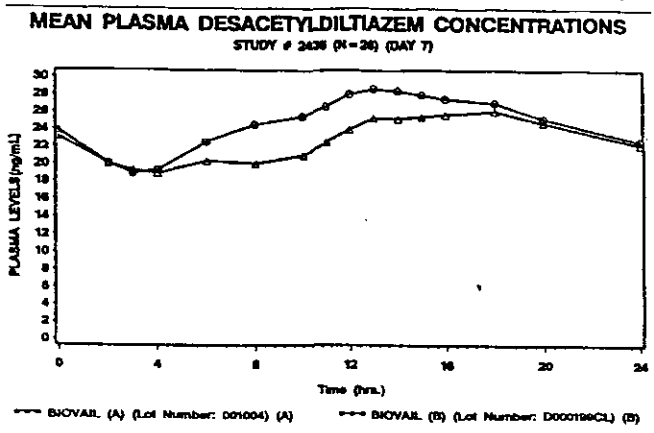
Diltiazem:

Mean steady-state C_{max} of diltiazem from the 1 x 360 mg extended release tablet was not bioequivalent to 2 x 180 mg capsules administered at night time in the fasted state. Mean C_{max} of diltiazem from the extended release tablet was 12% lower compared to 2 x 180-mg capsules and the lower limit of the 90% confidence interval for C_{max} was 0.792 which was below the bioequivalence limit of 0.8. Mean steady-state AUC_{0-24} from the tablet was 10% lower with a relative bioavailability of 90%. The lower limit of the 90% confidence interval for AUC_{0-24} from the tablet was above 0.80 compared to capsules. The intra-subject variability in C_{max} and AUC_{0-24} were 22.5% and 15.7%, respectively. Mean fluctuation of peak-to-trough concentrations of diltiazem was lower when diltiazem was administered as 360 mg tablet compared to 2 x 180 mg extended release capsules. The T_{max} of diltiazem from the tablet formulation occurred about 1.5 hours later compared to the capsule formulation.



Desacetyldiltiazem:

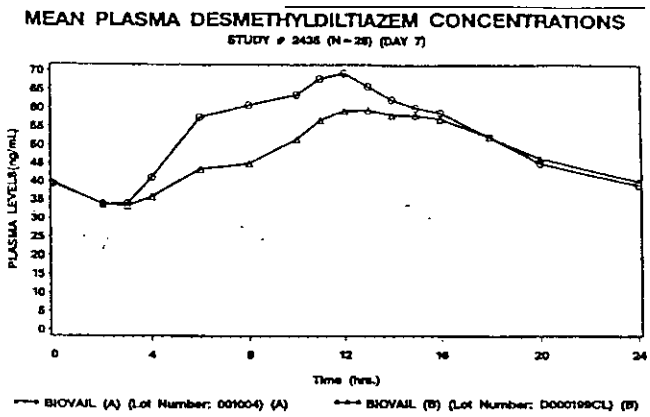
Mean C_{max} and AUC_{0-24} of desacetyldiltiazem from the 1 x 360 mg extended release tablet were bioequivalent to 2 x 180 mg capsules administered night time under fasting conditions. Ratio of mean C_{max} and AUC_{0-24} of desacetyldiltiazem from the extended tablet formulation to those obtained with 2 x 180-mg capsules was lower by 7% and 3%, respectively. Mean fluctuation of peak-to-trough concentrations of desacetyldiltiazem was similar when administered as 360 mg tablet or 2 x 180 mg extended release capsules. The intra-subject variability in C_{max} and AUC_{inf} were 17.1% and 12.7%, respectively. The



T_{max} of desacetyldiltiazem from the tablet formulation occurred about 2 hours later compared to the capsule formulation.

Desmethyldiltiazem:

Mean C_{max} and AUC_{0-24} of desmethyldiltiazem from the 1 x 360 mg extended release tablet were bioequivalent to 2 x 180 mg capsules administered night time in the fasted state. Mean C_{max} and AUC_{0-24} of desmethyldiltiazem from the extended tablet formulation was lower by 12% and 10%, respectively, compared to 2 x 180-mg capsules. The intra-subject variability in C_{max} and AUC_{0-24} were 13.7% and 11.3%, respectively. Mean fluctuation of peak-to-trough concentrations of desmethyldiltiazem was lower when administered as 360 mg tablet compared to 2 x 180 mg extended release capsules. The T_{max} of desmethyldiltiazem from the tablet formulation occurred about 2 hours later compared to the capsule formulation.



CONCLUSIONS:

The C_{max}, AUC_{0-24}, $C_{average}$ of diltiazem were lower by 12%, 10% and 10%, respectively when administered as 360 mg extended release tablet compared to administration of 2 x 180 mg extended release capsules administered night time in the fasted state. The C_{max}, AUC_{0-24}, $C_{average}$ of desmethyldiltiazem were lower by a similar degree as diltiazem when administered as 360 mg extended release tablet compared to administration of 2 x 180 mg extended release capsules. However, C_{max}, AUC_{0-24}, $C_{average}$ of desacetyldiltiazem were lower by only 7%, 3% and 6%, respectively, when administered as a tablet compared to capsule.

The mean relative bioavailability of diltiazem at steady-state from the 360 mg extended release tablet formulation was 90% compared to 2 x 180 mg extended release capsule formulation.

The lower limit of the 90% confidence intervals for C_{max} of diltiazem was not contained within the bioequivalence limits of 0.80 and 1.25. However, the point estimate for the ratio and 90% confidence intervals for C_{max} and AUC of desacetyldiltiazem and desmethyldiltiazem, and AUC of diltiazem were contained within the bioequivalence

limits of 0.80 and 1.25. The two formulations, 360 mg diltiazem extended release bead tablets and 2 x 180 mg diltiazem extended release capsules are not bioequivalent with respect to diltiazem but are bioequivalent with respect to its metabolites, desacetyldiltiazem and desmethyldiltiazem at steady-state, administered night time in the fasted state.

STUDY 2492 (B01-543PK-DILG99)– 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 INVESTIGATOR AND SITE:

Bioavail Contract Research
460 Comstock Road
Toronto, Ontario
Canada M1L 4R6

Volumes: 39 to

OBJECTIVE:

To evaluate the relative bioavailability of diltiazem hydrochloride 360 mg extended release bead tablets relative to diltiazem hydrochloride 360 mg extended release bead capsules administered night time under steady state fasting conditions.

FORMULATIONS:

A. **Test** - Diltiazem hydrochloride extended release bead tablets –360 mg (Lot #: 001004) manufactured by Bioavail Technologies, Ltd. Batch size: — tablets
B. **Reference** - Diltiazem hydrochloride extended release capsules –360 mg (Lot #: T990805CL manufactured by Bioavail Laboratories Inc. Batch size: capsules

STUDY DESIGN:

This was a randomized, open-label, two-treatment, multiple-dose, night time administration, crossover, single center study in 28 normal, healthy, non-smoking male (n=21) and female (n=7) volunteers under fasting conditions. The volunteers were between 19 and 44 years of age (mean: 30 yr) and weighed between 134 and 199 lb (mean: 171 lb). Subject # 7, 12, 14, 15, 19, 22 and 26 were either dismissed or withdrew from the study. Pharmacokinetic and statistical analyses were conducted on 21 evaluable subjects. On Day 1 of Period I, subjects were randomized to receive either, **Treatment A:** 360 mg diltiazem hydrochloride extended release bead tablet at 10:00 PM following a fast of at least 2 hours, or **Treatment B:** 360 mg diltiazem hydrochloride extended release capsule at 10:00 PM following a fast of at least 2 hours. Each formulation was administered once-daily orally at 10:00 PM following a fast of at least 2 hours on Days 1, 2, 3, 4, 5, 6 and 7. Following a washout interval of 1 week between treatments all subjects received alternate formulation in Period II.

ASSAY:

Compound	Matrix	Method	Range (ng/ml)	Linearity	LOQ (ng/ml)	QC (ng/ml)	CV%	Accuracy (% Bias)

Diltiazem	Plasma	HPLC/UV					8.9 3.9 3.4 4.0	
Desacetyl diltiazem	Plasma	HPLC/UV					10.1 4.6 3.3 4.1	
Desmethyl diltiazem	Plasma	HPLC/UV					8.0 4.0 3.0 3.1	

Sample Collection:

Blood samples were taken for assessment of pharmacokinetic parameters of diltiazem, desacetyldiltiazem and desmethyldiltiazem predose on Days 1, 4, 5, 6, 7 and after dosing at 2, 3, 4, 6, 8, 10, 11, 12, 13, 14, 15, 16, 18, 20 and 24 hours on Day 7 in each period.

RESULTS

The following table lists the mean steady-state pharmacokinetic parameters of diltiazem, desacetyldiltiazem and desmethyldiltiazem obtained following multiple oral administration of a 360 mg diltiazem extended release tablet or 360 mg diltiazem extended release capsule following night time administration in the fasted state.

Table 1: Mean (SD) Steady-state Pharmacokinetic Parameters of Diltiazem & Metabolites

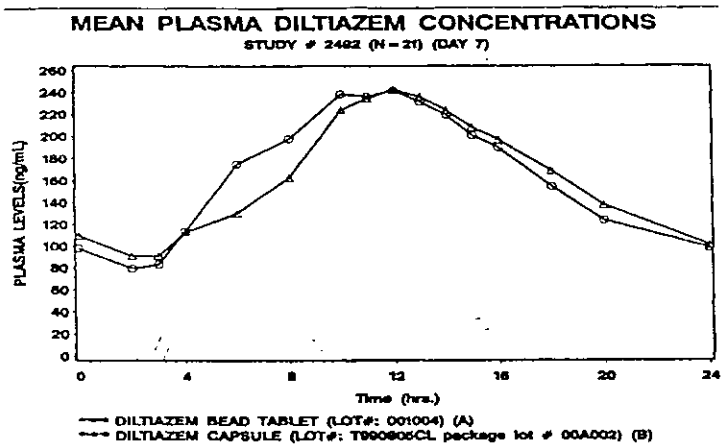
	Diltiazem		Desacetyldiltiazem		Desmethyldiltiazem	
Parameter	360 mg Tablet	360 mg Capsule	360 mg Tablet	360 mg Capsule	360 mg Tablet	360 mg Capsule
C_{max} (ng/ml)	259.72 (112.21)	263.38 (117.63)	28.41 (21.73)	24.55 (15.08)	73.94 (24.61)	72.79 (18.98)
AUC_{0-24} (ng.h/ml)	3818.95 (1643.07)	3861.81 (1690.59)	513.42 (411.40)	444.06 (270.36)	1287.32 (389.39)	1310.40 (400.77)
C_{min} (ng/ml)	100.86 (57.44)	98.41 (54.59)	20.87 (21.18)	16.05 (10.02)	43.38 (15.56)	43.31 (17.94)
T_{max} (h)	12.10 (1.73)	11.00 (1.82)	14.33 (3.14)	14.00 (2.24)	12.43 (2.34)	11.90 (1.87)
$C_{average}$ (ng/ml)	159.12 (68.46)	160.91 (70.44)	21.39 (17.14)	18.50 (11.26)	53.64 (16.22)	54.60 (16.70)
Fluctuation (ng/ml)	107.03 (43.74)	106.24 (33.01)	44.10 (29.34)	47.87 (22.95)	59.86 (31.25)	58.18 (24.91)

Table 2: Mean Ratios and 90% Confidence Intervals for Diltiazem and Metabolites

	Diltiazem		Desacetyldiltiazem		Desmethyldiltiazem	
Parameter	Ratio Tab/Capsule	90% CI	Ratio Tab/Capsule	90% CI	Ratio Tab/Capsule	90% CI
C_{max}	0.987	0.905 – 1.08	1.06	0.960 – 1.16	1.00	0.932 – 1.07
AUC_{0-24}	0.976	0.891 – 1.07	1.05	0.946 – 1.16	0.974	0.914 – 1.04

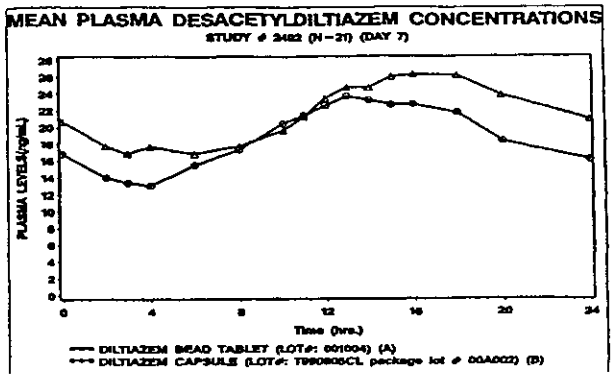
Diltiazem:

Mean steady-state C_{max} and AUC_{0-24} of diltiazem from the 360 mg extended release tablet were bioequivalent to 360 mg capsule administered at night time in the fasted state. Mean C_{max} and AUC_{0-24} of diltiazem from the tablet were slightly lower (<2.4%) compared to 360 mg capsule. Mean steady-state relative bioavailability from tablet was 97.6% compared to capsule. The intra-subject variability in C_{max} and AUC_{0-24} were 16.3% and 17.0%, respectively. Mean average concentration at steady-state and mean fluctuation of peak-to-trough concentrations of diltiazem were similar when diltiazem was administered as 360 mg tablet or as 360 mg extended release capsule. The T_{max} of diltiazem from the tablet formulation occurred about 1 hour later compared to the capsule formulation.



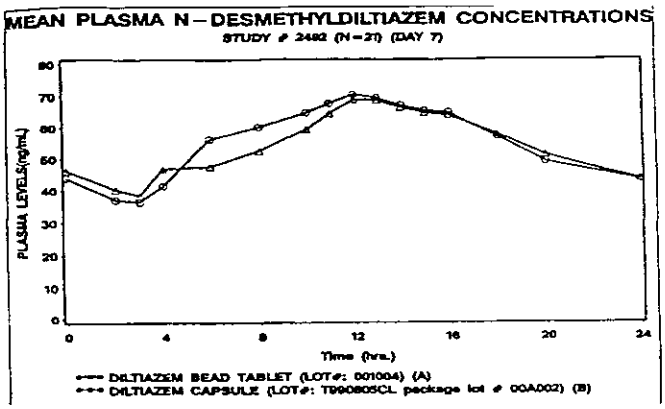
Desacetyldiltiazem:

Mean C_{max} and AUC_{0-24} of desacetyldiltiazem from the 360 mg extended release tablet were bioequivalent to 360 mg capsule administered night time under fasting conditions. Ratio of mean C_{max} and AUC_{0-24} of desacetyldiltiazem from the extended tablet formulation to those obtained with 360 mg capsule were slightly higher by 6% and 5%, respectively. Mean average concentration at steady-state was slightly higher with tablet but mean fluctuation of peak-to-trough concentrations of desacetyldiltiazem was similar when administered as tablet or capsule. The intra-subject variability in C_{max} and AUC_{0-24} were 17.9% and 19.2%, respectively. The T_{max} of desacetyldiltiazem from both tablet and capsule formulations were similar.



Desmethyldiltiazem:

Mean C_{max} and AUC_{0-24} of desmethyldiltiazem from 360 mg extended release tablet were bioequivalent to 2 x 180 mg capsules administered night time in the fasted state. Mean C_{max} and AUC_{0-24} of desmethyldiltiazem from the extended tablet formulation were very similar to capsule formulation. The intra-subject variability in C_{max} and AUC_{0-24} were 13.3% and 12.0%, respectively. Mean average steady-state concentration, T_{max} and mean fluctuation of peak-to-trough concentrations of desmethyldiltiazem were similar between 360 mg tablet and 360 mg extended release capsule.



CONCLUSIONS:

Mean steady-state C_{max}, AUC_{0-24}, $C_{average}$ of diltiazem, desacetyldiltiazem and desmethyldiltiazem were similar when administered as 360 mg extended release tablet or 360 mg extended release capsule administered night time in the fasted state.

The mean relative bioavailability of diltiazem at steady-state from the 360 mg extended release tablet was 97.6% compared to 360 mg extended release capsule. The mean ratios and 90% confidence intervals for C_{max} and AUC_{0-24} for diltiazem, desacetyldiltiazem and desmethyldiltiazem were contained within the bioequivalence limits of 0.80 and 1.25. The two formulations, 360 mg diltiazem extended release bead tablet and 360 mg diltiazem extended release capsule are bioequivalent with respect to diltiazem and its metabolites, desacetyldiltiazem and desmethyldiltiazem, at steady-state when administered night time in the fasted state.

STUDY 2434 (B00-515PK-DILG99)– 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 INVESTIGATOR AND SITE:

Bioavail Contract Research
Bioavail Corporation
Toronto, Ontario
CANADA

Volumes: 49-55

OBJECTIVE:

To compare the rate and extent of absorption of the diltiazem hydrochloride 360 mg extended release bead tablets following morning and evening administration in the fasted state.

FORMULATIONS:

Diltiazem hydrochloride extended release bead tablets –360 mg (Lot #: 001004) manufactured by Bioavail Technologies, Ltd. Batch size: — tablets

STUDY DESIGN:

This was a randomized, open-label, two-treatment, two-period, single-dose, morning and evening administration, crossover study conducted under fasted conditions in 24 healthy non-smoking, male (n=20) and female (n=4), volunteers between 20 and 45 years of age (mean: 31 yr) weighing between 117 and 195 lb (mean: 167 lb). Subject # 1 was dismissed pre-dose and # 23 withdrew post dose, Period 1. Pharmacokinetic and statistical analyses were conducted on 22 evaluable subjects. On Day 1 subjects were randomized to receive, **Treatment A:** 360 mg diltiazem hydrochloride extended release bead tablet administered at 7:00 AM following an overnight fast of 10 hours, or **Treatment B:** 360 mg diltiazem hydrochloride extended release bead tablet administered at 10:00 PM following a fast of at least 2 hours. In Period 2, subjects crossed over to receive alternate treatment following a 1-week washout interval.

ASSAY:

Compound	Matrix	Method	Range (ng/ml)	Linearity	LOQ (ng/ml)	QC (ng/ml)	CV%	Accuracy (% Bias)
Diltiazem	Plasma	HPLC/UV					7.6 4.0 2.7 3.6	

Desacetyl diltiazem	Plasma	HPLC/UV		7.6 5.1 2.4 3.4	
Desmethyl diltiazem	Plasma	HPLC/UV		11.3 3.9 2.1 2.1	

Sample Collection:

Blood samples were taken for assessment of pharmacokinetic parameters of diltiazem, desacetyldiltiazem and desmethyldiltiazem, predose and at 2, 3, 4, 6, 8, 10, 11, 12, 13, 14, 15, 16, 18, 20, 24, 30, 36, 42 and 48 hours post dose in each period.

RESULTS

The mean pharmacokinetic parameters of diltiazem and its metabolites-desacetyldiltiazem and desmethyldiltiazem, obtained following administration of a 360-mg diltiazem extended release bead tablet administered at 7:00 AM and at 10:00 PM in t fasted state are presented in the following table.

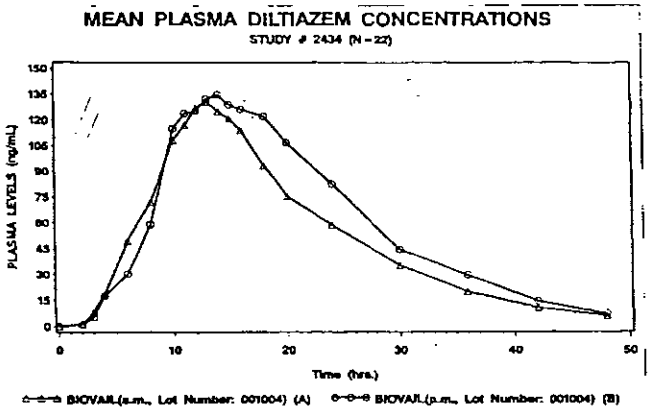
Table 1: Mean (SD) Pharmacokinetic Parameters of Diltiazem, Desacetyldiltiazem and Desmethyldiltiazem

	DILTIAZEM			
Parameter	**360 mg TABLET 7:00 AM FASTING**	**360 mg TABLET 10:00 PM FASTING**	**POINT ESTIMATE**	**90% CI**
C_{max} (ng/ml)	139.35 (69.30)	147.62 (51.41)	0.900	0.780 – 1.04
AUC_{0-last} (ng.h/ml)	2347.65 (964.57)	2741.92 (1048.18)	0.845	0.763 – 0.936
AUC_{0-inf} (ng.h/ml)	2421.08 (1000.29)	2830.36 (1114.81)	0.847	0.765 – 0.938
T_{max} (h)	13.09 (1.48)	13.92 (2.41)		
$T_{1/2}$ (h)	7.17 (1.65)	6.86 (0.98)		
	DESACETYLDILTIAZEM			
Parameter	**360 mg TABLET 7:00 AM FASTING**	**360 mg TABLET 10:00 PM FASTING**	**POINT ESTIMATE**	**90% CI**
C_{max} (ng/ml)	17.53 (15.96)	17.78 (15.71)	0.970	0.885 – 1.06
AUC_{0-last} (ng.h/ml)	461.68 (509.56)	477.20 (482.64)	0.921	0.834 – 1.02
AUC_{0-inf} (ng.h/ml)	418.66 (399.38)	619.16 (751.84)	0.911	0.815 – 1.02
T_{max} (h)	19.82 (4.85)	20.00 (2.96)		
$T_{1/2}$ (h)	9.65 (2.27)	10.81 (3.64)		
	DESMETHYLDILTIAZEM			
Parameter	**360 mg TABLET 7:00 AM FASTING**	**360 mg TABLET 10:00 PM FASTING**	**POINT ESTIMATE**	**90% CI**

C_{max} (ng/ml)	44.90 (11.39)	49.05 (9.37)	0.904	0.821 – 0.995
AUC_{0-last} (ng.h/ml)	995.13 (277.86)	1153.44 (268.88)	0.854	0.791 – 0.923
AUC_{0-inf} (ng.h/ml)	1076.01 (320.28)	1266.28 (343.76)	0.839	0.776 – 0.907
T_{max} (h)	15.09 (1.97)	15.42 (3.18)		
$T_{1/2}$ (h)	9.61 (1.75)	9.86 (2.00)		

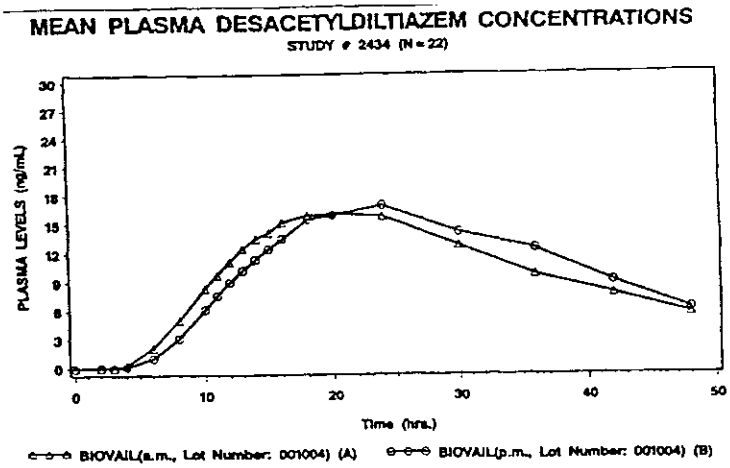
Diltiazem:

Mean C_{max} and AUC of diltiazem from the 360 mg extended release tablet administered in the morning were not bioequivalent to evening administration in the fasted state. Mean C_{max} and AUC of diltiazem from the extended release tablet formulation in the morning were 10% and 15% lower than evening administration. The relative bioavailability of diltiazem following morning administration from the tablet formulation was 85% compared to evening administration. The lower limit of the 90% confidence intervals for C_{max} and AUC were 0.780 and 0.765, which were below the bioequivalence limit of 0.80. The intra-subject variability in C_{max} and AUC_{inf} were 27.5% and 19.6%, respectively. Mean T_{max} and $T_{1/2}$ of diltiazem were similar following morning and evening administration in the fasted state.



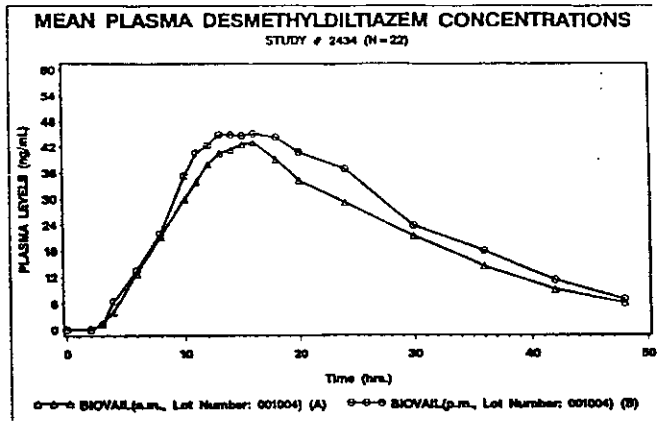
Desacetyldiltiazem:

Mean C_{max} and AUC of desacetyldiltiazem from the 360 mg extended release tablet administered in the morning were bioequivalent to evening administration in the fasted state. Mean C_{max} and AUC following morning administration were lower by 3% and 9%, respectively, compared to evening administration of the tablet formulation. The intra-subject variability in C_{max} and AUC_{inf} were 17.5% and 19.7%, respectively. Mean desacetyldiltiazem T_{max} was similar but mean $T_{1/2}$ was shorter by 1 h when the tablet formulation was administered in the morning compared to the evening in the fasted state.



Desmethyldiltiazem:

Mean C_{max} of desmethyldiltiazem following administration of 360 mg extended release tablet in the morning was bioequivalent to evening administration in the fasted state, however, mean AUC of desmethyldiltiazem was not bioequivalent to evening administration. The lower limit of the 90% confidence interval for AUC following morning administration was 0.776, which is below the bioequivalence limit of 0.80. Mean C_{max} and AUC_{inf} of desmethyldiltiazem from the extended tablet in the morning was lower by 10% and 16%, respectively, compared to evening administration. The intra-subject variability in C_{max} and AUC_{inf} were 18.4% and 14.5%, respectively. Mean T_{max} and $T_{1/2}$ of desmethyldiltiazem were similar from the tablet formulation following morning and evening administration.



CONCLUSIONS:

Mean C_{max} and AUC of diltiazem from the 360 mg extended release tablet administered in the morning were not bioequivalent to evening administration in the fasted state. Mean C_{max} and AUC of diltiazem from the extended release tablet formulation in the morning were 10% and 15% lower than evening administration. The relative bioavailability of diltiazem was following morning administration from the tablet formulation was 85%

compared to evening administration. However, mean C_{max} and AUC of desacetyldiltiazem from the 360 mg extended release tablet administered in the morning were bioequivalent to evening administration in the fasted state. Mean C_{max} of desmethyldiltiazem following administration of 360 mg extended release tablet in the morning was bioequivalent to evening administration in the fasted state, however, mean AUC of desmethyldiltiazem was not bioequivalent to evening administration. The lower limit of the 90% confidence interval for AUC following morning administration was 0.776, which is below the bioequivalence limit of 0.80.

STUDY 2463 (B01-530PK-DILG99)– A TWO-WAY, CROSSOVER, OPEN-LABEL, MULTIPLE-DOSE, FASTING, COMPARATIVE BIOAVAILABILITY STUDY BETWEEN 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 INVESTIGATOR AND SITE:

Bioavail Contract Research
460 Comstock Road
Toronto, Ontario
Canada M1L 4R6

Volumes: 55 to 64

OBJECTIVE:

To compare rate and extent of absorption of diltiazem hydrochloride 2 x 180 mg extended release bead capsules administered in the morning (8:00 AM) and evening (10:00 PM) under steady state fasting conditions.

FORMULATION:

Diltiazem hydrochloride extended release capsules – 180 mg (Lot #: D000199CL manufactured by Bioavail Corporation. Batch size: —

STUDY DESIGN:

This was a randomized, open-label, two-treatment, multiple-dose, crossover, single center study in 28 normal, healthy, non-smoking male (n=14) and female (n=14) volunteers under fasting conditions. The volunteers were between 19 and 46 years of age (mean: 33 yr) and weighed between 113 and 205 lb (mean: 159 lb). Subject # 11 and 12 withdrew from the study and Subject # 17, 19, 22, 23 and 28 were dismissed from the study. Pharmacokinetic and statistical analyses were conducted on 21 evaluable subjects. On Day 1 of Period I, subjects were randomized to receive either, **Treatment A:** 2 x 180 mg diltiazem hydrochloride extended release capsules administered at 8:00 AM following an overnight fast of at least 10 hours, or **Treatment B:** 2 x 180 mg diltiazem hydrochloride extended release capsules administered at 10:00 PM following a fast of at least 2 hours. Each formulation was administered once-daily orally at either 8:00 AM or 10:00 PM following in the fasted state on Days 1, 2, 3, 4, 5, 6 and 7. Following a washout interval of 1 week between treatments all subjects received alternate formulation in Period II.

ASSAY:

Compound	Matrix	Method	Range (ng/ml)	Linearity	LOQ (ng/ml)	QC (ng/ml)	CV%	Accuracy (% Bias)
Diltiazem	Plasma	HPLC/UV	[			]	6.6	[ ]

							3.7 3.1 3.9	
Desacetyl diltiazem	Plasma	HPLC/UV					11.2 5.4 3.0 3.7	
Desmethyl diltiazem	Plasma	HPLC/UV					7.8 3.9 2.9 3.6	

Sample Collection:

Blood samples were taken for assessment of pharmacokinetic parameters of diltiazem, desacetyldiltiazem and desmethyldiltiazem pre-dose on Days 1, 4, 5, 6, 7 and after dosing at 2, 3, 4, 6, 8, 10, 11, 12, 13, 14, 15, 16, 18, 20, 22 and 24 hours on Day 7 in each period.

RESULTS

The following table lists the mean steady-state pharmacokinetic parameters of diltiazem, desacetyldiltiazem and desmethyldiltiazem obtained following multiple oral administration of 2 x 180 mg diltiazem extended release capsules in the morning (8:00 AM) or in the evening (10:00 PM) in the fasted state.

Table 1: Mean (SD) Steady-state Pharmacokinetic Parameters of Diltiazem & Metabolites

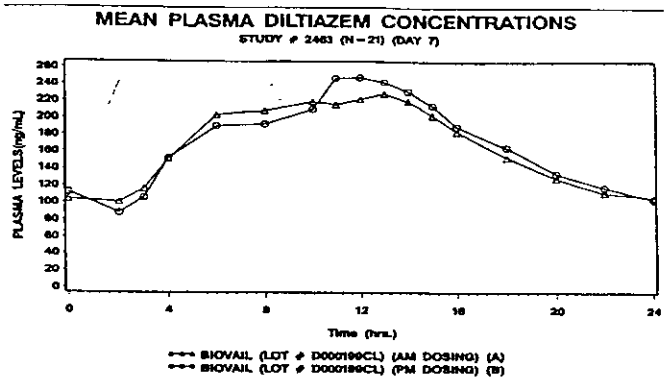
	Diltiazem		Desacetyldiltiazem		Desmethyldiltiazem	
Parameter	2 x 180 mg Capsule 8:00 AM	2 x 180 mg Capsule 10:00 PM	2 x 180 mg Capsule 8:00 AM	2 x 180 mg Capsule 10:00 PM	2 x 180 mg Capsule 8:00 AM	2 x 180 mg Capsule 10:00 PM
C_{max} (ng/ml)	251.29 (87.72)	260.87 (81.86)	37.60 (28.80)	38.33 (31.58)	83.40 (23.49)	78.48 (16.81)
AUC_{0-24} (ng.h/ml)	4008.16 (1507.24)	4074.46 (1531.92)	741.28 (577.70)	702.35 (584.94)	1496.75 (418.49)	1416.76 (338.77)
C_{min} (ng/ml)	107.00 (48.86)	104.72 (50.04)	29.31 (21.59)	28.80 (29.11)	49.50 (16.23)	46.28 (14.05)
T_{max} (h)	10.48 (3.06)	11.53 (2.47)	13.33 (3.77)	14.53 (2.66)	12.77 (2.45)	12.39 (2.67)
$C_{average}$ (ng/ml)	167.01 (62.80)	169.77 (63.83)	30.89 (24.07)	29.26 (24.37)	62.36 (17.44)	59.03 (14.12)
Fluctuation (%)	89.42 (30.99)	98.05 (36.45)	27.15 (14.47)	45.62 (28.06)	54.98 (18.57)	56.65 (23.91)
$AUC_{6\ AM\ -\ 12\ PM}$ (ng.h/ml)	657.68 (290.20)	1370.09 (443.33)	164.85 (142.33)	188.38 (138.23)	275.85 (84.42)	415.48 (85.55)
$C_{ss,\ 6\ AM\ -\ 12\ PM}$ (ng/ml)	109.61 (48.37)	228.35 (73.89)	27.48 (23.72)	31.40 (23.04)	45.97 (14.07)	69.25 (14.26)

Table 2: Mean Ratios and 90% Confidence Intervals for Diltiazem and Metabolites

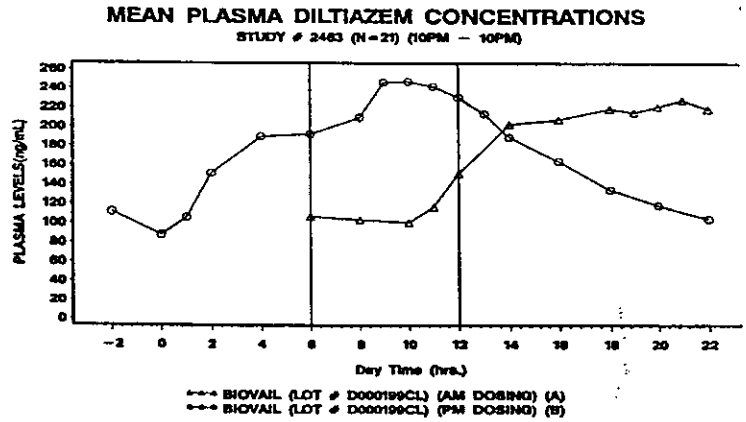
Parameter	Diltiazem		Desacetyldiltiazem		Desmethyldiltiazem	
	Ratio 8 AM/10 PM	90% CI	Ratio 8 AM/10 PM	90% CI	Ratio 8 AM/10 PM	90% CI
C_{max}	0.950	0.859 – 1.05	0.991	0.912 – 1.08	1.05	0.983 – 1.11
AUC_{0-24}	0.975	0.900 – 1.06	1.07	0.988 – 1.15	1.05	0.985 – 1.11
$AUC_{6\ AM-12\ PM}$	0.461	0.424 – 0.500	0.825	0.763 – 0.892	0.650	0.612 – 0.691

Diltiazem:

Mean steady-state C_{max} and AUC_{0-24} of diltiazem from 2 x 180 mg extended release capsules administered in the morning were bioequivalent to those administered in the evening in the fasted state. Mean steady-state C_{max} and AUC_{0-24} of diltiazem following morning administration were slightly lower by 5% and 2.5%, respectively, compared to evening administration. The intra-subject variability in C_{max} and AUC_{0-24} were 18.5% and 14.9%, respectively. Mean $C_{average}$ and fluctuation of peak-to-trough concentrations of diltiazem were similar when administered in the morning and evening. The T_{max} of diltiazem from the tablet formulation occurred about 1 hour later in the evening.

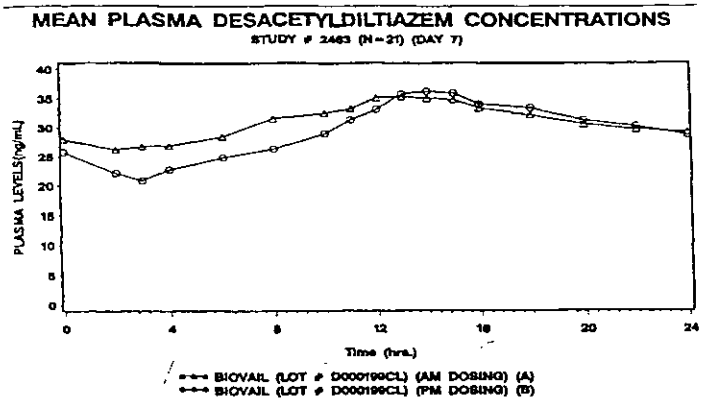


Mean $C_{ss,6AM-12PM}$ and $AUC_{6AM-12PM}$ of diltiazem were 52% and 54% lower, respectively, when the capsules were administered in the morning compared to evening administration.

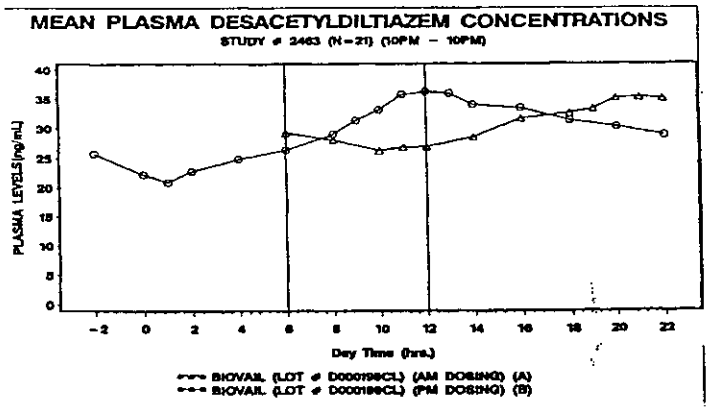


Desacetyldiltiazem:

Mean steady-state C_{max} and AUC_{0-24} of desacetyldiltiazem from 2 x 180 mg extended release capsules administered in the morning were bioequivalent to those administered in the evening in the fasted state. Mean steady-state C_{max} and AUC_{0-24} of desacetyldiltiazem following morning administration were similar or slightly higher by 7%, respectively, compared to evening administration. Mean $C_{average}$ was similar but mean fluctuation of peak-to-trough concentrations of desacetyldiltiazem was 40% lower with morning administration compared to evening. The intra-subject variability in C_{max} and AUC_{0-24} were 15.3% and 14.5%, respectively. The T_{max} of desacetyldiltiazem from the tablet formulation occurred about 1 hour later following evening administration.



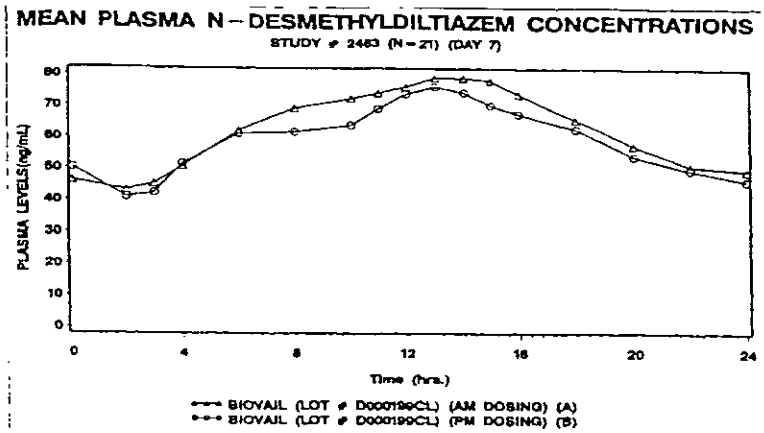
Mean $C_{ss,6AM-12PM}$ of desacetyldiltiazem was similar but $AUC_{6AM-12PM}$ of desacetyldiltiazem was 17% lower when the capsules were administered in the morning compared to evening administration.



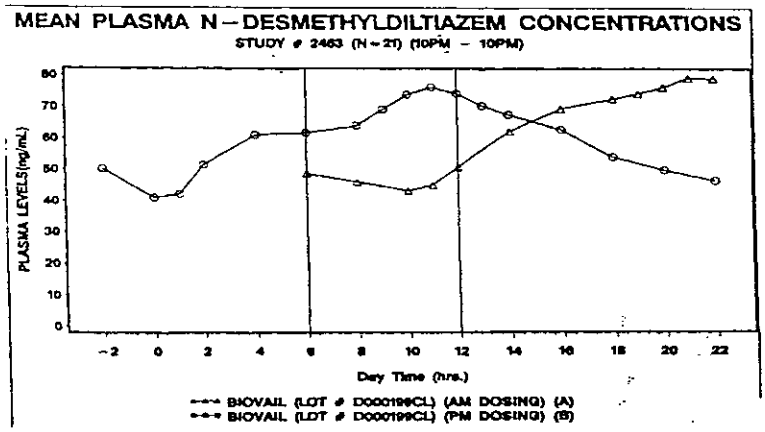
Desmethyldiltiazem:

Mean steady-state C_{max} and AUC_{0-24} of desmethyldiltiazem from 2 x 180 mg extended release capsules administered in the morning were bioequivalent to those administered in the evening in the fasted state. Mean steady-state C_{max} and AUC_{0-24} of desmethyldiltiazem following morning administration were slightly higher by 5%, respectively, compared to evening administration. The intra-subject variability in C_{max} and AUC_{0-24} were 11.6% and 10.9%, respectively. Mean $C_{average}$, T_{max} and mean

fluctuation of peak-trough concentrations of desmethyldiltiazem were similar with morning and evening administration.



Mean $C_{ss,6AM-12PM}$ and $AUC_{6AM-12PM}$ of desmethyldiltiazem were lower by 34% and 35%, respectively, when the capsules were administered in the morning compared to evening administration.



CONCLUSIONS:

Mean steady-state C_{max} and AUC_{0-24} of diltiazem, desacetyldiltiazem and desmethyldiltiazem from 2 x 180 mg extended release capsules administered in the morning were bioequivalent to those administered in the evening in the fasted state.

Mean $C_{ss,6AM-12PM}$ and $AUC_{6AM-12PM}$ of diltiazem were 52% and 54% lower, respectively, and mean $C_{ss,6AM-12PM}$ and $AUC_{6AM-12PM}$ of desmethyldiltiazem were lower by 34% and 35%, respectively, when the capsules were administered in the morning compared to evening administration. However, mean $C_{ss,6AM-12PM}$ of desacetyldiltiazem was similar but $AUC_{6AM-12PM}$ of desacetyldiltiazem was 17% lower when the capsules were administered in the morning compared to evening administration.

STUDY 2438 (B00-518PK-DILG99)– 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

STUDY INVESTIGATOR AND SITE:

Bioavail Contract Research
Bioavail Corporation
Toronto, Ontario
CANADA

Volumes: 99-

OBJECTIVE:

To generate in vivo pharmacokinetic data to establish in vitro/in vivo correlation and validate dissolution specifications for the test product, Diltiazem HCl 360 mg Extended Release Bead Tablets intended for marketing.

FORMULATIONS:

1. Diltiazem hydrochloride extended release bead tablets –360 mg (Lot #: 001004) manufactured by Bioavail Technologies, Ltd. Batch size: — tablets.
2. Diltiazem hydrochloride extended release bead tablets –360 mg (Lot #: 010309) manufactured by Bioavail Technologies, Ltd. Batch size: tablets.
3. Diltiazem hydrochloride extended release bead tablets –360 mg (Lot #: 010207) manufactured by Bioavail Technologies, Ltd. Batch size: tablets.
4. Diltiazem hydrochloride USP – Lot #: 10000299, manufactured by Bioavail Corporation, Batch size: .

STUDY DESIGN:

This was a randomized, open-label, four-way, single-dose, crossover study conducted under fasted conditions in 16 healthy non-smoking male volunteers between 23 and 46 years of age (mean: 30 yr) weighing between 140 and 194 lb (mean: 164 lb). Subject # 8 and 12 withdrew from the study, while, Subject # 3, 4, 6 and 7 were dismissed from the study because of adverse events or low hemoglobin levels. Pharmacokinetic and statistical analyses were conducted on 10 evaluable subjects. On Day 1 subjects were randomized to receive, **Treatment A:** 360 mg diltiazem hydrochloride extended release bead tablet, Lot # 010309 administered at 7:30 AM following an overnight fast of 10 hours, or **Treatment B:** 360 mg diltiazem hydrochloride extended release bead tablet, Lot # 001014 administered at 7:30 AM following an overnight fast of 10 hours, or **Treatment C:** 360 mg diltiazem hydrochloride extended release bead tablet, Lot # 010207 administered at 7:30 AM following an overnight fast of 10 hours, or **Treatment D:** 120 mg diltiazem hydrochloride as 50 ml solution administered at 7:30 AM following

an overnight fast of 10 hours. Consecutive treatments were separated by a wash-out interval of 1 week. Subjects crossed over to receive alternate treatments in a randomized pre-determined sequence.

ASSAY:

Compound	Matrix	Method	Range (ng/ml)	Linearity	LOQ (ng/ml)	QC (ng/ml)	CV%	Accuracy (% Bias)
Diltiazem	Plasma	HPLC/UV					6.0 9.6 5.2 4.9	
Desacetyl diltiazem	Plasma	HPLC UV					8.4 7.9 4.7 4.5	
Desmethyl diltiazem	Plasma	HPLC UV					11.1 4.8 1.8 2.5	

For Treatments A, B and C, blood samples were taken for assessment of pharmacokinetic parameters of diltiazem, desacetyldiltiazem and desmethyldiltiazem, predose and at 2, 3, 4, 6, 8, 10, 11, 12, 13, 14, 16, 20, 24, 30, 36, 42 and 48 hours post dose in each period. For Treatment D (solution) blood samples were collected predose and at 0.5, 1, 1.5,2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 30, 36, 42 and 48 hours post dose.

RESULTS

The mean pharmacokinetic parameters of diltiazem and its metabolites-desacetyldiltiazem and desmethyldiltiazem, obtained following administration of a 360-mg diltiazem extended release bead tablets of different lots and diltiazem HCl solution in the morning in the fasted state are presented in the following table.

Table 1: Mean (SD) Pharmacokinetic Parameters of Diltiazem, Desacetyldiltiazem and Desmethyldiltiazem

	DILTIAZEM			
Parameter	**360 mg TABLET Lot 010309 FASTING**	**360 mg TABLET Lot 001004 FASTING**	**360 mg TABLET Lot 010207 FASTING**	**120 mg SOLUTION FASTING**
C_{max} (ng/ml)	146.00 (91.89)	131.53 (117.27)	127.45 (100.72)	194.14 (104.15)
AUC_{0-last} (ng.h/ml)	2792.79 (1489.39)	2561.32 (1963.54)	2620.60 (1966.01)	1031.60 (582.48)
AUC_{0-inf} (ng.h/ml)	2867.78 (1515.89)	2661.60 (2025.88)	2846.88 (2088.82)	1063.00 (583.62)
T_{max} (h)	14.10 (2.13)	11.60 (3.86)	15.10 (3.35)	0.90 (0.46)
$T_{1/2}$ (h)	6.47 (0.99)	6.96 (0.77)	7.37 (1.54)	4.98 (1.49)
	DESACETYLDILTIAZEM			
Parameter	**360 mg TABLET Lot 010309**	**360 mg TABLET Lot 001004**	**360 mg TABLET Lot 010207**	**120 mg SOLUTION**

	FASTING	FASTING	FASTING	FASTING
C_{max} (ng/ml)	12.77 (5.87)	11.30 (7.00)	11.48 (5.58)	6.60 (2.65)
AUC_{0-last} (ng.h/ml)	313.25 (138.45)	280.43 (177.55)	303.90 (152.52)	76.64 (39.71)
AUC_{0-inf} (ng.h/ml)	346.50 (162.20)	317.14 (202.13)	346.41 (184.33)	88.31 (40.90)
T_{max} (h)	20.40 (5.40)	17.60 (4.60)	22.50 (5.44)	4.20 (0.63)
$T_{1/2}$ (h)	9.36 (1.63)	9.66 (1.69)	11.15 (3.12)	6.64 (1.72)

	DESMETHYLDILTIAZEM			
Parameter	**360 mg TABLET Lot 010309 FASTING**	**360 mg TABLET Lot 001004 FASTING**	**360 mg TABLET Lot 010207 FASTING**	**120 mg SOLUTION FASTING**
C_{max} (ng/ml)	41.94 (14.31)	35.85 (18.87)	33.21 (13.48)	38.23 (8.26)
AUC_{0-last} (ng.h/ml)	993.95 (272.01)	867.13 (486.31)	856.95 (333.28)	423.02 (143.45)
AUC_{0-inf} (ng.h/ml)	1087.32 (303.01)	985.02 (58.09)	998.04 (379.42)	461.37 (144.30)
T_{max} (h)	15.40 (1.35)	15.31 (2.57)	16.60 (3.27)	1.60 (0.97)
$T_{1/2}$ (h)	9.52 (1.58)	10.86 (1.82)	11.07 (2.58)	7.37 (1.57)

Table 2: Mean Ratios and 90% Confidence Intervals for Diltiazem and Metabolites

	Diltiazem		Desacetyldiltiazem		Desmethyldiltiazem	
Parameter	**Ratio Lot 010309/ Lot 001004**	**90% CI**	**Ratio Lot 010309/ Lot 001004**	**90% CI**	**Ratio Lot 010309/ Lot 001004**	**90% CI**
C_{max}	1.27	0.992 – 1.61	1.28	0.933 – 1.76	1.25	1.03 – 1.54
AUC_{inf}	1.27	0.905 – 1.78	1.27	0.83 – 1.86	1.27	0.958 – 1.67

	Diltiazem		Desacetyldiltiazem		Desmethyldiltiazem	
Parameter	**Ratio Lot 010207/ Lot 001004**	**90% CI**	**Ratio Lot 010207/ Lot 001004**	**90% CI**	**Ratio Lot 010207/ Lot 001004**	**90% CI**
C_{max}	1.04	0.826 – 1.32	1.09	0.805 – 1.48	0.989	0.815 – 1.20
AUC_{inf}	1.10	0.788 – 1.54	1.15	0.792 – 1.67	1.08	0.817 – 1.41

Diltiazem:

Mean C_{max} and AUC of diltiazem from the 360 mg extended release tablet Lot 010309 was not bioequivalent to Lot 001004. Mean Cmax and AUC were both 27% higher from Lot 010309. Similarly, mean C_{max} and AUC of diltiazem from the 360 mg extended release tablet Lot 010207 was not bioequivalent to Lot 001004. Mean Cmax and AUC were higher by 4% and 10%, respectively, but the confidence 90% confidence interval was not contained within the bioequivalence limits of 0.8 and 1.25.

The mean Cmax and AUC of diltiazem from the solution formulation was 194 ng/ml and 1063 ng.h/ml, respectively. The time to peak concentration occurred by 1 hour and the half-life after solution administration was 5 h. The difference in $T_{1/2}$ between solution (5

hours) and after sustained release tablet administration (6-7 hours) indicates dissolution rate limited absorption in the sustained release preparations.

Desacetyldiltiazem:

Mean C_{max} and AUC of desacetyldiltiazem from the 360 mg extended release tablet Lot 010309 was not bioequivalent to Lot 001004. Mean Cmax and AUC were 27% and 28% higher, respectively, from Lot 010309 compared to Lot 001004. Similarly, mean C_{max} and AUC of desacetyldiltiazem from the 360 mg extended release tablet Lot 010207 was not bioequivalent to Lot 001004. Mean Cmax and AUC were higher by 9% and 15%, respectively, but the 90% confidence interval was not contained within the bioequivalence limits of 0.8 and 1.25.

Mean Cmax of desacetyldiltiazem was 6.6 ng/ml which occurred at 4 hours post dose. The half-life of desacetyldiltiazem were different between solution (6.6 hours) and sustained release tablets (9-11 hours).

Desmethyldiltiazem:

Mean C_{max} and AUC of desmethyldiltiazem from the 360 mg extended release tablet Lot 010309 was not bioequivalent to Lot 001004. Mean Cmax and AUC were 25% and 27% higher from Lot 010309, respectively. Mean AUC of desmethyldiltiazem from the 360 mg extended release tablet Lot 010207 was not bioequivalent to Lot 001004. Mean Cmax was similar and bioequivalent while mean AUC was 8% higher but the confidence 90% confidence interval was not contained within the bioequivalence limits of 0.8 and 1.25.

Mean Cmax of desmethyldiltiazem was 38 ng/ml which occurred at 1.6 hours post dose. The half-life of desmethyldiltiazem were different between solution (7 hours) and sustained release tablets (9-11 hours).

The sponsor attempted to construct an in vivo-in vitro correlation but the correlation was poor probably because of the similarity of the different lots of diltiazem.

CONCLUSIONS:

Mean C_{max} and AUC of diltiazem from Lots 010309 and Lot 010207 were not bioequivalent to the reference lot of 001004. An attempt by the sponsor to construct an in vivo-in vitro correlation was not successful.

STUDY 2464 (B01-531PK-DILG99)– A TWO-WAY, CROSSOVER, OPEN-LABEL, MULTIPLE-DOSE, FASTING, COMPARATIVE BIOAVAILABILITY STUDY BETWEEN DILTIAZEM HCl EXTENDED RELEASE BEAD TABLETS (360 mg) WITH EVENING DRUG ADMINISTRATION (10:00 P.M.) AND DILTIAZEM HCl EXTENDED RELEASE BEAD TABLETS (360 mg) WITH MORNING (8:00 A.M.) DRUG ADMINISTRATION IN NORMAL HEALTHY NON-SMOKING MALE AND FEMALE SUBJECTS

STUDY INVESTIGATOR AND SITE:

Bioavail Contract Research
460 Comstock Road
Toronto, Ontario
Canada M1L 4R6

Volumes: 2 to 12

OBJECTIVE:

To compare rate and extent of absorption of diltiazem hydrochloride 360 mg extended release bead tablets administered in the evening (10:00 PM) and morning (8:00 AM) under steady state fasting conditions in normal healthy non-smoking male and female volunteers.

FORMULATION:

Diltiazem hydrochloride extended release bead tablets – 360 mg (Lot #: 001004) manufactured by Bioavail Corporation.

STUDY DESIGN:

This was a randomized, open-label, two-treatment, multiple-dose, crossover, single center study in 28 normal, healthy, non-smoking male (n=23) and female (n=5) volunteers under fasting conditions. The volunteers were between 18 and 46 years of age (mean: 32 yr) and weighed between 128 and 200 lb (mean: 159 lb). Subject # 4 and 22 discontinued from the study. Pharmacokinetic and statistical analyses were conducted on 26 evaluable subjects. On Day 1 of Period I, subjects were randomized to receive either, **Treatment A:** 360 mg diltiazem hydrochloride extended release bead tablet administered at 8:00 AM following an overnight fast of at least 10 hours (reference), or **Treatment B:** 360 mg diltiazem hydrochloride extended release bead tablet administered at 10:00 PM following a fast of at least 2 hours (test). In each Period, 360 mg diltiazem hydrochloride was administered once-daily orally at either 8:00 AM or 10:00 PM on Days 1, 2, 3, 4, 5, 6 and 7. Following a washout interval of 1 week between treatments all subjects received extended release bead tablets at the alternate time in Period II.

ASSAY:

Compound	Matrix	Method	Range	Linearity	LOQ	QC	CV%	Accuracy

			(ng/ml)	(ng/ml)	(ng/ml)		(% Bias)
Diltiazem	Plasma	HPLC/UV				7.5 4.9 4.8 3.8	
Desacetyl diltiazem	Plasma	HPLC/UV				8.4 4.3 5.7 4.8	
Desmethyl diltiazem	Plasma	HPLC/UV				5.3 3.0 1.9 2.0	

Sample Collection:

Blood samples were taken for assessment of pharmacokinetic parameters of diltiazem, desacetyldiltiazem and desmethyldiltiazem pre-dose on Days 1, 4, 5, 6, 7 and after dosing at 2, 3, 4, 6, 8, 10, 11, 12, 13, 14, 15, 16, 18, 20, 22 and 24 hours on Day 7 in each period.

RESULTS

The following table lists the mean steady-state pharmacokinetic parameters of diltiazem, desacetyldiltiazem and desmethyldiltiazem obtained following multiple oral administration of 360 mg diltiazem extended release bead tablets in the fasted state in the morning (8:00 AM) or in the evening (10:00 PM).

Table 1: Mean (SD) Steady-state Pharmacokinetic Parameters of Diltiazem & Metabolites

	Diltiazem		Desacetyldiltiazem		Desmethyldiltiazem	
Parameter	360 mg ER Tablet 8:00 AM (REF)	360 mg ER Tablet 10:00 PM (TEST)	360 mg ER Tablet 8:00 AM (REF)	360 mg ER Tablet 10:00 PM (TEST)	360 mg ER Tablet 8:00 AM (REF)	360 mg ER Tablet 10:00 PM (TEST)
C_{max} (ng/ml)	274.48 (149.02)	290.90 (93.38)	29.33 (26.36)	35.71 (35.61)	72.32 (23.17)	77.61 (16.08)
AUC_{0-24} (ng.h/ml)	3690.47 (1449.35)	4251.20 (1218.91)	553.33 (532.59)	670.36 (743.75)	43.22 (18.66)	53.95 (14.88)
$AUC_{6AM-12PM}$ (ng.h/ml)	607.30 (260.69)	1369.67 (430.65)	138.67 (142.46)	164.47 (177.19)	252.57 (94.11)	391.97 (82.66)
C_{min} (ng/ml)	96.14 (51.71)	125.94 (43.30)	19.31 (16.46)	28.13 (35.58)	43.22 (18.66)	53.95 (14.88)
T_{max} (h)	11.62 (2.90)	12.88 (1.31)	13.62 (5.40)	15.51 (3.98)	12.85 (2.81)	14.19 (1.96)
$C_{average}$ (ng/ml)	153.77 (60.39)	177.13 (50.79)	23.06 (22.19)	27.93 (30.99)	53.14 (17.68)	59.73 (13.28)
Fluctuation (%)	118.94 (70.76)	93.64 (29.48)	41.92 (29.53)	36.73 (21.13)	58.82 (31.23)	40.69 (16.69)
C_{ss} (ng/ml)	101.22 (43.45)	228.28 (71.78)	23.11 (23.74)	27.41 (29.53)	42.10 (15.68)	65.33 (13.78)

MRT (h)	11.85 (1.24)	13.04 (0.60)	12.16 (1.06)	12.84 (0.47)	12.29 (0.88)	12.78 (0.47)

Table 2: Mean Ratios and 90% Confidence Intervals for Diltiazem and Metabolites

	Diltiazem		Desacetyldiltiazem		Desmethyldiltiazem	
Parameter	Ratio 10 PM/8 AM	90% CI	Ratio 10 PM/8 AM	90% CI	Ratio 10 PM/8 AM	90% CI
C_{max}	1.16	0.980 – 1.37	1.15	1.01 – 1.30	1.12	0.999 – 1.26
AUC_{0-24}	1.22	1.03 – 1.45	1.12	0.987 – 1.27	1.18	1.05 – 1.33
$AUC_{6\ AM-12\ PM}$	2.42	2.00 – 2.93	1.20	1.05 – 1.37	1.66	1.46 – 1.88

Diltiazem:

Mean steady-state C_{max} and AUC_{0-24} of diltiazem from 360 mg extended release bead tablets administered in the fasted state in the morning were not bioequivalent to those administered in the evening. Mean steady-state C_{max} and AUC_{0-24} of diltiazem following evening (10 PM) administration was higher by 16% and 22%, respectively, compared to morning administration. The intra-subject variability in C_{max} and AUC_{0-24} were 35% and 36%, respectively. Similarly, mean $C_{average}$ and fluctuation of peak-to-trough concentrations of diltiazem were higher following evening administration. The T_{max} of diltiazem in the evening however occurred 1 hour later compared to morning administration.

Mean $AUC_{6AM-12PM}$ of diltiazem was 142% higher following evening administration compared to morning administration.

Desacetyldiltiazem:

Mean steady-state C_{max} and AUC_{0-24} of desacetyldiltiazem from 360 mg extended release bead tablet administered in the morning was not bioequivalent to those administered in the evening. Mean steady-state C_{max} and AUC_{0-24} of desacetyldiltiazem following evening administration was higher by 15% and 12%, respectively, compared to morning administration. Mean $C_{average}$ was slightly lower but mean fluctuation of peak-to-trough concentrations of desacetyldiltiazem was 14% higher with morning administration compared to evening. The intra-subject variability in C_{max} and AUC_{0-24} were 26% and 27%, respectively. The T_{max} of desacetyldiltiazem following evening administration occurred about 2 hours later compared to morning administration.

Mean $AUC_{6AM-12PM}$ of desacetyldiltiazem was 20% higher when the bead tablets were administered in the evening compared to morning administration.

Desmethyldiltiazem:

Mean steady-state C_{max} and AUC_{0-24} of desmethyldiltiazem from 360 mg extended release bead tablets administered in the morning were not bioequivalent to those administered in the evening in the fasted state. Mean steady-state C_{max} and AUC_{0-24} of desmethyldiltiazem following evening administration were higher by 12% and 18%, respectively, compared to morning administration. The intra-subject variability for both

C_{max} and AUC_{0-24} was 25%. Mean $C_{average}$ was slightly lower and T_{max} occurred 1 hour earlier following morning administration compared to evening. Mean fluctuation of desmethyldiltiazem concentrations was 45% higher when administered in the morning compared to evening administration.

Mean $AUC_{6AM-12PM}$ of desmethyldiltiazem was 66% higher when administered in the evening compared to morning administration.

CONCLUSIONS:

The pharmacokinetics of diltiazem and its metabolites administered in the morning (8 AM) were not bioequivalent to night time (10 PM) administration. Following night time administration of 360 mg extended release bead tablet mean steady-state C_{max} of diltiazem, desacetyldiltiazem and desmethyldiltiazem were higher by 16%, 15% and 12%, respectively, and AUC_{0-24} was higher by 22%, 12% and 18%, respectively, compared to morning (8:00 AM) administration in the fasted state.

Mean steady-state C_{max} and AUC_{0-24} of diltiazem, desacetyldiltiazem and desmethyldiltiazem were higher following evening 10 PM administration compared to morning 8 AM administration. Similarly, mean $AUC_{6AM-12PM}$ of diltiazem, desacetyldiltiazem and desmethyldiltiazem was higher by 142%, 20% and 66%, respectively, following evening administration compared to morning administration.

STUDY 2532 (B01-561PK-DILG99)– A TWO-WAY, CROSSOVER, OPEN-LABEL, SINGLE-DOSE, FASTING, COMPARATIVE BIOAVAILABILITY STUDY OF DILTIAZEM HCl EXTENDED RELEASE 360 mg BEAD TABLETS (MANUFACTURED AT STEINBACH, MANITOBA) VERSUS DILTIAZEM HCl EXTENDED RELEASE 360 mg BEAD TABLETS (MANUFACTURED AT CHANTILLY, VIRGINIA) IN NORMAL HEALTHY NON-SMOKING MALE SUBJECTS

STUDY INVESTIGATOR AND SITE:

Bioavail Contract Research
460 Comstock Road
Toronto, Ontario
Canada M1L 4R6

Volumes: 13 to 20

OBJECTIVE:

To compare rate and extent of absorption of single dose diltiazem hydrochloride 360 mg extended release bead tablet manufactured at 2 different sites, Steinbach, Canada and Chantilly, Virginia, under fasting conditions in normal healthy non-smoking male volunteers.

FORMULATION:

Diltiazem hydrochloride extended release bead tablets – 360 mg (Lot #: 01A176) manufactured by Bioavail Corporation, Manitoba, Canada.
Diltiazem hydrochloride extended release bead tablets – 360 mg (Lot #: 001004) manufactured by Bioavail Corporation Ltd., Chantilly, Virginia.

STUDY DESIGN:

This was a randomized, open-label, two-treatment, single-dose, crossover, single center study in 36 normal, healthy, non-smoking male volunteers under fasting conditions. The volunteers were between 21 and 55 years of age (mean: 33 yr) and weighed between 145 and 186 lb (mean: 167 lb). Subject # 19 withdrew from the study. Pharmacokinetic and statistical analyses were conducted on 35 evaluable subjects. On Day 1 of Period I, subjects were randomized to receive either, **Treatment A:** single dose of 360 mg diltiazem hydrochloride extended release bead tablet (manufactured in Steinbach, Canada) following an overnight fast of at least 10 hours, or **Treatment B:** single dose of 360 mg diltiazem hydrochloride extended release bead tablet (manufactured in Chantilly, Virginia) following an overnight fast of at least 10 hours. Following a washout interval of 1 week between treatments all subjects received the extended release bead tablet manufactured at the alternate site in Period II.

ASSAY:

Compound	Matrix	Method	Range (ng/ml)	Linearity	LOQ (ng/ml)	QC (ng/ml)	CV%	Accuracy (% Bias)
Diltiazem	Plasma	HPLC/UV					12.9 6.6 6.2 6.2	
Desacetyl diltiazem	Plasma	HPLC/UV					12.9 11 7.3 0.7	
Desmethyl diltiazem	Plasma	HPLC/UV					11.8 8.1 8.9 10.7	

Sample Collection:

Blood samples were taken for assessment of pharmacokinetic parameters of diltiazem, desacetyldiltiazem and desmethyldiltiazem pre-dose on Day 1 prior to dosing and at 2, 3, 4, 6, 8, 10, 11, 12, 13, 14, 15, 16, 18, 20, 24, 30, 36, 42 and 48 hours post dose in each period.

RESULTS

The following table lists the mean single dose pharmacokinetic parameters of diltiazem, desacetyldiltiazem and desmethyldiltiazem obtained following a single oral dose of 360 mg diltiazem extended release bead tablet manufactured in Steinbach, Canada or Chantilly, Virginia in the fasted state.

Table 1: Mean (%CV) Single Dose Pharmacokinetic Parameters of Diltiazem & Metabolites – Desacetyldiltiazem and desmethyldiltiazem

	Diltiazem		Desacetyldiltiazem		Desmethyldiltiazem	
Parameter	**360 mg ER Tablet Canada (test)**	**360 mg ER Tablet Virginia (reference)**	**360 mg ER Tablet Canada (test)**	**360 mg ER Tablet Virginia (reference)**	**360 mg ER Tablet Canada (test)**	**360 mg ER Tablet Virginia (reference)**
C_{max} (ng/ml)	147.77 (40.25)	142.53 (45.20)	17.50 (111.07)	16.50 (105.22)	44.19 (26.00)	42.36 (27.38)
AUC_{0-last} (ng.h/ml)	2857.95 (36.04)	2743.52 (42.98)	459.95 (135.97)	434.14 (130.71)	1068.95 (28.15)	1026.15 (28.78)
AUC_{0-inf} (ng.h/ml)	2977.57 (36.84)	2860.34 (42.79)	585.74 (176.62)	542.18 (167.26)	1190.85 (30.26)	1132.98 (30.02)
T_{max} (h)	14.34 (20.77)	14.40 (21.32)	20.26 (22.91)	19.80 (25.06)	16.12 (14.81)	16.63 (24.22)

$T_{1/2}$ (h)	7.15 (23.26)	7.15 (33.69)	10.93 (34.64)	10.32 (32.88)	10.22 (21.51)	9.54 (17.91)

Table 2: Mean Ratios and 90% Confidence Intervals for Diltiazem and Metabolites

	Diltiazem		Desacetyldiltiazem		Desmethyldiltiazem	
Parameter	Ratio Canada/Virg	90% CI	Ratio Canada/Virg	90% CI	Ratio Canada/Virg	90% CI
C_{max}	1.11	1.03 – 1.19	1.10	1.01-1.19	1.09	1.02-1.17
AUC_{0-t}	1.09	1.00 – 1.18	1.10	1.02-1.18	1.09	1.02-1.15

Diltiazem:

Mean C_{max} and AUC_{0-t} of diltiazem from 360 mg extended release bead tablets manufactured at the two manufacturing sites, Steinbach, Canada and Chantilly, Virginia were bioequivalent. The mean C_{max} and AUC_{0-t} of diltiazem manufactured at Steinbach, Canada were 11% and 9% higher respectively. The intra-subject variability of diltiazem manufactured at Steinbach, Canada in AUC_{0-t} and C_{max} were 18% and 20% respectively. The T_{max} of diltiazem manufactured at both manufacturing sites was 14 hours.

Desacetyldiltiazem:

Mean C_{max} and AUC_{0-t} of desacetyldiltiazem from 360 mg extended release bead tablet manufactured at the two manufacturing sites, Steinbach, Canada and Chantilly, Virginia were bioequivalent. The mean C_{max} and AUC_{0-t} compared to Chantilly, Virginia were 10% higher. The intra-subject variability in C_{max} and AUC_{0-t} were 20% and 18% respectively. The T_{max} of desacetyldiltiazem following administration of diltiazem manufactured at either site was 20 hours.

Desmethyldiltiazem:

Mean C_{max} and AUC_{0-24} of diltiazem from 360 mg extended release bead tablets manufactured at the two different manufacturing sites were bioequivalent. The mean C_{max} and AUC of diltiazem manufactured at Steinbach, Canada were 9% higher. The intra-subject variability for C_{max} and AUC_{0-t} were 16% and 15% respectively. The T_{max} of desmethyldiltiazem following administration of diltiazem manufactured at Steinbach, Canada was 16 hours compared to 17 hours at Chantilly, Virginia.

CONCLUSIONS:

The pharmacokinetics of diltiazem and its metabolites, desacetyldiltiazem and desmethyldiltiazem, following administration of a single dose of 360mg extended release bead tablet manufactured at the proposed site, Steinbach, Canada was bioequivalent to the diltiazem reference site, Chantilly, Virginia under fasting conditions.

The point estimates and their associated 90% confidence intervals met the bioequivalence goal criteria of 0.8 – 1.25. Based on results from the 35 subjects, the mean Cmax and

AUC of diltiazem manufactured at the proposed site was on average 10% higher compared to the reference site.

DISSOLUTION:

Dissolution Method:

In vitro dissolution testing of diltiazem extended release tablets comparing dissolution from 240 mg and 300 mg tablets to 360 mg extended release tablets - which were found to be bioequivalent to 2 x 180 mg extended release capsules in an in vivo bioequivalence study. Dissolution data was not provided for the proposed new strengths – 120 mg and 180 mg in any media. Testing was performed using 12 units each in USP Apparatus II (paddle) at a rotation speed of 100 rpm in 4 different dissolution media: water, acetate buffer pH 4.2, phosphate buffers pH 5.8 and pH 6.8. Dissolution samples were withdrawn from the vessels at: 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 and 24 hours.

FORMULATIONS:

TABLETS - Diltiazem hydrochloride extended release tablets.
240 mg - Lot #: 001002
300 mg - Lot #: 001005
360 mg - Lot #: 001004 - bioequivalence study conducted on highest strength.

RESULTS:

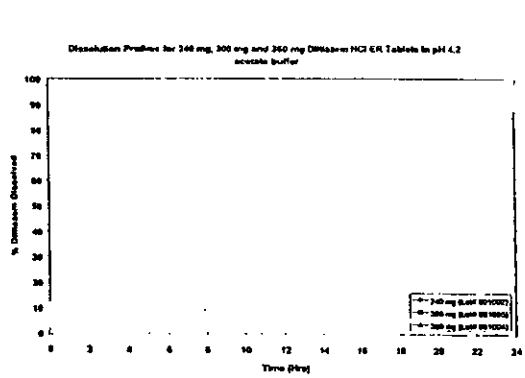
The results of the dissolution study in 4 media comparing 240 mg extended release tablets to 360 mg extended release tablets are presented in the table below.

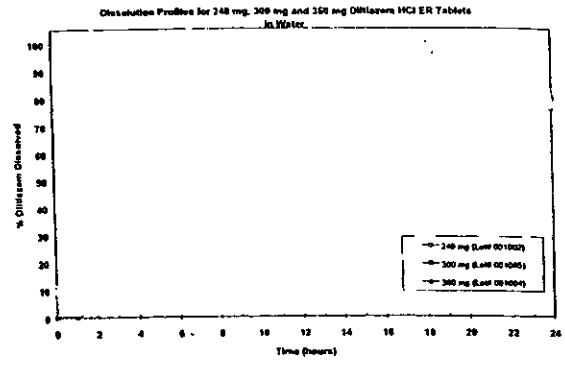
	240-mg Tablets, Mean % Dissolved (N=12)									
	0.1 N HCl		Water		Acetate Buffer pH 4.2		Phosphate Buffer pH 5.8		Phosphate Buffer pH 6.8	
Time (h)	240 mg	360 mg	240 mg	360 mg	240 mg	360 mg	240 mg	360 mg	240 mg	360 mg
0	NP	NP	0	0	0	0	0	0	0	0
1	NP	NP	0 (0)	2 (50)	2 (50)	3 (33)	2 (50)	1 (100)	0 (0)	2 (50)
2	NP	NP	4 (50)	6 (17)	7 (29)	9 (11)	18 (25)	7 (29)	5 (20)	8 (13)
3	NP	NP	10 (30)	11 (9)	16 (25)	19 (11)	19 (11)	17 (12)	15 (13)	16 (19)
4	NP	NP	17 (24)	18 (11)	30 (13)	31 (6)	29 (10)	26 (12)	24 (8)	25 (12)
5	NP	NP	24 (21)	25 (12)	42 (12)	42 (7)	39 (8)	34 (9)	33 (9)	34 (9)
6	NP	NP	31 (16)	32 (9)	52 (10)	52 (6)	48 (8)	42 (10)	41 (7)	41 (10)
7	NP	NP	37 914)	39 (10)	61 (8)	60 (5)	55 (7)	49 (8)	48 (6)	48 (8)
8	NP	NP	43 (14)	44 (9)	68 (9)	67 (4)	62 (6)	56 (7)	54 (7)	55 (7)
9	NP	NP	47 (13)	49 (8)	74 (8)	72 (4)	68 (6)	61 (8)	59 (7)	60 (7)
10	NP	NP	52 (12)	53 (8)	78 (8)	76 (4)	73 (5)	66 (8)	64 (6)	64 (6)
11	NP	NP	55 (11)	57 (9)	82 (7)	80 (4)	77 (5)	70 (7)	68 (6)	68 (6)
12	NP	NP	58 (10)	60 (8)	85 (7)	83 (4)	80 (5)	74 (7)	71 (6)	71 (6)
13	NP	NP	61 (10)	63 (8)	88 (7)	85 (5)	83 (5)	76 (7)	74 (5)	74 (5)
14	NP	NP	63 (10)	65 (8)	90 (7)	87 (5)	85 (5)	79 (6)	76 (5)	77 (5)
15	NP	NP	66 (11)	68 (7)	92 (8)	89 (4)	87 (5)	81 (6)	78 (5)	79 (5)
16	NP	NP	67 (10)	69 (7)	93 (8)	91 (4)	89 (4)	83 (6)	80 (5)	81 (5)
17	NP	NP	69 (10)	71 (7)	94 (7)	92 (4)	91 (4)	85 (6)	82 (6)	83 (5)
18	NP	NP	70 (10)	73 (7)	95 (7)	93 (4)	93 (4)	86 (6)	83 (6)	84 (6)
19	NP	NP	72 (10)	74 (7)	96 (7)	94 (4)	94 (4)	87 (6)	85 (6)	85 (6)
20	NP	NP	73 (10)	75 (7)	97 (7)	95 (4)	95 (4)	88 (6)	86 (6)	87 (6)
21	NP	NP	74 (9)	76 (7)	98 (7)	96 (4)	96 (4)	89 (6)	87 (6)	88 (6)
22	NP	NP	75 (9)	78 (6)	98 (7)	96 (4)	97 (4)	90 (6)	88 (6)	89 (6)
23	NP	NP	76 (9)	78 (6)	99 (7)	97 (4)	98 (5)	91 (5)	89 (5)	90 (6)
24	NP	NP	76 (9)	79 (6)	99 (7)	97 (4)	98 (5)	92 (5)	90 (5)	90 (5)
F2			83		83		62		91	

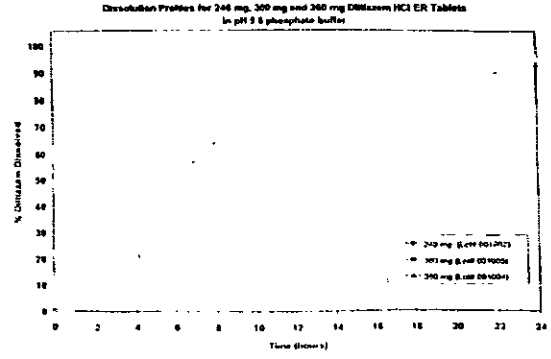
The f2 values comparing 240 mg extended release tablets and 360 mg extended release tablets were above 50 in all 4 media, indicating that the dissolution of 240 mg and 360 mg tablets were similar.

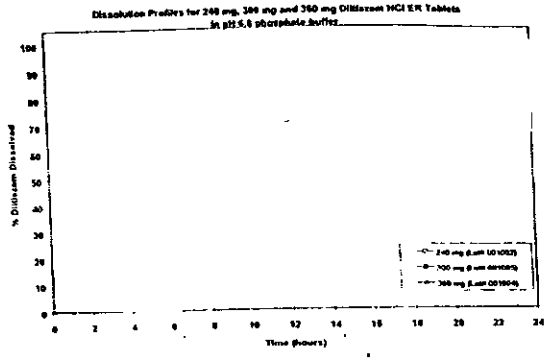
The results of the dissolution study in 4 media comparing 300 mg extended release tablets to 360 mg extended release tablets are presented in the table below.

	300-mg Tablets, Mean % Dissolved (N=12)									
	0.1 N HCl		Water		Acetate Buffer pH 4.2		Phosphate Buffer pH 5.8		Phosphate Buffer pH 6.8	
Time (h)	300 mg	360 mg	300 mg	360 mg	300 mg	360 mg	300 mg	360 mg	300 mg	360 mg
0	0	0	0	0	0	0	0	0	0	0
1	NP	NP	1 (100)	2 (50)	1 (0)	3 (33)	1 (200)	1 (100)	1 (100)	2 (50)
2	NP	NP	4 (25)	6 (17)	6 (17)	9 (11)	7 (86)	7 (29)	6 (17)	8 (13)
3	NP	NP	10 (20)	11 (9)	16 (19)	19 (11)	18 (50)	17 (12)	16 (6)	16 (19)
4	NP	NP	16 (19)	18 (11)	29 (14)	31 (6)	30 (33)	26 (12)	26 (8)	25 (12)
5	NP	NP	24 (17)	25 (12)	42 (10)	42 (7)	40 (25)	34 (9)	35 (9)	34 (9)
6	NP	NP	31 (13)	32 (9)	53 (6)	52 (6)	49 (20)	42 (10)	44 (9)	41 (10)
7	NP	NP	38 (13)	39 (10)	61 (7)	60 (5)	56 (18)	49 (8)	51 (8)	48 (8)
8	NP	NP	44 (11)	44 (9)	68 (6)	67 (4)	63 (14)	56 (7)	58 (9)	55 (7)
9	NP	NP	49 (10)	49 (8)	74 (5)	72 (4)	68 (13)	61 (8)	63 (8)	60 (7)
10	NP	NP	53 (9)	53 (8)	78 (5)	76 (4)	73 (11)	66 (8)	68 (7)	64 (6)
11	NP	NP	57 (9)	57 (9)	82 (5)	80 (4)	76 (9)	70 (7)	72 (7)	68 (6)
12	NP	NP	60 (10)	60 (8)	85 (5)	83 (4)	80 (9)	74 (7)	75 (7)	71 (6)
13	NP	NP	63 (10)	63 (8)	87 (5)	85 (5)	82 (7)	76 (7)	78 (6)	74 (5)
14	NP	NP	66 (9)	65 (8)	89 (4)	87 (5)	84 (7)	79 (6)	81 (6)	77 (5)
15	NP	NP	67 (9)	68 (7)	91 (4)	89 (4)	86 (7)	81 (6)	83 (6)	79 (5)
16	NP	NP	70 (9)	69 (7)	92 (4)	91 (4)	88 (6)	83 (6)	85 (6)	81 (5)
17	NP	NP	71 (10)	71 (7)	94 (4)	92 (4)	89 (6)	85 (6)	87 (6)	83 (5)
18	NP	NP	73 (10)	73 (7)	94 (4)	93 (4)	91 (5)	86 (6)	88 (6)	84 (6)
19	NP	NP	74 (9)	74 (7)	96 (4)	94 (4)	92 (5)	87 (6)	89 (6)	85 (6)
20	NP	NP	76 (8)	75 (7)	97 (4)	95 (4)	93 (5)	88 (6)	91 (7)	87 (6)
21	NP	NP	77 (8)	76 (7)	97 (4)	96 (4)	94 (5)	89 (6)	92 (7)	88 (6)
22	NP	NP	78 (8)	78 (6)	98 (4)	96 (4)	95 (5)	90 (6)	93 (6)	89 (6)
23	NP	NP	79 (8)	78 (6)	98 (4)	97 (4)	95 (5)	91 (5)	93 (5)	90 (6)
24	NP	NP	80 (8)	79 (6)	99 (4)	97 (4)	96 (4)	92 (5)	94 (6)	90 (6)
F2			**93**		**83**		**63**		**73**	









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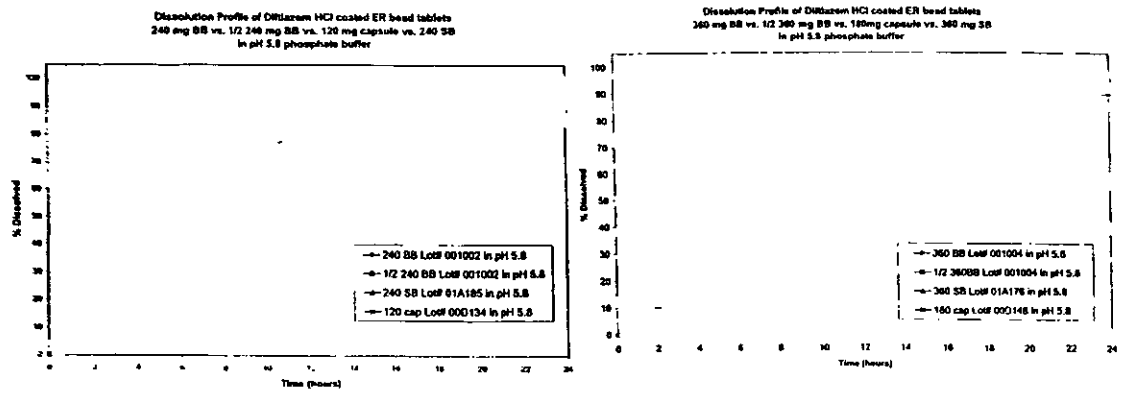
The f2 values comparing 300 mg extended release tablets and 360 mg extended release tablets were above 50 in all 4 media, indicating that the dissolution of 300 mg and 360 mg tablets were similar.

HALF-TABLET vs. FULL TABLET:

The results of the dissolution study of ½ and full 240 mg and 360 mg bead tablets in phosphate buffer pH 5.8 are presented in the table below.

DOSE STRENGTH	240-mg		360-mg	
	Phosphate Buffer pH 5.8		Phosphate Buffer pH 5.8	
Time (h)	FULL	HALF	FULL	HALF
0	0	0	0	0
1	2 (50)	3 (67)	1 (100)	2 (50)
2	8 (25)	10 (30)	7 (29)	10 (40)
3	19 (11)	20 (15)	17 (12)	19 (21)
4	29 (10)	30 (13)	26 (12)	28 (18)
5	39 (8)	40 (13)	34 (9)	37 (16)
6	48 (8)	48 (10)	42 (10)	44 (14)
7	55 (7)	56 (11)	49 (8)	51 (14)
8	62 (6)	62 (10)	56 (7)	57 (12)
9	68 (6)	68 (9)	61 (8)	62 (13)
10	73 (5)	72 (10)	66 (8)	67 (12)
11	77 (5)	76 (9)	70 (7)	71 (11)
12	80 (5)	79 (9)	74 (7)	74 (12)
13	83 (5)	82 (9)	76 (7)	77 (12)
14	85 (5)	85 (9)	79 (6)	79 (11)
15	87 (5)	87 (8)	81 (6)	81 (11)
16	89 (4)	88 (9)	83 (6)	83 (11)
17	91 (4)	90 (9)	85 (6)	85 (12)
18	93 (4)	91 (9)	86 (6)	86 (12)
19	94 (4)	93 (9)	87 (6)	87 (11)
20	95 (4)	94 (9)	88 (6)	88 (11)
21	96 (4)	95 (8)	89 (6)	89 (11)
22	97 (4)	95 (8)	90 (6)	90 (11)
23	98 (5)	96 (8)	91 (5)	91 (11)
24	98 (5)	97 (8)	92 (5)	92 (11)
F2	**93**		**87**	



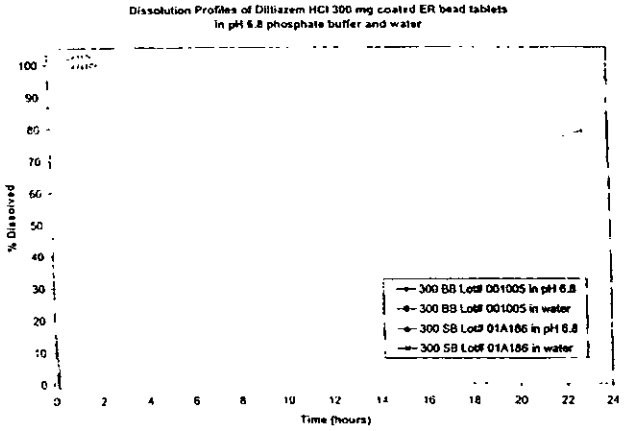
SITE CHANGE:

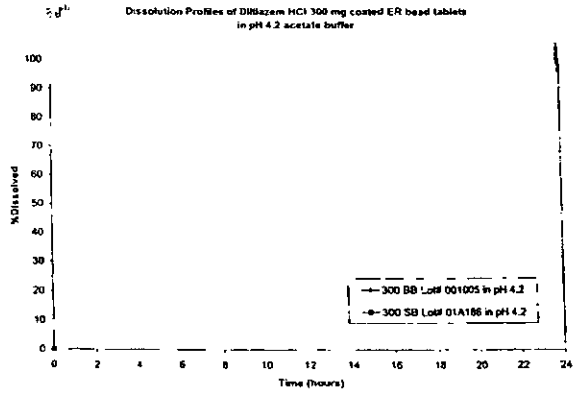
The proposed commercial manufacturing site, Biovail Corporation Manufacturing Division, Steinbach, Manitoba, which is also the site used for manufacture of the stability batches (SB)- Lot#: 01A186 tablets. However, the clinical batches (BB), including the lot used in the pharmacokinetic studies, were manufactured at a different site (Biovail Technologies Ltd and [ ], - Lot #: 001005 tablets. Dissolution of batches manufactured at the 2 sites were compared.

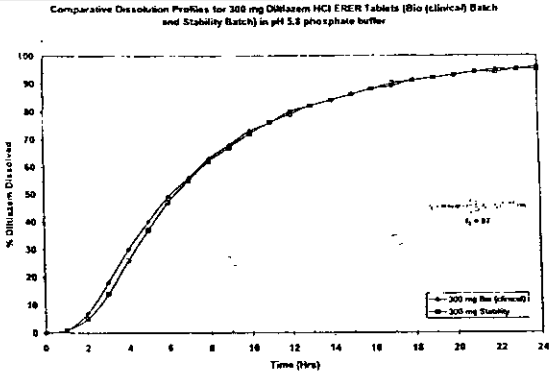
The FDA guidance recommends the use of 0.1N HCl as the acidic media, when performing comparative dissolution studies in three different media conditions. The Sponsor indicates that data from pervious comparative dissolution studies using 0.1 N HCl with other Diltiazem preparations, which demonstrates, that prolonged exposure of Diltiazem to 0.1N HCl causes the Diltiazem to degrade substantially, affecting the dissolution profile. Therefore, in the comparative dissolution studies were done with the phosphate buffer pH 4.2 (the pH of the stomach under fed conditions) has been used as the acidic media.

Based on dissolution data from previous submissions in 0.1 N HCl, where diltiazem was found to be stable, the sponsor is urged to provide dissolution data for 0.1N HCl for all strengths (120mg, 180mg, 240mg, 300mg, and 360mg). Furthermore, the sponsor is urged to provide dissolution profiles for the lower strengths of 120, 180, 240 and 300 mg tablets in the other dissolution media (water, acetate buffer pH 4.2, phosphate buffer pH 5.8, phosphate buffer pH 6.8).

	300-mg Tablets, Mean % Dissolved (N=12)									
	0.1 N HCl		Water		Acetate Buffer pH 4.2		Phosphate Buffer pH 5.8		Phosphate Buffer pH 6.8	
Time (h)	BB	SB	BB	SB	BB	SB	BB	SB	BB	SB
0	0	0	0	0	0	0	0	0	0	0
1	NP	NP	1 (100)	1 (100)	1 (0)	1 (0)	1	1	1 (100)	0 (0)
2	NP	NP	4 (25)	4 (25)	6 (17)	4 (25)	7	5	6 (17)	4 (25)
3	NP	NP	10 (20)	11 (18)	16 (19)	13 (8)	18	14	16 (6)	11 (9)
4	NP	NP	16 (19)	19 (21)	29 (14)	26 (8)	30	26	26 (8)	23 (4)
5	NP	NP	24 (17)	28 (14)	42 (10)	40 (5)	40	37	35 (9)	33 (3)
6	NP	NP	31 (13)	36 (14)	53 (6)	52 (4)	49	47	44 (9)	42 (2)
7	NP	NP	38 (13)	43 (12)	61 (7)	61 (5)	56	55	51 (8)	50 (4)
8	NP	NP	44 (11)	50 (12)	68 (6)	68 (4)	63	62	58 (9)	56 (4)
9	NP	NP	49 (10)	55 (13)	74 (5)	74 (5)	68	67	63 (8)	61 (3)
10	NP	NP	53 (9)	59 (10)	78 (5)	78 (5)	73	72	68 (7)	66 (3)
11	NP	NP	57 (9)	63 (11)	82 (5)	81 (5)	76	76	72 (7)	69 (3)
12	NP	NP	60 (10)	66 (9)	85 (5)	84 (5)	80	79	75 (7)	72 (3)
13	NP	NP	63 (10)	69 (10)	87 (5)	86 (5)	82	82	78 (6)	75 (3)
14	NP	NP	66 (10)	71 (8)	89 (4)	88 (5)	84	84	81 (6)	77 (3)
15	NP	NP	67 (9)	74 (11)	91 (4)	90 (4)	86	86	83 (6)	79 (3)
16	NP	NP	70 (9)	76 (8)	92 (4)	91 (4)	88	88	85 (6)	81 (2)
17	NP	NP	71 (9)	78 (10)	94 (4)	92 (4)	89	90	87 (6)	82 (2)
18	NP	NP	73 (10)	79 (9)	94 (4)	93 (4)	91	91	88 (6)	83 (4)
19	NP	NP	74 (9)	80 (10)	96 (4)	94 (4)	92	92	89 (6)	84 (4)
20	NP	NP	76 (8)	81 (9)	97 (4)	95 (4)	93	93	91 (7)	85 (4)
21	NP	NP	77 (8)	83 (10)	97 (4)	96 (4)	94	94	92 (7)	86 (2)
22	NP	NP	78 (8)	83 (8)	98 (4)	96 (4)	95	94	93 (6)	87 (3)
23	NP	NP	79 (8)	85 (9)	98 (4)	97 (4)	95	95	93 (5)	87 (2)
24	NP	NP	80 (8)	85 (8)	99 (4)	97 (4)	96	95	94 (6)	88 (3)
F2			**63.47**		**87.32**		**84.80**		**71.70**	

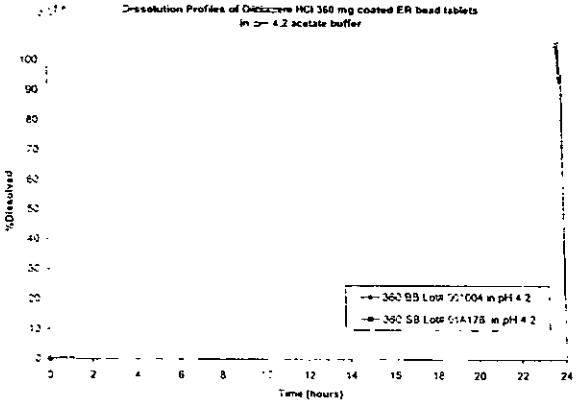


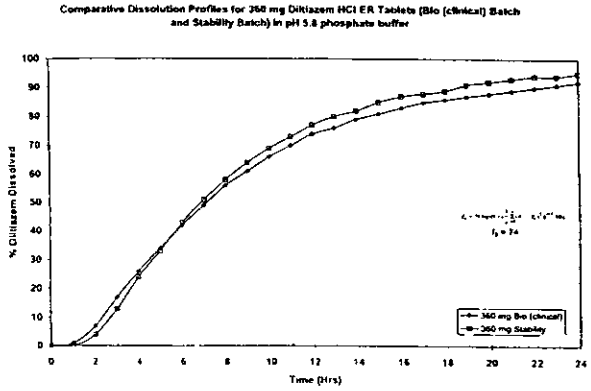




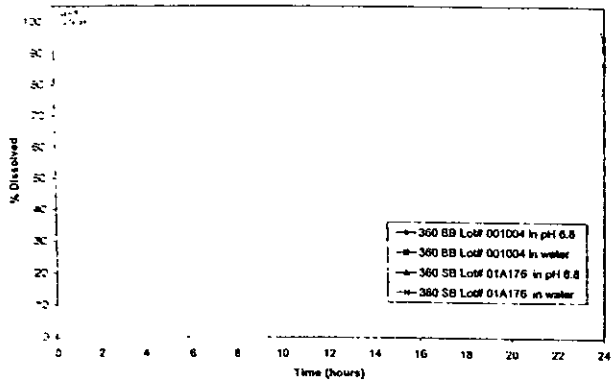
	360-mg Tablets, Mean % Dissolved (N=12)									
	0.1 N HCl		Water		Acetate Buffer pH 4.2		Phosphate Buffer pH 5.8		Phosphate Buffer pH 6.8	
Time (h)	BB	SB	BB	SB	BB	SB	BB	SB	BB	SB
0	0	0	0	0	0	0	0	0	0	0
1	NP	NP	2 (50)	1 (0)	3 (33)	1 (100)	1 (100)	0 (0)	2 (50)	1 (100)
2	NP	NP	6 (17)	4 (25)	9 (11)	5 (20)	7 (29)	4 (25)	8 (13)	4 (25)
3	NP	NP	11 (9)	9 (11)	19 (11)	13 (15)	17 (12)	13 (15)	16 (19)	12 (17)
4	NP	NP	18 (11)	15 (13)	31 (6)	25 (12)	26 (12)	24 (8)	25 (12)	23 (13)
5	NP	NP	25 (12)	23 (9)	42 (7)	37 (8)	34 (9)	33 (6)	34 (9)	32 (13)
6	NP	NP	32 (9)	31 (10)	52 (6)	48 (6)	42 (10)	43 (5)	41 (10)	41 (10)
7	NP	NP	39 (10)	38 (8)	60 (5)	57 (5)	55 (8)	51 (6)	48 (8)	49 (8)
8	NP	NP	44 (9)	44 (7)	67 (4)	65 (5)	62 (7)	58 (5)	55 (7)	56 (9)
9	NP	NP	49 (8)	49 (6)	72 (4)	71 (6)	68 (8)	64 (5)	60 (7)	61 (8)
10	NP	NP	53 (8)	53 (8)	76 (4)	76 (5)	73 (8)	69 (4)	64 (6)	66 (8)
11	NP	NP	57 (9)	57 (7)	80 (4)	79 (5)	77 (7)	73 (4)	68 (6)	70 (7)
12	NP	NP	60 (8)	60 (7)	83 (4)	83 (5)	80 (7)	77 (4)	71 (6)	73 (7)
13	NP	NP	63 (8)	63 (6)	85 (5)	85 (5)	83 (7)	80 (4)	74 (5)	76 (7)
14	NP	NP	65 (8)	65 (6)	87 (5)	87 (5)	85 (6)	82 (4)	77 (5)	79 (6)
15	NP	NP	68 (7)	68 (6)	89 (4)	89 (4)	87 (6)	85 (5)	79 (5)	81 (6)
16	NP	NP	69 (7)	70 (6)	91 (4)	91 (4)	89 (6)	87 (5)	81 (5)	83 (7)
17	NP	NP	71 (7)	71 (6)	92 (4)	92 (4)	91 (6)	88 (3)	83 (5)	85 (7)
18	NP	NP	73 (7)	73 (5)	93 (4)	93 (4)	93 (6)	89 (4)	84 (6)	86 (7)
19	NP	NP	74 (7)	74 (5)	94 (4)	94 (4)	94 (6)	91 (4)	85 (6)	87 (7)

20	NP	NP	75 (7)	76 (5	95 (4)	95 (4)	95 (6)	92 (4)	87 (6)	89 (7)
21	NP	NP	76 (7)	77 (5)	96 (4)	95 (4)	96 (6)	93 (4)	88 (6)	90 (7)
22	NP	NP	78 (6)	78 (5)	96 (4)	96 (4)	97 (6)	94 (4)	89 (6)	91 (7)
23	NP	NP	78 (6)	79 (5)	97 (4)	97 (4)	98 (5)	94 (4)	90 (6)	91 (7)
24	NP	NP	79 (6)	79 (5)	97 (4)	97 (4)	98 (5)	95 (4)	90 (6)	92 (7)
F2			91.61		73.42		75.68		81.69	





Dissolution Profiles of Diltiazem HCl 360 mg coated ER bead tablets
in pH 6.8 phosphate buffer and water



DISSOLUTION METHOD

The sponsor proposes the following dissolution method and apparatus for diltiazem extended release tablets.

Apparatus: USP Apparatus 2 (Paddle)
Media: 900 ml of pH 5.8 phosphate buffer at 37^0C
Speed: 100 rpm

DISSOLUTION SPECIFICATIONS:

The sponsor proposed dissolution specification is listed in the Table below.

Time (h)	Mean % Dissolved	Range (n=6)	SPONSOR Dissolution Specifications
2	10	—	NMT —
8	59	—	—
14	80	—	NLT —
24	93	—	NLT —

COMMENTS:

The sponsor proposed dissolution method of USP Apparatus 2 (Paddle) at 100 rpm in 900 ml of pH 5.8 phosphate buffer at 37^0C is acceptable The dissolution time points of 8, 14 and 24 hours chosen by the sponsor for dissolution specification are inappropriate because of almost complete dissolution at earlier time points. OCPB considers that dissolution sampling at 2, 6, 12 and 16 hours will provide more appropriate information on the release characteristics of the product. Based on the dissolution data provided by the sponsor supporting biowaiver OCPB recommends the following dissolution times and specifications.

Time (h)	FDA PROPOSES Dissolution Specifications
2	NMT —
6	—
12	—
16	NLT —

However, considering that all the stability data were generated using 2, 8, 14 and 24 hours sampling, OCPB will accept on an interim basis the dissolution time points studied by the sponsor with the following altered specifications.

Time (h)	FDA PROPOSES Interim Dissolution Specifications
2	NMT —
8	—
14	—
24	NLT —

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