

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

75-401

Trade Name: Taztia XT Capsules

Generic Name: Diltiazem Hydrochloride Extended-
release Capsules, 120mg, 180mg, 240mg,
300mg, and 360mg

Sponsor: Andrx Pharmaceuticals, L.L.C.

Approval Date: April 10, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-401

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**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75-401

APPROVAL LETTER

APR 10 2003

Andrx Pharmaceuticals, L.L.C.
Attention: Janet Vaughn
4955 Orange Drive
Fort Lauderdale, FL 33314

Dear Madam:

This is in reference to your abbreviated new drug application dated June 22, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Taztia XT™ Capsules (Diltiazem Hydrochloride Extended-release Capsules USP), 120 mg, 180 mg, 240 mg, 300 mg and 360 mg, (Once-a-Day Dosage).

Reference is also made to our Tentative Approval letter issued on May 14, 2001, and to your amendments dated October 5, October 24, and November 8, 2001; May 22, September 30, October 29, November 22 and December 10, 2002; and January 14, March 17, and March 18, 2003.

The listed drug product referenced in your application, Tiazac® Extended-release Capsules of Biovail Corporation International, is subject to a period of patent protection. As noted in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the "Orange Book", U.S. patent 5,529,791 (the '791 patent) is due to expire on June 25, 2013. Your application contains a paragraph IV certification to the '791 patent under Section 505(j)(2)(A)(vii)(IV) of the Act stating that the patent will not be infringed by your manufacture, use, or sale of Diltiazem Hydrochloride Extended-release Capsules, USP under this ANDA. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA may be made effective immediately, unless an action is brought against Andrx Pharmaceuticals L.L.C. (Andrx) for infringement of the '791 patent. This action must be brought against Andrx prior to the expiration of 45 days from the date the notice you provided under paragraph (2)(B)(i) was received by the NDA/patent holder(s).

You have notified the agency that Andrx has complied with the requirements of Section 505(j)(2)(B) of the Act, and that Biovail Corporation initiated a patent infringement action against you in United States District Court for the Southern District of Florida (Biovail Corporation International, Biovail Laboratories, Inc., and Galephar P.R., Inc., Ltd. v. Andrx Pharmaceuticals, Inc., Civil Action No. 98-7096). You have notified us that Andrx prevailed in this District Court case. You have also notified the agency that Biovail appealed the District Court's decision to the United States Court of Appeals for the Federal Circuit (Case 00-1260), and that the Appeals Court affirmed the earlier District Court decision that Andrx does not infringe the '791 patent.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Taztia XT™ Capsules (Diltiazem Hydrochloride Extended-release Capsules USP), 120 mg, 180 mg, 240 mg, 300 mg, and 360 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug Tiazac® Extended-release Capsules 120 mg, 180 mg, 240 mg, 300 mg and 360 mg, respectively, of Biovail Corporation International.

Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application. The "interim" dissolution specifications are as follows:

Dissolution testing should be conducted in _____ using _____ at _____
The test product should meet the following interim specifications:

2h	NMT
4h	_____
8h	_____
12h	NLT
16h	NLT

During the developmental stages of the dissolution testing, you used _____ for the _____ testing. Please note that in the future, you should use _____ for _____ dissolution testing as recommended in the _____. The pH range of the _____ is _____.

The "interim" dissolution test(s) and tolerances should be finalized by submitting dissolution data for the first three production size batches. Data should be submitted as a Special Supplement - Changes Being Effectuated when there are no revisions to the "interim" specifications or when the final specifications are tighter than the "interim" specifications. In all other instances, the information should be submitted in the form of a Prior Approval Supplement.

We note that Andrx was the first ANDA applicant to submit a substantially complete ANDA containing a paragraph IV certification to the '791 patent for Diltiazem Hydrochloride Extended-release Capsules USP, 120 mg, 180 mg, 240 mg, 300 mg, and 360 mg (Once-a-Day Dosage). Andrx became eligible for 180-days of generic drug market exclusivity with respect to the '791 patent. Andrx's exclusivity, which was triggered by the February 13, 2001, decision of the U.S. Appeals Court, has expired.

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FDA 2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Gary Buehler". The signature is fluid and cursive, with the first name "Gary" and last name "Buehler" clearly distinguishable.

Gary Buehler 4/10/03
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75-401

**TENTATIVE APPROVAL
LETTER(S)**

ANDA 75-401

MAY 14 2001

Andrx Pharmaceuticals, Inc.
Attention: Diane Servello
4001 S.W. 47th Avenue
Fort Lauderdale, FL 33314

Dear Madam:

This is in reference to your abbreviated new drug application dated June 22, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for TaztiaTM XT (diltiazem hydrochloride extended-release capsules USP), 120 mg, 180 mg, 240 mg, 300 mg and 360 mg.

Reference is also made to the Tentative Approval letter issued on September 29, 2000 and to your amendments dated February 16, February 28, and March 8, 2001.

We have completed the review of this abbreviated application and have concluded that, based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. Therefore, the application is **tentatively approved**. This determination is based upon information available to the Agency at this time (i.e., information in your application and the status of current good manufacturing practices of the facilities used in the manufacturing and testing of the drug product) and is therefore subject to change on the basis of new information that may come to our attention. This letter does not address notice issues related to the 180-day exclusivity provisions under section 505(j)(5)(B)(iv) of the Act.

The listed drug product (RLD) referenced in your application is subject to periods of patent protection which expire on June 25, 2013 (Patent No. 5,529,791, the '791 patent) and April 28, 2018 (Patent No. 6,162,463, the '463 patent). You informed us that Biovail Corporation International, Biovail Laboratories, Inc. and Galephar P.R., Inc., Ltd. initiated a patent infringement action against you, regarding the '791 patent, in the United States District Court for the Southern District of Florida (Civil Action No. 98-7096). You have also notified us that you prevailed in both the district court and in the court of appeals for this patent.

You also informed us that litigation is underway in the United States District Court for the Southern District of Florida involving a challenge to the '463 patent (Biovail Laboratories, Inc. v. Andrx Pharmaceuticals, Inc., Civil Action No. 01-6548). Therefore, final approval cannot be granted until:

1.
 - a. The expiration of the 30-month period provided for in section 505(j)(5)(B)(iii) since the date of receipt of the 45-day notice required under section 505(j)(2)(B)(i), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or,
 - b. The date of court decision [505(j)(5)(B)(iii)(I), (II), or (III)], which has been interpreted by the Agency to mean the date of the final order or judgement of that court from which no appeal can be or has been taken, or,
 - c. The '463 patent has expired, and
2. The Agency is assured there is no new information that would affect whether final approval should be granted.

Because the Agency is granting a tentative approval for this application, when you believe that your application may be considered for final approval, you must amend your application to notify the Agency whether circumstances have or have not arisen that may affect the effective date of final approval. Your amendment must provide:

1. A copy of a final order or judgement from which no appeal may be taken (which might not be the one from the district court), or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information, and
2.
 - a. Updated information related to labeling or chemistry, manufacturing and controls data, or any other change in the conditions outlined in this abbreviated application, or
 - b. A statement that no such changes have been made to the application since the date of tentative approval.

Any changes in the conditions outlined in this abbreviated application and the status of the manufacturing and testing facilities' compliance with current good manufacturing procedures are subject to Agency review before final approval of the application will be made.

In addition to, or instead of, the amendments referred to above, the Agency may, at any time prior to the final date of approval, request that you submit amendments containing the information requested above.

Failure to submit either or both amendments may result in rescission of this tentative approval determination, or delay in issuance of the final approval letter.

The drug product that is the subject of this abbreviated application may not be marketed without final Agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug before the effective final approval date is prohibited under section 501 of the Act. Also, until the Agency issues the final approval letter, this drug product will not be listed in the Agency's "Approved Drug Products with Therapeutic Equivalence Evaluations" list.

The amendment should be designated as a MINOR AMENDMENT in your cover letter. Before you submit the amendment, please contact Bonnie McNeal, Project Manager, at (301) 827-5849, for further instructions.

Sincerely yours,



Gary Buehler 5/14/01
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

SEP 29 2000

Andrx Pharmaceuticals, Inc.
Attention: Diane Servello
4001 S.W. 47th Avenue
Fort Lauderdale, FL 33314

Dear Madam:

This is in reference to your abbreviated new drug application dated June 22, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Taztia XTTM (Diltiazem Hydrochloride Extended-release Capsules USP, 120 mg, 180 mg, 240 mg, 300 mg and 360 mg).

Reference is also made to your amendments dated May 4, October 29, November 1, and December 3, 1999; and January 14, 19, 24, March 29, April 11, 28, June 26, and September 12, 18, 2000.

We have completed the review of this abbreviated application and have concluded that, based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. Therefore, the application is **tentatively approved**. This determination is based upon information available to the Agency at this time (i.e., information in your application and the status of current good manufacturing practices of the facilities used in the manufacturing and testing of the drug product) and is therefore subject to change on the basis of new information that may come to our attention. This letter does not address notice issues related to the 180-day exclusivity provisions under section 505(j)(5)(B)(iv) of the Act.

The listed drug product referenced in your application is subject to a period of patent protection which expires on June 25, 2013, (Patent No. 5,529,791). However, litigation is underway in the United States Court of Appeals for the Federal Circuit. Therefore, final approval cannot be granted until:

1.
 - a. The expiration of the 30-month period provided for in section 505(j)(5)(B)(iii) since the date of receipt of the 45-day notice required under section 505(j)(2)(B)(i), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or,
 - b. The date of the U.S. Court of Appeals for the Federal Circuit.
 - c. The patent has expired, and
2. The Agency is assured there is no new information that would affect whether final approval should be granted.

Because the Agency is granting a tentative approval for this application, when you believe that your application may be considered for final approval, you must amend your application to notify the Agency whether circumstances have or have not arisen that may affect the effective date of final approval. Your amendment must provide:

1. A copy of a final order or judgement from which no appeal may be taken (which might not be the one from the district court), or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information, and
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 - a. Updated information related to labeling or chemistry, manufacturing and controls data, or any other change in the conditions outlined in this abbreviated application, or
 - b. A statement that no such changes have been made to the application since the date of tentative approval.

Any changes in the conditions outlined in this abbreviated application and the status of the manufacturing and testing facilities' compliance with current good manufacturing procedures

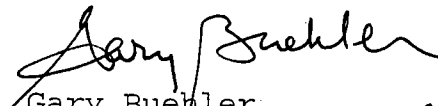
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In addition to, or instead of, the amendments referred to above, the Agency may, at any time prior to the final date of approval, request that you submit amendments containing the information requested above. Failure to submit either or both amendments may result in rescission of this tentative approval determination, or delay in issuance of the final approval letter.

The drug product that is the subject of this abbreviated application may not be marketed without final Agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug before the effective final approval date is prohibited under section 501 of the Act. Also, until the Agency issues the final approval letter, this drug product will not be listed in the Agency's "Approved Drug Products with Therapeutic Equivalence Evaluations" list.

The amendment should be designated as a MINOR AMENDMENT in your cover letter. Before you submit the amendment, please contact Timothy Ames, Project Manager, at (301) 827-5849, for further instructions.

Sincerely yours,



Gary Buehler

Acting Director

Office of Generic Drugs

Center for Drug Evaluation and Research

9/29/00

**CENTER FOR DRUG
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RESEARCH**

APPLICATION NUMBER:

75-401

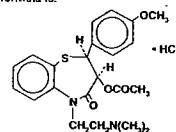
FINAL PRINTED LABELING

TAZTIA XT™ br ad of
DILTIAZEM
HYDROCHLORIDE
EXTENDED-RELEASE
CAPSULES USP
(ONCE-A-DAY DOSAGE)

B-Only

DESCRIPTION

Diltiazem hydrochloride is a calcium ion cellular influx inhibitor (slow channel blocker). Chemically, diltiazem hydrochloride is 1,5-benzothiazepin-4(5H)-one, 3-(acetyloxy)-2-(dimethylamino)ethyl-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride, (+)-cis. The structural formula is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol and chloroform and has a molecular weight of 450.98. Its molecular formula is $C_{22}H_{26}N_2O_6 \cdot HCl$. Diltiazem Hydrochloride Extended-Release Capsules USP (Once-a-Day Dosage) for oral administration, contain diltiazem hydrochloride in extended-release pellets at doses of 120, 180, 240, 300 and 360 mg.

Diltiazem Hydrochloride Extended-Release Capsules USP (Once-a-Day Dosage) also contain: black iron oxide, corn starch, D&C Yellow #10 Aluminum Lake, ethylcellulose, FD&C Blue #1, FD&C Blue #1 Aluminum Lake, FD&C Blue #2 Aluminum Lake, FD&C Red #40 Aluminum Lake, gelatin, hydroxypropyl methylcellulose, magnesium stearate, nonoxonyl 100, polyacrylic dispersion, polysorbate 80, povidone, propylene glycol, sucrose, talc, and titanium dioxide. In addition, the 120 mg, 240 mg and 300 mg capsules also contain D&C Red #28 and FD&C Red #40, and the 180 mg and 300 mg capsules also contain D&C Yellow #10 and FD&C Yellow #6.

For oral administration.

USP drug release test pending.

CLINICAL PHARMACOLOGY

The therapeutic effects of diltiazem hydrochloride are believed to be related to its ability to inhibit the cellular influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action

Hypertension

Diltiazem produces its antihypertensive effect primarily by relaxation of vascular smooth muscle and the resultant decrease in peripheral vascular resistance. The magnitude of blood pressure reduction is related to the degree of hypertension; thus hypertensive individuals experience an antihypertensive effect, whereas there is only a modest fall in blood pressure in normotensives.

Angina

Diltiazem hydrochloride has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal work loads.

Diltiazem has been shown to be a potent dilator of coronary arteries, both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by diltiazem.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of the coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant

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Hemodynamic and

Electrophysiologic Effects

Like other calcium channel antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure in normotensive individuals and in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. Such data has no predictive value with respect to effects in patients with poor ventricular function, and increased heart failure has been reported in patients with pre-existing impairment of ventricular function. There are as yet few data on the interaction of diltiazem and beta-blockers in patients with poor ventricular function. Resting heart rate is usually slightly reduced by diltiazem.

Diltiazem hydrochloride extended-release capsules (once-a-day dosage) produce antihypertensive effects both in the supine and standing positions. Postural hypotension is infrequently noted upon suddenly assuming an upright position. No reflex tachycardia is associated with the chronic antihypertensive effects.

Diltiazem hydrochloride decreases vascular resistance, increases cardiac output (by increasing stroke volume), and produces a slight decrease or no change in heart rate. During dynamic exercise, increases in diastolic pressure are inhibited while maximum achievable systolic pressure is usually reduced. Chronic therapy with diltiazem hydrochloride produces no change or an increase in plasma catecholamines. No increased activity of the renin-angiotensin-aldosterone axis has been observed. Diltiazem hydrochloride reduces the renal and peripheral effects of angiotensin II. Hypertensive animal models respond to diltiazem with reductions in blood pressure and increased urinary output and natriuresis without a change in urinary sodium/potassium ratio. In man, transient natriuresis and kaliuresis have been reported, but only in high intravenous doses of 0.5 mg/kg of body weight.

Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases). Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods by approximately 20%.

In two short term, double-blind, placebo-controlled studies in 256 hypertensive patients with doses up to 640 mg/day, diltiazem hydrochloride extended-release capsules (once-a-day dosage) showed a clinically unimportant but statistically significant, dose-related increase in PR interval (0.008 seconds). There were no instances of greater than first-degree AV block in any of the clinical trials (see WARNINGS).

Pharmacodynamics

Hypertension

In short term, double-blind, placebo-controlled clinical trials diltiazem hydrochloride extended-release capsules (once-a-day dosage) demonstrated a dose-related antihypertensive response among patients with mild to moderate hypertension. In one parallel-group study of 198 patients diltiazem hydrochloride extended-release capsules (once-a-day dosage) produced a dose-related antihypertensive response.

Pharmacodynamics

Hypertension
In short term, double-blind, placebo-controlled clinical trials diltiazem hydrochloride extended-release capsules (once-a-day dosage) demonstrated a dose-related antihypertensive response among patients with mild to moderate hypertension. In one parallel-group study of 198 patients diltiazem hydrochloride extended-release capsules (once-a-day dosage) were given for four weeks. The changes in diastolic blood pressure measured at trough (24 hours after the dose) for placebo, 90 mg, 180 mg, 360 mg and 540 mg were -5.4, -6.3, -6.2, -8.2 and -11.8 mm Hg, respectively. Supine diastolic blood pressure as well as standing diastolic and systolic blood pressures also showed statistically significant linear dose response effects.

In another clinical trial that followed a dose-escalation design, diltiazem hydrochloride extended-release capsules (once-a-day dosage) also reduced blood pressure in a linear dose-related manner. Supine diastolic blood pressure measured following two week intervals of treatment was reduced by -3.7 mm Hg with 120 mg/day versus -2.0 mm Hg with placebo, by -7.6 mm Hg after escalation to 240 mg/day versus -2.3 mm Hg with placebo, by -8.1 mm Hg after escalation to 360 mg/day versus -0.9 mm Hg with placebo, and by -10.3 mm Hg after escalation to 480/540 mg/day versus -2.2 mm Hg with placebo.

Angina

In a double-blind parallel group placebo controlled trial (approximately 50 patients/group, in patients with chronic stable angina), diltiazem hydrochloride at doses of 120 to 540 mg/day increased exercise tolerance time. At trough, 24 hours after dosing, exercise tolerance times using a Bruce exercise protocol, increased by 14, 26, 41, 33, and 32 seconds over baseline for placebo and the 120 mg, 240 mg, 360 mg, and 540 mg/day treated patient groups, respectively. At peak, 8 hours after dosing, exercise tolerance times relative to baseline were statistically significantly increased by 13, 38, 64, 55 and 42 seconds for placebo and 120 mg, 240 mg, 360 mg and 540 mg/day diltiazem hydrochloride treated patients, respectively. Compared to baseline, diltiazem hydrochloride treated patients experienced statistically significant reductions in anginal attacks and decreased nitroglycerin requirements when compared to placebo treated patients.

Pharmacokinetics and Metabolism
Diltiazem is well absorbed from the gastrointestinal tract but undergoes substantial hepatic first-pass effect. The absolute bioavailability of an oral dose of an immediate release formulation (compared to intravenous administration) is approximately 40%. Only 2% to 4% of unchanged diltiazem appears in the urine. The plasma elimination half-life of diltiazem is approximately 3.0-4.5 h. Drugs which induce or inhibit hepatic microsomal enzymes may alter diltiazem disposition. Therapeutic blood levels of diltiazem appear to be in the range of 40-200 ng/mL. There is a departure from linearity when dose strengths are increased; the half-life is slightly increased with dose.

The two primary metabolites of diltiazem are desacetyldiltiazem and desmethyldiltiazem. The desacetyl metabolite is approximately 25% to 50% as potent a coronary vasodilator as diltiazem and is present in plasma at concentrations of 10% to 20% of parent diltiazem. However, recent studies employing sensitive and specific analytical methods have confirmed the existence of several sequential metabolic pathways of diltiazem. As many as nine diltiazem metabolites have been identified in the urine of humans. Total radioactivity measurements following single intravenous dose administration in healthy volunteers suggest the presence of other unidentified metabolites. These metabolites are more slowly excreted (with a half-life of total radioactivity of approximately 20 hours) and attain concentrations in excess of diltiazem.

In vitro binding studies show diltiazem is 70% to 80% bound to plasma proteins. Competitive *in vitro* ligand binding studies have also shown diltiazem binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. A study that compared patients with normal hepatic function to patients with cirrhosis who received immediate release diltiazem found an increase in diltiazem elimination half-life and a 69% increase in bioavailability in the hepatically impaired patients. Patients with severely impaired renal function (creatinine clearance <50 mL/min) who received immediate release diltiazem had modestly increased diltiazem concentrations compared to patients with normal renal function.

Diltiazem Hydrochloride Extended-Release Capsules (Once-a-Day Dosage)

When compared to a regimen of immediate-release tablets at steady-state, approximately 93% of drug is absorbed from the diltiazem hydrochloride extended-release capsule formulation. When diltiazem hydrochloride extended-release capsules (once-a-day dosage) were coadministered with a high fat content breakfast, the extent of diltiazem absorption was not affected; T_{max} , however, occurred slightly earlier. The apparent elimination half-life after single or multiple dosing is 4 to 9.5 hours (mean 6.5 hours).

Diltiazem hydrochloride extended-release capsules (once-a-day

4
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Diltiazem hydrochloride extended-release capsules (once-a-day dosage) demonstrate non-linear pharmacokinetics. As the daily dose of diltiazem hydrochloride extended-release capsules (once-a-day dosage) is increased from 120 to 540 mg, there was a more than proportional increase in diltiazem plasma concentrations as evidenced by an increase of AUC, C_{max} and C_{min} of 6.8, 6 and 6.6 times, respectively, for a 4.5 times increase in dose.

INDICATIONS AND USAGE

Hypertension

Diltiazem Hydrochloride Extended-Release Capsules USP (Once-a-Day Dosage) are indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive medications.

Chronic Stable Angina

Diltiazem Hydrochloride Extended-Release Capsules USP (Once-a-Day Dosage) are indicated for chronic stable angina.

CONTRAINDICATIONS

Diltiazem is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second or third degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with severe hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

WARNINGS

1. Cardiac Conduction

Diltiazem prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (13 of 3007 patients or 0.43%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.

2. Congestive Heart Failure

Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction $24\% \pm 5\%$) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of diltiazem in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

3. Hypotension

Decreases in blood pressure associated with diltiazem therapy may occasionally result in symptomatic hypotension.

4. Acute Hepatic Injury

Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, and SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 6 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to diltiazem is uncertain in some cases, but probable in some (see PRECAUTIONS).

PRECAUTIONS

General

Diltiazem is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters of renal and hepatic function should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were

9.5 hours (mean 6.5 hours).

Diltiazem hydrochloride extended-release capsules (once-a-day dosage) demonstrate non-linear pharmacokinetics. As the daily dose of diltiazem hydrochloride extended-release capsules (once-a-day dosage) is increased from 120 to 540 mg, there was a more than proportional increase in diltiazem plasma concentrations as evidenced by an increase of AUC, C_{max} and C_{min} of 6.8, 6 and 0.5 times, respectively, for a 4.5 times increase in dose.

INDICATIONS AND USAGE

Hypertension

Diltiazem Hydrochloride Extended-Release Capsules USP (Once-a-Day Dosage) are indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive medications.

Chronic Stable Angina

Diltiazem Hydrochloride Extended-Release Capsules USP (Once-a-Day Dosage) are indicated for chronic stable angina.

CONTRAINDICATIONS

Diltiazem is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second or third degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with severe hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

WARNINGS

1. Cardiac Conduction

Diltiazem prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (13 of 3007 patients or 0.43%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.

2. Congestive Heart Failure

Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction $24\% \pm 6\%$) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of diltiazem in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

3. Hypotension

Decreases in blood pressure associated with diltiazem therapy may occasionally result in symptomatic hypotension.

4. Acute Hepatic Injury

Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, and SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to diltiazem is uncertain in some cases, but probable in some (see PRECAUTIONS).

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Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of diltiazem. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interactions

Due to the potential for additive effects, caution and careful titration are warranted in patients receiving diltiazem concomitantly with other agents known to affect cardiac contractility and/or conduction (see WARNINGS). Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using

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beta-blockers or digitalis concomitantly with diltiazem hydrochloride extended-release capsules (once-a-day dosage) (see WARNINGS). As with all drugs, care should be exercised when treating patients with multiple medications. Diltiazem is both a substrate and an inhibitor of the cytochrome P-450 3A4 enzyme system. Other drugs that are specific substrates, inhibitors, or inducers of the enzyme system may have a significant impact on the efficacy and side effect profile of diltiazem. Patients taking other drugs that are substrates of CYP450 3A4, especially patients with renal and/or hepatic impairment, may require dosage adjustment when starting or stopping concomitantly administered diltiazem in order to maintain optimum therapeutic blood levels.

Beta-Blockers

Controlled and uncontrolled domestic studies suggest that concomitant use of diltiazem and beta-blockers is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities. Administration of diltiazem concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. *In vitro*, propranolol appears to be displaced from its binding sites by diltiazem. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted (see WARNINGS).

Cimetidine

A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine 1200 mg per day and a single dose of diltiazem 60 mg. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digoxin

Administration of diltiazem with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing diltiazem therapy to avoid possible over- or under-digitalization (see WARNINGS).

Anesthetics

The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Cyclosporine

A pharmacokinetic interaction between diltiazem and cyclosporine has been observed during studies involving renal and cardiac transplant patients. In renal and cardiac transplant recipients, a reduction of cyclosporine dose ranging from 15% to 48% was necessary to maintain cyclosporine trough concentrations similar to those seen prior to the addition of diltiazem. If these agents are to be administered concurrently, cyclosporine concentrations should be monitored, especially when diltiazem therapy is initiated, adjusted, or discontinued.

The effect of cyclosporine on diltiazem plasma concentrations has not been evaluated.

Carbamazepine

Concomitant administration of diltiazem with carbamazepine has been reported to result in elevated serum levels of carbamazepine (40% to 72% increase), resulting in toxicity in some cases. Patients receiving these drugs concurrently should be monitored for a potential drug interaction.

Benzodiazepines

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

Lovastatin

In a ten-subject study, coadministration of diltiazem (120 mg bid) with lovastatin resulted in a 304 times increase in mean lovastatin AUC and C_{max} was observed during diltiazem coadministration. Diltiazem plasma levels were not significantly affected by lovastatin or pravastatin.

Rifampin

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 24 month study in rats at oral dosage levels of up to 100 mg/kg/day, and a 21 month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response *in vitro* or *in vivo* in mammalian cell assays or *in vitro* in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

Pregnancy

affected by kavastatin or pravastatin.

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Pregnancy

Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from 4 to 6 times (depending on species) the upper limit of the optimum dosage range in clinical trials (480 mg q.d. or 8 mg/kg q.d. for a 60 kg patient) resulted in embryo and fetal lethality. These studies revealed, in one species or another, a propensity to cause abnormalities of the skeleton, heart, retina, and tongue. Also observed were reductions in early individual pup weights and pup survival, prolonged delivery and increased incidence of stillbirths. There are no well-controlled studies in pregnant women; therefore, use diltiazem in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of diltiazem hydrochloride extended-release capsules (once-a-day dosage) is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

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

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies with diltiazem hydrochloride extended-release capsules (once-a-day dosage), as well as with other diltiazem formulations. It should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies. A total of 258 hypertensives were treated for between 4 and 8 weeks; a total of 207 patients with chronic stable angina were treated for 3 weeks with doses of diltiazem hydrochloride extended-release capsules (once-a-day dosage) ranging from 120 to 540 mg once daily. Two patients experienced first-degree AV block at 540 mg dose. The following table presents the most common adverse reactions, whether or not drug-related, reported in placebo-controlled trials in patients receiving diltiazem hydrochloride extended-release capsules (once-a-day dosage) up to 360 mg and up to 540 mg with rates in placebo patients shown for comparison.

MOST COMMON ADVERSE EVENTS IN DOUBLE-BLIND PLACEBO-CONTROLLED HYPERTENSION TRIALS*				
Adverse Event (Term)	Placebo n=57 # pts (%)	Diltiazem Hydrochloride Extended-Release Capsules USP (Once-a-Day Dosage) Up to 360 mg/800-540 mg n=148 # pts (%)		
		n=48 # pts (%)	n=48 # pts (%)	
edema, peripheral	1 (2)	8 (5)	7 (15)	
dizziness	4 (7)	6 (4)	2 (4)	
vasodilation	1 (2)	5 (3)	1 (2)	
dyspepsia	0 (0)	7 (5)	0 (0)	
pharyngitis	2 (4)	3 (2)	3 (6)	
cough	0 (0)	3 (2)	0 (0)	
infection	2 (4)	2 (1)	3 (6)	
diarrhea	0 (0)	2 (1)	1 (2)	
palpitations	0 (0)	2 (1)	1 (2)	
nervousness	0 (0)	3 (2)	0 (0)	

*Adverse events occurring in treated patients at 2% or more than placebo-treated patients.

MOST COMMON ADVERSE EVENTS IN DOUBLE-BLIND PLACEBO-CONTROLLED ANGINA TRIALS*				
Adverse Event (Term)	Placebo n=50 # pts (%)	Thiazap® Up to 360 mg n=158 # pts (%)		540 mg n=48 # pts (%)
headache	1 (2)	15 (8)	4 (8)	
edema, peripheral	1 (2)	3 (2)	5 (10)	
pain	1 (2)	10 (6)	3 (6)	
dizziness	0 (0)	5 (3)	5 (10)	
asthenia	0 (0)	1 (1)	2 (4)	
dyspepsia	0 (0)	2 (1)	3 (6)	
dyspnea	0 (0)	1 (1)	3 (6)	
bronchitis	0 (0)	1 (1)	2 (4)	
AV block	0 (0)	0 (0)	2 (4)	
infection	0 (0)	2 (1)	1 (2)	
flu syndrome	0 (0)	0 (0)	1 (2)	
cough increase	0 (0)	2 (1)	1 (2)	
extrasystoles	0 (0)	0 (0)	1 (2)	
joint	0 (0)	2 (1)	2 (4)	
myalgia	0 (0)	0 (0)	1 (2)	
impotence	0 (0)	0 (0)	1 (2)	
conjunctivitis	0 (0)	0 (0)	1 (2)	
rash	0 (0)	2 (1)	1 (2)	
abdominal enlargement	0 (0)	0 (0)	1 (2)	

*Adverse events occurring in treated patients at 2% or more than placebo-treated patients.

In addition, the following events have been reported infrequently (less than 2%) in clinical trials with other diltiazem products:

concomitant	0	(0)	0	(0)	1	(2)
rash	0	(0)	2	(1)	1	(2)
abdominal enlargement	0	(0)	0	(0)	1	(2)

*Adverse events occurring in treated patients at 2% or more than placebo-treated patients.

In addition, the following events have been reported infrequently (less than 2%) in clinical trials with other diltiazem products:

Cardiovascular

Angina, arrhythmia, AV block (second- or third-degree), bundle branch block, congestive heart failure, ECG abnormalities, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles.

Nervous System

Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor.

Gastrointestinal

Anorexia, constipation, diarrhea, dry mouth, dyspepsia, mild elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see hepatic warnings), thirst, vomiting, weight increase.

Dermatological

Petechiae, photosensitivity, pruritus.

Other

Albuminuria, allergic reaction, amblyopia, asthenia, CPK increase, crystalluria, dyspnea, edema, epistaxis, eye irritation, headache, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarthralgia, polyuria, rhinitis, sexual difficulties, gynecomastia.

In addition the following postmarketing events have been reported infrequently in patients receiving diltiazem: alopecia, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A number of well documented cases of generalized rash, characterized as leukocytoclastic vasculitis, have been reported. However, a definitive cause and effect relationship between these events and diltiazem therapy is yet to be established.

OVERDOSAGE

The oral LD50's in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD50's in these species were 60 and 38 mg/kg, respectively. The oral LD50 in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg.

The toxic dose in man is not known. Due to extensive metabolism, blood levels after a standard dose of diltiazem can vary over tenfold, limiting the usefulness of blood levels in overdose cases. There have been 29 reports of diltiazem overdose in doses ranging from less than 1 gm to 10.8 gm. Sixteen of these reports involved multiple drug ingestions. Twenty-two reports indicated patients had recovered from diltiazem overdose ranging from less than 1 gm to 10.8 gm. There were seven reports with a fatal outcome; although the amount of diltiazem ingested was unknown, multiple drug ingestions were confirmed in six of the seven reports.

Events observed following diltiazem overdose included bradycardia, hypotension, heart block, and cardiac failure. Most reports of overdose described some supportive medical measure and/or drug treatment. Bradycardia frequently responded favorably to atropine as did heart block, although cardiac pacing was also frequently utilized to treat heart block. Fluids and vasopressors were used to maintain blood pressure, and in cases of cardiac failure, inotropic agents were administered. In addition, some patients received treatment with ventilatory support, activated charcoal, and/or intravenous calcium. Evidence of the effectiveness of intravenous calcium administration to reverse the pharmacological effects of diltiazem overdose was conflicting.

In the event of overdose or exaggerated response, appropriate supportive measures should be employed in addition to gastrointestinal decontamination. Diltiazem does not appear to be removed by peritoneal or hemodialysis. Based on the known pharmacological effects of diltiazem and/or reported clinical experiences, the following measures may be considered:

Bradycardia: Administer atropine (0.60 to 1 mg) if there is no response to vagal blockage, administer isoproterenol cautiously.

High-Degree AV Block: Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.

Cardiac Failure: Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.

Hypotension: Vasopressors (e.g., dopamine or norepinephrine). Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

In a few reported cases, overdosage with calcium channel blockers has been associated with hypotension and bradycardia, initially refractory to atropine but becoming more responsive to this treatment when the patients received large doses (close to 1 gram/hour for more than 24 hours) of calcium chloride.

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Due to extensive metabolism, plasma concentrations after a standard dose of diltiazem can vary over tenfold, which significantly limits their value in evaluation cases of overdosage.

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

DOSEAGE AND ADMINISTRATION

Hypertension

Dosage needs to be adjusted by titration to individual patient needs. When used as monotherapy, usual starting doses are 120 to 240 mg once daily. Maximum antihypertensive effect is usually observed by 14 days of chronic therapy; therefore, dosage adjustments should be scheduled accordingly. The usual dosage range studied in clinical trials was 120 to 540 mg once daily. Current clinical experience with 540 mg dose is limited, however, the dose may be increased to 540 mg once daily.

Angina

Dosages for the treatment of angina should be adjusted to each patient's needs, starting with a dose of 120 mg to 180 mg once daily. Individual patients may respond to higher doses of up to 540 mg once daily. When necessary, titration should be carried out over 7 to 14 days.

Concomitant use with Other Cardiovascular Agents

1. Sublingual nitroglycerin may be taken as required to abort acute anginal attacks during diltiazem hydrochloride therapy.
2. Prophylactic Nitrate Therapy — Diltiazem hydrochloride may be safely coadministered with short- and long-acting nitrates.
3. Beta-blockers. (See WARNINGS and PRECAUTIONS.)
4. Antihypertensives — Diltiazem has an additive antihypertensive effect when used with other antihypertensive agents. Therefore, the dosage of diltiazem or the concomitant antihypertensive may need to be adjusted when adding one to the other.

Hypertensive or anginal patients who are treated with other formulations of diltiazem can safely be switched to diltiazem hydrochloride extended-release capsules (once-a-day dosage) at the nearest equivalent total daily dose. Subsequent titration to higher or lower doses may be necessary and should be initiated as clinically indicated.

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

HOW SUPPLIED

STRENGTH	DESCRIPTION	QUANTITY	NDC
120 mg	Diltiazem Hydrochloride Extended-Release Capsules USP, 120 mg capsules, 100 capsules	100's	62337-688-90
180 mg	Diltiazem Hydrochloride Extended-Release Capsules USP, 180 mg capsules, 100 capsules	100's	62337-689-90
240 mg	Diltiazem Hydrochloride Extended-Release Capsules USP, 240 mg capsules, 100 capsules	100's	62337-690-90
300 mg	Diltiazem Hydrochloride Extended-Release Capsules USP, 300 mg capsules, 100 capsules	100's	62337-691-90
360 mg	Diltiazem Hydrochloride Extended-Release Capsules USP, 360 mg capsules, 100 capsules	100's	62337-692-90
480 mg	Diltiazem Hydrochloride Extended-Release Capsules USP, 480 mg capsules, 100 capsules	100's	62337-693-90
540 mg	Diltiazem Hydrochloride Extended-Release Capsules USP, 540 mg capsules, 100 capsules	100's	62337-694-90
720 mg	Diltiazem Hydrochloride Extended-Release Capsules USP, 720 mg capsules, 100 capsules	100's	62337-695-90
900 mg	Diltiazem Hydrochloride Extended-Release Capsules USP, 900 mg capsules, 100 capsules	100's	62337-696-90
1080 mg	Diltiazem Hydrochloride Extended-Release Capsules USP, 1080 mg capsules, 100 capsules	100's	62337-697-90
1260 mg	Diltiazem Hydrochloride Extended-Release Capsules USP, 1260 mg capsules, 100 capsules	100's	62337-698-90
1440 mg	Diltiazem Hydrochloride Extended-Release Capsules USP, 1440 mg capsules, 100 capsules	100's	62337-699-90
1620 mg	Diltiazem Hydrochloride Extended-Release Capsules USP, 1620 mg capsules, 100 capsules	100's	62337-700-90
1800 mg	Diltiazem Hydrochloride Extended-Release Capsules USP, 1800 mg capsules, 100 capsules	100's	62337-701-90

Storage conditions:
Store at controlled room temperature 15° to 30°C (59° to 86°F) [see USP].
Avoid excessive humidity. Dispense in tight containers with safety closures.

agents (isoproterenol, dopamine, or dobutamine) and diuretics.

Hypotension: Vasopressors (e.g. dopamine or norepinephrine). Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

In a few reported cases, overdosage with calcium channel blockers has been associated with hypotension and bradycardia, initially refractory to atropine but becoming more responsive to this treatment when the patients received large doses (close to 1 gram/hour for more than 24 hours) of calcium chloride.

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3. Beta-blockers. (See WARNINGS and PRECAUTIONS.)
4. Antihypertensives - Diltiazem has an additive antihypertensive effect when used with other antihypertensive agents. Therefore, the dosage of diltiazem or the concomitant antihypertensive may need to be adjusted when adding one to the other.

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HOW SUPPLIED

Diltiazem Hydrochloride Extended-Release Capsules USP		QUANTITY	UNIT OF MEASURE
120 mg	24 pink/white opaque capsules	30's	100's
180 mg	12 light blue/white opaque capsules	30's	100's
180 mg	12 light blue/white opaque capsules	30's	100's
240 mg	6 light blue/white opaque capsules	30's	100's
240 mg	6 light blue/white opaque capsules	30's	100's
300 mg	4 light blue/white opaque capsules	30's	100's
300 mg	4 light blue/white opaque capsules	30's	100's
360 mg	3 light blue/white opaque capsules	30's	100's
360 mg	3 light blue/white opaque capsules	30's	100's

Storage conditions:
Store at controlled room temperature 15° to 30°C (59° to 86°F) [see USP].
Avoid excessive humidity. Dispense in tight containers with safety closures.

Manufactured by:
Andrx Pharmaceuticals, Inc.
FT. Lauderdale, FL 33314

Rev. date: 11/02

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ANDA #75-401

Taztia™ (Diltiazem Hydrochloride Extended-release Capsules)

120 mg, 180 mg, 240 mg, 300 mg and 360 mg

FINAL PRINTED LABELING

NDC 62037-696-30

ONCE DAILY
Taztia™
(diltiazem HCl extended-release capsules, USP)
ONCE-A-DAY DOSAGE

120 mg
30 CAPSULES

Rx ONLY

Usual Dosage: Administer once daily, see insert for full prescribing information. Store at controlled room temperature, 15° to 30°C (59° to 86°F) [see USP]. Dispense in tight containers with safety closures. Keep this and all medication out of the reach of children.

Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314

LOT: APR 10 2003
EXP: APR 10 2003
N 3 62037-696-30 5

NDC 62037-696-10

ONCE DAILY
Taztia™
(diltiazem HCl extended-release capsules, USP)
ONCE-A-DAY DOSAGE

120 mg
1000 CAPSULES

Rx ONLY

Usual Dosage: Administer once daily, see insert for full prescribing information. Store at controlled room temperature, 15° to 30°C (59° to 86°F) [see USP]. Dispense in tight containers with safety closures. Keep this and all medication out of the reach of children.

Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314

APR 10 2003
EXP: APR 10 2003
LOT: APR 10 2003
N 3 62037-696-10 7

NDC 62037-696-90

ONCE DAILY
Taztia™
(diltiazem HCl extended-release capsules, USP)
ONCE-A-DAY DOSAGE

120 mg
90 CAPSULES

Rx ONLY

Usual Dosage: Administer once daily, see insert for full prescribing information. Store at controlled room temperature, 15° to 30°C (59° to 86°F) [see USP]. Dispense in tight containers with safety closures. Keep this and all medication out of the reach of children.

Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314

LOT: APR 10 2003
EXP: APR 10 2003
N 3 62037-696-90 6

ANDA #75-401

Taztia™ (Diltiazem Hydrochloride Extended-release Capsules)

120 mg, 180 mg, 240 mg, 300 mg and 360 mg

FINAL PRINTED LABELING

NDC 62037-697-30

180 mg
30 CAPSULES

Rx ONLY

Andrx
Pharmaceuticals, Inc.

Taztia
(diltiazem HCl extended-release capsules, USP)
ONCE-A-DAY DOSAGE

Usual Dosage: Administer once daily, see insert for full prescribing information.
Store at controlled room temperature, 15° to 30°C (59° to 86°F) [see USP].
Dispense in tight containers with safety closures.
Keep this and all medication out of the reach of children.

LOT: 3 62037-697-30 2
EXP: APR 10 2003

7094 (01/03)

NDC 62037-697-10

180 mg
1000 CAPSULES

Rx ONLY

Andrx
Pharmaceuticals, Inc.

Taztia
(diltiazem HCl extended-release capsules, USP)
ONCE-A-DAY DOSAGE

Usual Dosage: Administer once daily, see insert for full prescribing information.
Store at controlled room temperature, 15° to 30°C (59° to 86°F) [see USP].
Dispense in tight containers with safety closures.
Keep this and all medication out of the reach of children.

LOT: 3 62037-697-10 4
EXP: APR 10 2003

7095 (01/03)

NDC 62037-697-90

180 mg
30 CAPSULES

Rx ONLY

Andrx
Pharmaceuticals, Inc.

Taztia
(diltiazem HCl extended-release capsules, USP)
ONCE-A-DAY DOSAGE

Usual Dosage: Administer once daily, see insert for full prescribing information.
Store at controlled room temperature, 15° to 30°C (59° to 86°F) [see USP].
Dispense in tight containers with safety closures.
Keep this and all medication out of the reach of children.

LOT: 3 62037-697-90 6
EXP: APR 10 2003

7105 (01/03)

ANDA #75-401

TAZTIA (diltiazem hydrochloride extended-release capsules, USP),
120 mg, 180 mg, 240 mg, 300 mg and 360 mg.

FINAL PRINTED LABELING

NDC 62037-698-30

Andrx
PHARMACEUTICALS, INC.

TaztiaXTM
(diltiazem HCl extended-release capsules, USP)
ONCE-A-DAY DOSAGE

240 mg

Usual Dosage: Administer once daily, see insert for full prescribing information.

Store at controlled room temperature, 15° to 30°C (59° to 86°F) [see USP].

Dispense in tight containers with safety closures.

Keep this and all medication out of the reach of children.

Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314

LOT: 7096 (03/03)

EXP: APR 10 2003

3 62037-698-30 9

APPROVED

Rx ONLY 30 CAPSULES

NDC 62037-698-10

Andrx
PHARMACEUTICALS, INC.

TaztiaXTM
(diltiazem HCl extended-release capsules, USP)
ONCE-A-DAY DOSAGE

240 mg

Usual Dosage: Administer once daily, see insert for full prescribing information.

Store at controlled room temperature, 15° to 30°C (59° to 86°F) [see USP].

Dispense in tight containers with safety closures.

Keep this and all medication out of the reach of children.

Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314

LOT: 7097 (03/03)

EXP: APR 10 2003

3 62037-698-10 1

APPROVED

NDC 62037-698-90

Andrx
PHARMACEUTICALS, INC.

TaztiaXTM
(diltiazem HCl extended-release capsules, USP)
ONCE-A-DAY DOSAGE

240 mg

Usual Dosage: Administer once daily, see insert for full prescribing information.

Store at controlled room temperature, 15° to 30°C (59° to 86°F) [see USP].

Dispense in tight containers with safety closures.

Keep this and all medication out of the reach of children.

Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314

LOT: 7106 (01/03)

EXP: APR 10 2003

3 62037-698-90 3

APPROVED

ANDA #75-401

TAZTIA (diltiazem hydrochloride extended-release capsules, USP),
120 mg, 180 mg, 240 mg, 300 mg and 360 mg
FINAL PRINTED LABELING

NDC 62037-699-90



TaztiaXTM

(diltiazem HCl extended-release capsules, USP)

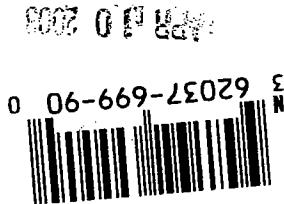
ONCE-A-DAY DOSAGE

300 mg

Rx ONLY 90 CAPSULES

Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314

Usual Dosage: Administer once daily,
see insert for full prescribing
information.
Store at controlled room temperature,
15° to 30°C (59° to 86°F) (see USP).
Dispense in tight containers with
safety closures.
Keep this and all medication out of
the reach of children.



LOT:
EXP:

NDC 62037-699-10



TaztiaXTM

(diltiazem HCl extended-release capsules, USP)

ONCE-A-DAY DOSAGE

300 mg

Rx ONLY

1000 CAPSULES

Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314

Usual Dosage: Administer once
daily, see insert for full prescribing
information.

Store at controlled room temperature,
15° to 30°C (59° to 86°F) (see USP).

Dispense in tight containers with
safety closures.

Keep this and all medication out of
the reach of children.



7099 (01/03)

LOT:
EXP:

APR 10 2003

NDC 62037-699-30



TaztiaXTM

(diltiazem HCl extended-release capsules, USP)

ONCE-A-DAY DOSAGE

300 mg

Rx ONLY

30 CAPSULES

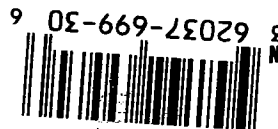
Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314

Usual Dosage: Administer once daily,
see insert for full prescribing
information.

Store at controlled room temperature,
15° to 30°C (59° to 86°F) (see USP).

Dispense in tight containers with
safety closures.

Keep this and all medication out of
the reach of children.



7098 (03/03)

LOT:
EXP:

ANDA #75-401

TAZTIA (diltiazem hydrochloride extended-release capsules, USP),
120 mg, 180 mg, 240 mg, 300 mg and 360 mg

FINAL PRINTED LABELING

Usual Dosage: Administer once daily, see insert for full prescribing information.
Store at controlled room temperature, 15° to 30°C (59° to 86°F) [see USP].
Dispense in tight containers with safety closures.
Keep this and all medication out of the reach of children.

TaztiaX™
(diltiazem HCl extended-release capsules, USP)
ONCE-A-DAY DOSAGE

360 mg

Rx ONLY 30 CAPSULES

Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314

LOT: 62037-700-30
EXP: 03/03

7100 (03/03)

NDC 62037-700-10

TaztiaX™
(diltiazem HCl extended-release capsules, USP)
ONCE-A-DAY DOSAGE

360 mg

Rx ONLY 1000 CAPSULES

Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314

Usual Dosage: Administer once daily, see insert for full prescribing information.
Store at controlled room temperature, 15° to 30°C (59° to 86°F) [see USP].
Dispense in tight containers with safety closures.
Keep this and all medication out of the reach of children.

APPROVED

LOT: 62037-700-10
EXP: 03/03

7101 (03/03)

NDC 62037-700-90

TaztiaX™
(diltiazem HCl extended-release capsules, USP)
ONCE-A-DAY DOSAGE

360 mg

Rx ONLY 90 CAPSULES

Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314

Usual Dosage: Administer once daily, see insert for full prescribing information.
Store at controlled room temperature, 15° to 30°C (59° to 86°F) [see USP].
Dispense in tight containers with safety closures.
Keep this and all medication out of the reach of children.

LOT: 62037-700-90
EXP: 03/03

7108 (03/03)

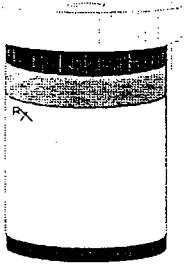
**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75-401

CSO LABELING REVIEW(S)

FAX COVER SHEET



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Rockville, Maryland

Date: April 26, 2000
TO: Jackie Davis - ANDRX
Phone: (954) 321-5229 Fax: (954) 587-1054
From: Adolph Vezza - Labeling Review Branch
Phone: (301) 827-5846 Fax: (301) 443-3847
Number of Pages: 3
(Including Cover Sheet)

Comments:

This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

DILTIAZEM HCl EXTENDED-RELEASE CAPSULES (ONCE A DAY DOSAGE)

PRECAUTIONS

1. Drug Interactions

- a. First paragraph - Replace the text after the third sentence with the following text:

... multiple medications. Diltiazem is both a substrate and an inhibitor of the cytochrome P-450 3A4 enzyme system. Other drugs that are specific substrates, inhibitors, or inducers of the enzyme system may have a significant impact on the efficacy and side effect profile of diltiazem. Patients taking other drugs that are substrates of CYP450 3A4, especially patients with renal and/or hepatic impairment, may require dosage adjustment when starting or stopping concomitantly administered diltiazem in order to maintain optimum therapeutic blood levels.

- b. Add the following subsections after the "Carbamazepine" subsection.

Benzodiazepines

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

← text missing here - corrected text
refaxed 4/26/00 A. Vezza

Lovastatin

In a ten-subject study, coadministration of diltiazem (120 mg bid) with lovastatin resulted in a 304 times increase in mean lovastatin AUC and C_{max} was observed during diltiazem coadministration. Diltiazem plasma levels were not significantly affected by lovastatin or pravastatin.

Rifampin

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

2. Add the following subsection as the last subsection of the PRECAUTIONS section:

Geriatric Use

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

APPEARS THIS WAY
ON ORIGINAL

**APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: **75-401**

Dates of Submission: **November 22 and December 10, 2002 and January 14 and March 18, 2003**

Applicant's Name: **Andrx Pharmaceuticals, Inc.**

Proprietary Name: **Taztia XT™**

Established Name: **Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-Day Dosage), 120 mg, 180 mg, 240 mg, 300 mg, and 360 mg**

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? **YES**

Container Labels: **30s, 90s, and 1000s**

*Satisfactory in FPL as of **January 14, 2003 submission [v 11.1]***

*Satisfactory in FPL as of **March 18, 2003 submission. [v 12.1]* (see below)***

Professional Package Insert Labeling:

*Satisfactory in FPL as of **January 15, 2003 submission.***

Revisions needed post-approval: ~~DMETS has~~ asked for revisions to the container labels - These were faxed out to the firm on March 14, 2003 - ANDRX has agreed to make these changes after approval - Because their diltiazem product line was approved with the current labeling format and since OGD has previously tentatively approved this application with this labeling it was felt that the changes suggested by DMETS could be done post-approval. They are as seen below:

1. The "sun" image as it appears in front of the proprietary name may be construed to be the letter "O" since the proprietary name also contains a modifier (XT) in a similar color. The "sun" image also contains "rays" that cover some of the first letter "T" in the proprietary name and interfere with the appearance of the proprietary name. Delete the "sun" image to increase the prominence of the proprietary name.
2. The "ONCE DAILY" phrase that appears in conjunction with the proprietary name should be deleted. It not only distracts from the visual appearance of the proprietary name, but also is redundant to the "ONCE-A-DAY DOSAGE" statement on the principal display panel.
3. The large "XT" design covers approximately 50% of the total area of the label. This "XT" design distracts from the prominence of the proprietary name. DMETS recommends deleting the design as it obscures the readability of the name.
4. DMETS recommends moving the dosage strength to be directly beneath the proprietary and established name and away from the net quantity statement.
5. DMETS recommends increasing the prominence of the phrase "ONCE -A-DAY DOSAGE".
6. DMETS recommends increasing the prominence of the dosage strength on the 180 mg container label. This may be accomplished with a different background color in the boxed area.

DMETS recommends using a different background color to display the dosage strength for either the 300 mg or 360 mg container label. Both the 300 mg and 360 mg dosage strengths will be placed next to each other on the pharmacy shelf. The similarity between the red and maroon colors may cause the bottles to be inadvertently interchanged and lead to medication errors.

ANDRX has e-mailed OGD color copies of what the new labeling and we forwarded it on to DMETS via e-mail. They had no objections except for one - the same one OGD picked up on - the boxing on the container labels for the 240 mg and 360 mg capsule strengths were very similar in color - kind of an "orangy". ANDRX was notified of this and they immediately e-mailed us a new container label for the 360 mg strength that had "black" boxing around the strength. This was found acceptable by all.

* ANDRX had packaged approximately one month's supply of this drug product with the old labeling. A representative of the firm requested of P. Rickman that the firm be allowed to use up all of this packaged drug product before using the new labeling which was submitted March 18, 2003 with the above requested revisions - **DOCUMENT ROOM - PLEASE STAMP BOTH SETS OF CONTAINER LABELS "APPROVED" - 1-15-03 and 3-18-03**

BASIS OF APPROVAL:

Was this approval based upon a petition? Yes

What is the RLD on the 356(h) form: Tiazac®

NDA Number: 20-401

NDA Drug Name: Tiazac® (diltiazem hydrochloride) Extended-release Capsules

NDA Firm: Biovail

Date of Approval of NDA Insert and supplement #: 4/5/00 (S-015)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: side-by-sides

Other Comments: I spoke to Jackie Davis of the firm. She asked some questions:

1. What if firm wants to change the proposed trade name - (a) before approval - send in new name and labeling which would be sent to OPDRA for evaluation (b) after approval - send in prior approval supplement with new name and labeling which would be sent to OPDRA for evaluation
2. What if firm drops the proposed trade name and goes with the established name - (a) before approval - send in new labels and labeling without the trade name (b) after approval - send in the new labels and labeling with out the trade name in an annual report.
3. I told Ms. Davis that the print size in the two tables in the PI is too small and that before full approval the firm will need to send in revised PI's with this deficiency corrected. The firm has done this with the April 28, 2000 amendment.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 25	X		
Is this name different than that used in the Orange Book?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? YES - SUBMITTED TO OPDRA - FOUND ACCEPTABLE	X		
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany		X	

the product?			
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?	X		
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD: (portions taken from previous review)

1. This review was based on the labeling for Tiazac® (S-015 - Approved 4-5-00; Revised 10-99). There is an SE1-007 supplement approved 1-30-98 which I have asked the project manager, Dave Roeder, to send me or at least let me know what changes were approved. I

received the labeling - SE1-007 provides for the use of Tiazac® for the treatment of chronic stable angina. This has exclusivity til 1/30/01.

The new labeling has 2 tables in the ADVERSE REACTIONS section, the second being adverse reaction rates which occurred in angina trials. Beneath the 2 tables is a listing of adverse reactions occurring in 2% or more than placebo-treated patients. The previous labeling has 1% table (S-006) and the 1% adverse reactions listing for this review. I have E-mailed Dave Roeder, the PM for this drug, and let him know our quandary. What do we do when another generic comes in and models after the SE1-007 labeling? This issue has been resolved - since the exclusivity has expired the information relating to the chronic stable angina indication has been included in the labeling.

The labeling (S-019) allows for the sprinkling of the capsule contents on applesauce. I have asked the generic to add this information to the DOSAGE AND ADMINISTRATION section as in the innovator. As a result of this, the generic will have to do a bio sprinkle study per Vijay. This will hold up their approval/tentative approval. I checked with the PM in New Drug about the possibility of this getting exclusivity and was told that it would not. The firm has done a sprinkle study and BIO has found it acceptable.

2. Andrx has filed this ANDA under paragraph IV. The patent for the RLD does not expire until June 25, 2013. Applicant's labeling revised to carve out "management of chronic stable angina" protected until 1-30-01. The firm has certified to this. Since it is now after this date we asked the firm to put this information back in and they have with the 3-8-01 amendment.

3. Storage/dispensing recommendations:

RLD - Store at CRT 20°-25°C

ANDA - Store at CRT 15°-30°C (59°-86°F)[see USP]

RLD - Dispense in well-closed containers with safety closures

ANDA - Dispense in tight containers with safety closures.

USP - Preserve in tight containers.

4. The inactives are listed accurately in the DESCRIPTION section.
 5. The firm has done single dose fasting, single dose food/fasting, and multiple dose steady state studies. The bio was found satisfactory. Waivers were granted for the 120 mg, 180 mg, 240 mg, and 300 mg capsules. The studies were done with the 360 mg capsule. Firm will have to do a bio sprinkle study however (see above).
 6. Container/closure

30s and 1000s - 120 mg, 180 mg, 240 mg, 300 mg, and 360 mg

The 120 mg, 180 mg, 240 mg, 300 mg and 360 mg 30s will have CRCs.
 7. The firm has submitted the proprietary name, "TAZTIA XT" and it has been sent to OPDRA. The firm is exploring possibilities of dropping the trade name and going with the established name or proposing a different trade name. See comments under "Other Comments" and telecon dated 1-28-00. OPDRA has found the proposed trade name acceptable.
 8. The firm has distinguished its different strengths by boxing in contrasting colors.
-
-

Date of Review: 3-24-03

Dates of Submission: 11-22 & 12-10-02 & 1-15 & 3-18-03

Primary Reviewer: Adolph Vezza

Date:

3/26/03

Team Leader: Lillie Golson

Date:

3/26/03

CC:

ANDA: 75-401

DUP/DIVISION FILE

HFD-613/AVezza/LGolson (no cc)

aev/3/24/03|V:\FIRMSAM\ANDRX\LTRS&REV\75401.APL4

Review

APPEARS THIS WAY
ON ORIGINAL

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: **75-401**

Dates of Submission: **November 22 and December 10, 2002 and January 15, 2003**

Applicant's Name: **Andrx Pharmaceuticals, Inc.**

Proprietary Name: **Taztia XT™**

Established Name: **Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-Day Dosage), 120 mg, 180 mg, 240 mg, 300 mg, and 360 mg**

Labeling Deficiencies:

The Division of Medication Errors and Technical Support (DMETS) has reviewed the proposed container labels for Taztia XT and approved container labels for Diltia XT and Cartia XT in an attempt to focus on safety issues to prevent possible medication errors. DMETS is concerned with potential confusion and medication errors due to labeling similarities across the product line. It appears Andrx Pharmaceuticals, Inc. has employed the same template for all three diltiazem hydrochloride extended release products. We have identified the following areas of improvement, in the interest of minimizing potential user error and patient safety. These recommendations should also help distinguish the Taztia XT container labeling from either the Diltia XT or Cartia XT container labeling.

1. The "sun" image as it appears in front of the proprietary name may be construed to be the letter "O" since the proprietary name also contains a modifier (XT) in a similar color. The "sun" image also contains "rays" that cover some of the first letter "T" in the proprietary name and interfere with the appearance of the proprietary name. Delete the "sun" image to increase the prominence of the proprietary name.
2. The "ONCE DAILY" phrase that appears in conjunction with the proprietary name should be deleted. It not only distracts from the visual appearance of the proprietary name, but also is redundant to the "ONCE-A-DAY DOSAGE" statement on the principal display panel.
3. The large "XT" design covers approximately 50% of the total area of the label. This "XT" design distracts from the prominence of the proprietary name. DMETS recommends deleting the design as it obscures the readability of the name.
4. DMETS recommends moving the dosage strength to be directly beneath the proprietary and established name and away from the net quantity statement.
5. DMETS recommends increasing the prominence of the phrase "ONCE -A-DAY DOSAGE".
6. DMETS recommends increasing the prominence of the dosage strength on the 180 mg container label. This may be accomplished with a different background color in the boxed area.

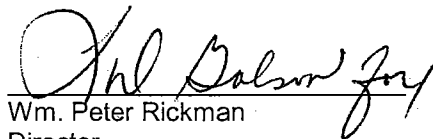
DMETS recommends using a different background color to display the dosage strength for either the 300 mg or 360 mg container label. Both the 300 mg and 360 mg dosage strengths will be placed next to each other on the pharmacy shelf. The similarity between the red and maroon colors may cause the bottles to be inadvertently interchanged and lead to medication errors.

Please revise your container labels, as instructed above, and submit 12 copies in final print for full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

<http://www.fda.gov/cder/cdernew/listserv.html>

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.



Wm. Peter Rickman

Director

Division of Labeling and Program Support

Office of Generic Drugs

Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? YES

Container Labels: 30s, 90s, and 1000s

Professional Package Insert Labeling:

Satisfactory in FPL as of January 15, 2003 submission.

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? Yes

What is the RLD on the 356(h) form: Tiazac®

NDA Number: 20-401

NDA Drug Name: Tiazac® (diltiazem hydrochloride) Extended-release Capsules

NDA Firm: Biovail

Date of Approval of NDA Insert and supplement #: 4/5/00 (S-015)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: side-by-sides

Other Comments: I spoke to Jackie Davis of the firm. She asked some questions:

1. What if firm wants to change the proposed trade name - (a) before approval - send in new name and labeling which would be sent to OPDRA for evaluation (b) after approval - send in prior approval supplement with new name and labeling which would be sent to OPDRA for evaluation
2. What if firm drops the proposed trade name and goes with the established name - (a) before approval - send in new labels and labeling without the trade name (b) after approval - send in the new labels and labeling with out the trade name in an annual report.
3. I told Ms. Davis that the print size in the two tables in the PI is too small and that before full approval the firm will need to send in revised PI's with this deficiency corrected. The firm has done this with the April 28, 2000 amendment.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 25	X		
Is this name different than that used in the Orange Book?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? YES - SUBMITTED TO OPDRA - FOUND ACCEPTABLE	X		
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartonning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be			

the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?	X		
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD: (portions taken from previous review)

1. This review was based on the labeling for Tiazac® (S-015 - Approved 4-5-00; Revised 10-99). There is an SE1-007 supplement approved 1-30-98 which I have asked the project manager, Dave Roeder, to send me or at least let me know what changes were approved. I received the labeling - SE1-007 provides for the use of Tiazac® for the treatment of chronic stable angina. This has exclusivity til 1/30/01.
The new labeling has 2 tables in the ADVERSE REACTIONS section, the second being adverse reaction rates which occurred in angina trials. Beneath the 2 tables is a listing of adverse reactions occurring in 2% or more than placebo-treated patients. The previous

labeling has 1% table (S-006) and the 1% adverse reactions listing for this review. I have E-mailed Dave Roeder, the PM for this drug, and let him know our quandary. What do we do when another generic comes in and models after the SE1-007 labeling?

The labeling (S-019) allows for the sprinkling of the capsule contents on applesauce. I have asked the generic to add this information to the DOSAGE AND ADMINISTRATION section as in the innovator. As a result of this, the generic will have to do a bio sprinkle study per Vijay. This will hold up their approval/tentative approval. I checked with the PM in New Drug about the possibility of this getting exclusivity and was told that it would not. The firm has done a sprinkle study and BIO has found it acceptable.

2. Andrx has filed this ANDA under paragraph IV. The patent for the RLD does not expire until June 25, 2013.

3. Storage/dispensing recommendations:

RLD - Store at CRT 20°-25°C

ANDA - Store at CRT 15°-30°C (59°-86°F)[see USP]

RLD - Dispense in well-closed containers with safety closures

ANDA - Dispense in tight containers with safety closures.

USP - Preserve in tight containers.

4. The inactives are listed accurately in the DESCRIPTION section.

5. The firm has done single dose fasting, single dose food/fasting, and multiple dose steady state studies. The bio was found satisfactory. Waivers were granted for the 120 mg, 180 mg, 240 mg, and 300 mg capsules. The studies were done with the 360 mg capsule. Firm will have to do a bio sprinkle study however (see above).

6. Container/closure

30s and 1000s - 120 mg, 180 mg, 240 mg, 300 mg, and 360 mg

The 120 mg, 180 mg, 240 mg, 300 mg and 360 mg 30s will have CRCs.

7. The firm has submitted the proprietary name, "TAZTIA XT" and it has been sent to OPDRA. The firm is exploring possibilities of dropping the trade name and going with the established name or proposing a different trade name. See comments under "Other Comments" and telecon dated 1-28-00. OPDRA has found the proposed trade name acceptable.

8. The firm has distinguished its different strengths by contrasting colors.

9. DMETS has done a "pre-approval" screen of the container labels with the firm's proposed proprietary name _____ and has found deficiencies with the container labels (but not the proposed name). The labeling deficiencies will be faxed out to the firm 3-14-03.

Date of Review: 3-14-03

Dates of Submission: 11-22 & 12-10-02 & 1-15-03

Primary Reviewer: Adolph Vezza

Date:

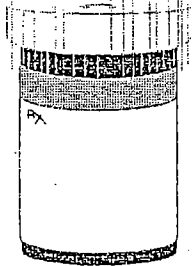
3/14/03

Team Leader: Lillie Golson

Date:

3/14/03

FAX COVER SHEET



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Rockville, Maryland

Date: March 14, 2003

TO: Bill Stahovec - Andrx

Phone: (954) 358-6124 Fax: (954) 358-6350

From: Adolph Vezza - Labeling Review Branch

Phone: (301) 827-5846 Fax: (301) 443-3847

Number of Pages: 3
(Including Cover Sheet)

Comments:

This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

C.V. 3/21/01
TENTATIVE APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-401**

Date of Submission: **March 8, 2001**

Applicant's Name: **Andrx Pharmaceuticals, Inc.**

Proprietary Name: **Taztia XT™**

Established Name: **Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-Day Dosage), 120 mg, 180 mg, 240 mg, 300 mg, and 360 mg**

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? **YES**

Container Labels: **30s and 1000s**
Satisfactory in FPL as of January 14, 2000 submission.

Professional Package Insert Labeling:
Satisfactory in FPL as of March 8, 2001 submission.

Revisions needed post-approval: **None**

BASIS OF APPROVAL:

Was this approval based upon a petition? **Yes**

What is the RLD on the 356(h) form: **Tiazac®**

NDA Number: **20-401**

NDA Drug Name: **Tiazac® (diltiazem hydrochloride) Extended-release Capsules**

NDA Firm: **Biovail**

Date of Approval of NDA Insert and supplement #: **4/5/00 (S-015)**

Has this been verified by the MIS system for the NDA? **Yes**

Was this approval based upon an OGD labeling guidance? **No**

Basis of Approval for the Container Labels: **side-by-sides**

Other Comments: I spoke to Jackie Davis of the firm. She asked some questions:

1. What if firm wants to change the proposed trade name - (a) before approval - send in new name and labeling which would be sent to OPDRA for evaluation (b) after approval - send in prior approval supplement with new name and labeling which would be sent to OPDRA for evaluation
2. What if firm drops the proposed trade name and goes with the established name - (a) before approval - send in new labels and labeling without the trade name (b) after approval - send in the new labels and labeling with out the trade name in an annual report.
3. I told Ms. Davis that the print size in the two tables in the PI is too small and that before full approval the firm will need to send in revised PI's with this deficiency corrected. The firm has done this with the April 28, 2000 amendment.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? YES - SUBMITTED TO OPDRA - FOUND ACCEPTABLE	X		
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode,		X	

Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?	X		
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List C _{max} , T _{max} , T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD: (portions taken from previous review)

- This review was based on the labeling for Tiazac® (S-015 - Approved 4-5-00; Revised 10-99). There is an SE1-007 supplement approved 1-30-98 which I have asked the project manager, Dave Roeder, to send me or at least let me know what changes were approved. I received the labeling - SE1-007 provides for the use of Tiazac® for the treatment of chronic stable angina. This has exclusivity til 1/30/01.

The new labeling has 2 tables in the ADVERSE REACTIONS section, the second being adverse reaction rates which occurred in angina trials. Beneath the 2 tables is a listing of adverse reactions occurring in 2% or more than placebo-treated patients. The previous labeling has 1% table (S-006) and the 1% adverse reactions listing for this review. I have E-mailed Dave Roeder, the PM for this drug, and let him know our quandary. What do we do when another generic comes in and models after the SE1-007 labeling?

The labeling (S-019) allows for the sprinkling of the capsule contents on applesauce. I have asked the generic to add this information to the DOSAGE AND ADMINISTRATION section as in the innovator. As a result of this, the generic will have to do a bio sprinkle study per Vijay. This will hold up their approval/tentative approval. I checked with the PM in New Drug about the possibility of this getting exclusivity and was told that it would not. The firm has done a sprinkle study and BIO has found it acceptable.
- Andrx has filed this ANDA under paragraph IV. The patent for the RLD does not expire until June 25, 2013. Applicant's labeling revised to carve out "management of chronic stable angina" protected until 1-30-01. The firm has certified to this. Since it is now after this date we asked the firm to put this information back in and they have with the 3-8-01 amendment.
- Storage/dispensing recommendations:

RLD - Store at CRT 20°-25°C
ANDA - Store at CRT 15°-30°C (59°-86°F)[see USP]

RLD - Dispense in well-closed containers with safety closures
ANDA - Dispense in tight containers with safety closures.
USP - Preserve in tight containers.
- The inactives are listed accurately in the DESCRIPTION section.

5. The firm has done single dose fasting, single dose food/fasting, and multiple dose steady state studies. The bio was found satisfactory. Waivers were granted for the 120 mg, 180 mg, 240 mg, and 300 mg capsules. The studies were done with the 360 mg capsule. Firm will have to do a bio sprinkle study however (see above).
6. Container/closure

30s and 1000s - 120 mg, 180 mg, 240 mg, 300 mg, and 360 mg

The 120 mg, 180 mg, 240 mg, 300 mg and 360 mg 30s will have CRCs.
7. The firm has submitted the proprietary name, "TAZTIA XT" and it has been sent to OPDRA. The firm is exploring possibilities of dropping the trade name and going with the established name or proposing a different trade name. See comments under "Other Comments" and telecon dated 1-28-00. OPDRA has found the proposed trade name acceptable.
8. The firm has distinguished its different strengths by contrasting colors.

Date of Review: 3-19-01

Date of Submission: 3-8-01

Primary Reviewer: Adolph Vezza

Date:

A. Vezza

3/20/01

Team Leader: Charlie Hoppes

Date:

[Signature]

3/20/01

cc:

ANDA: 75-401
DUP/DIVISION FILE
HFD-613/AVezza/CHoppes (no cc)
aev/3/19/01|V:\FIRMSAM\ANDRX\LTRS&REV\75401TAP.L3
Review

APPEARS THIS WAY
ON ORIGINAL

nervousness 0 (0) 3 (2) 0 (0)

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

Adverse Events (COSTART Term)	Placebo	Tiazac®	
	n=50 # pts (%)	Up to 360 mg n=158 # pts (%)	540 mg n=49 # pts (%)
headache	1 (2)	13 (8)	4 (8)
edema, peripheral	1 (2)	3 (2)	5 (10)
pain	1 (2)	10 (6)	3 (6)
dizziness	0 (0)	5 (3)	5 (10)
asthenia	0 (0)	1 (1)	2 (4)
dyspepsia	0 (0)	2 (1)	3 (6)
dyspnea	0 (0)	1 (1)	3 (6)
bronchitis	0 (0)	1 (1)	2 (4)
AV block	0 (0)	0 (0)	2 (4)
infection	0 (0)	2 (1)	1 (2)
flu syndrome	0 (0)	0 (0)	1 (2)
cough increase	0 (0)	2 (1)	1 (2)
extrasystoles	0 (0)	0 (0)	1 (2)
gout	0 (0)	2 (1)	1 (2)
myalgia	0 (0)	0 (0)	1 (2)
impotence	0 (0)	0 (0)	1 (2)
conjunctivitis	0 (0)	0 (0)	1 (2)
rash	0 (0)	2 (1)	1 (2)
abdominal enlargement	0 (0)	0 (0)	1 (2)

* Adverse events occurring in treated patients at 2% or more than placebo-treated patients.

In addition, the following events have been reported infrequently (less than 2%) in clinical trials with other diltiazem products:

Cardiovascular. Angina, arrhythmia, AV block (second- or third-degree), bundle branch block, congestive heart failure, ECG abnormalities, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles.

Nervous System. Abnormal dreams, amnesia, depression, gait abnormality, headache, insomnia, nervousness, paraesthesia, personality

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: **75-401**

Date of Submission: **February 28, 2001**

Applicant's Name: **Andrx Pharmaceuticals, Inc.**

Proprietary Name: **Taztia XT™**

Established Name: **Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-Day Dosage), 120 mg, 180 mg, 240 mg, 300 mg, and 360 mg**

Labeling Deficiencies:

INSERT

1. GENERAL COMMENT

Because the exclusivity for the indication of "chronic stable angina" expired January 31, 2001 the following information relating to this indication needs to be reinstated into the insert labeling.

2. CLINICAL PHARMACOLOGY

a. Mechanisms of Action

- i. Add the sub-subsection title "**Hypertension:**" to the first (and currently only) paragraph.
- ii. Add the following sub-subsection with associated text as the last sub-subsection:

Angina: Diltiazem hydrochloride has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal work loads.

Diltiazem has been shown to be a potent dilator of coronary arteries, both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by diltiazem.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of the coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

b. Pharmacodynamics

- i. Add the sub-subsection title "**Hypertension:**" to the first paragraph.
- ii. Add the following sub-subsection with associated text as the last sub-subsection:

Angina: In a double-blind parallel group placebo controlled trial (approximately 50 patients/group, in patients with chronic stable angina), diltiazem hydrochloride at

doses of 120 to 540 mg/day increased exercise tolerance time. At trough, 24 hours after dosing, exercise tolerance times using a Bruce exercise protocol, increased by 14, 26, 41, 33 and 32 seconds over baseline for placebo and the 120 mg, 240 mg, 360 mg, and 540 mg/day treated patient groups, respectively. At peak, 8 hours after dosing, exercise tolerance times relative to baseline were statistically significantly increased by 13, 38, 64, 55 and 42 seconds for placebo and 120 mg, 240 mg, 360 mg and 540 mg/day diltiazem hydrochloride treated patients, respectively. Compared to baseline, diltiazem hydrochloride treated patients experienced statistically significant reductions in anginal attacks and decreased nitroglycerin requirements when compared to placebo treated patients.

3. INDICATIONS AND USAGE

There are two indications for this drug product – add the following:

Hypertension:

Diltiazem Hydrochloride ... antihypertensive medications.

Chronic Stable Angina:

Diltiazem Hydrochloride ... (Once-a-Day Dosage) are indicated for chronic stable angina.”

4. ADVERSE REACTIONS

- a. First paragraph, third sentence – “... 4 and 8 weeks; a total of 207 patients with chronic stable angina were treated for 3 weeks with doses of diltiazem ...”
- b. Include the attached table immediately following the current table in this section.

5. DOSAGE AND ADMINISTRATION

- a. Add the subsection title “**Hypertension:**” to the first paragraph.
- b. Add the following as the next subsection:

Angina: Dosages for the treatment of angina should be adjusted to each patient's needs, starting with a dose of 120 mg to 180 mg once daily. Individual patients may respond to higher doses of up to 540 mg once daily. When necessary, titration should be carried out over 7 to 14 days.

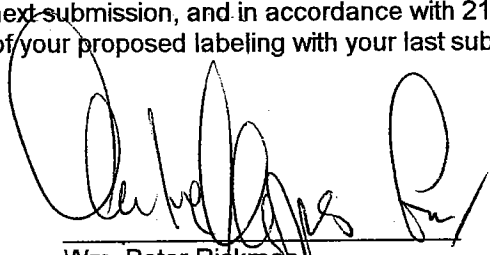
- c. Concomitant use with Other Cardiovascular Agents – Add the following as the first two items in this subsection:
 - i.
 - 1. Sublingual nitroglycerin may be taken as required to abort acute anginal attacks during diltiazem hydrochloride therapy.
 - 2. Prophylactic Nitrate Therapy – Diltiazem hydrochloride may be safely coadministered with short- and long-acting nitrates.
 - 3. Beta-blockers- ...
 - ii. Last paragraph, first sentence – “Hypertensive or anginal patients ...”

Please revise your insert labeling, as instructed above, and submit 12 final printed copies for a full approval of this application.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes -

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.



Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? YES (container labels) NO (PI)

Container Labels: 30s and 1000s
Satisfactory in FPL as of January 14, 2000 submission.

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? Yes

What is the RLD on the 356(h) form: Tiazac[®]

NDA Number: 20-401

NDA Drug Name: Tiazac[®] (diltiazem hydrochloride) Extended-release Capsules

NDA Firm: Biovail

Date of Approval of NDA Insert and supplement #: 4/5/00 (S-015)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: side-by-sides

Other Comments: I spoke to Jackie Davis of the firm. She asked some questions:

1. What if firm wants to change the proposed trade name - (a) before approval - send in new name and labeling which would be sent to OPDRA for evaluation (b) after approval - send in prior approval supplement with new name and labeling which would be sent to OPDRA for evaluation
2. What if firm drops the proposed trade name and goes with the established name - (a) before approval - send in new labels and labeling without the trade name (b) after approval - send in the new labels and labeling with out the trade name in an annual report.
3. I told Ms. Davis that the print size in the two tables in the PI is too small and that before full approval the firm will need to send in revised PI's with this deficiency corrected. The firm has done this with the April 28, 2000 amendment.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? YES - SUBMITTED TO OPDRA - FOUND ACCEPTABLE	X		
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
		X	

Does the package proposed have any safety and/or regulatory concerns?			
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed).		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?	X		
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
		X	

Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD: (portions taken from previous review)

1. This review was based on the labeling for Tiazac® (S-015 - Approved 4-5-00; Revised 10-99). There is an SE1-007 supplement approved 1-30-98 which I have asked the project manager, Dave Roeder, to send me or at least let me know what changes were approved. I received the labeling - SE1-007 provides for the use of Tiazac® for the treatment of chronic stable angina. This has exclusivity til 1/30/01.
The new labeling has 2 tables in the ADVERSE REACTIONS section, the second being adverse reaction rates which occurred in angina trials. Beneath the 2 tables is a listing of adverse reactions occurring in 2% or more than placebo-treated patients. The previous labeling has 1% table (S-006) and the 1% adverse reactions listing for this review. I have E-mailed Dave Roeder, the PM for this drug, and let him know our quandary. What do we do when another generic comes in and models after the SE1-007 labeling?
The labeling (S-019) allows for the sprinkling of the capsule contents on applesauce. I have asked the generic to add this information to the DOSAGE AND ADMINISTRATION section as in the innovator. As a result of this, the generic will have to do a bio sprinkle study per Vijay. This will hold up their approval/tentative approval. I checked with the PM in New Drug about the possibility of this getting exclusivity and was told that it would not.
2. Andrx has filed this ANDA under paragraph IV. The patent for the RLD does not expire until June 25, 2013. Applicant's labeling revised to carve out "management of chronic stable angina" protected until 1-30-01. The firm has certified to this. Since it is now after this date we will be asking the firm to put this information back in.
3. Storage/dispensing recommendations:

RLD - Store at CRT 20°-25°C
ANDA - Store at CRT 15°-30°C (59°-86°F)[see USP]

RLD - Dispense in well-closed containers with safety closures
ANDA - Dispense in tight containers with safety closures.
USP - Preserve in tight containers.
4. The inactives are listed accurately in the DESCRIPTION section.
5. The firm has done single dose fasting, single dose food/fasting, and multiple dose steady state studies. The bio was found satisfactory. Waivers were granted for the 120 mg, 180 mg, 240 mg, and 300 mg capsules. The studies were done with the 360 mg capsule. Firm will have to do a bio sprinkle study however (see above).
6. Container/closure

30s and 1000s - 120 mg, 180 mg, 240 mg, 300 mg, and 360 mg

The 120 mg, 180 mg, 240 mg, 300 mg and 360 mg 30s will have CRCs.
7. The firm has submitted the proprietary name, "TAZTIA XT" and it has been sent to OPDRA. The firm is exploring possibilities of dropping the trade name and going with the established name or proposing a different trade name. See comments under "Other Comments" and telecon dated 1-28-00. OPDRA has found the proposed trade name acceptable.
8. The firm has distinguished its different strengths by contrasting colors.

Date of Review: 3-1-01

Date of Submission: 2-28-01

Primary Reviewer: Adolph Vezza

Date:

3/2/01

Team Leader: Charlie Hoppes

Date:

3/2/01

cc:

ANDA: 75-401
DUP/DIVISION FILE
HFD-613/AVezza/CHoppes (no cc)
aev/3/1/01|V:\FIRMSAM\ANDRX\LTRS&REV\75401NA5.L
Review

APPEARS THIS WAY
ON ORIGINAL

**TENTATIVE APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: **75-401**

Date of Submission: **April 28, 2000**

Applicant's Name: **Andrx Pharmaceuticals, Inc.**

Proprietary Name: **Taztia XT™**

Established Name: **Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-Day Dosage), 120 mg, 180 mg, 240 mg, 300 mg, and 360 mg**

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? YES (container labels) NO (PI)

Container Labels: 30s and 1000s
Satisfactory in FPL as of January 14, 2000 submission.

Professional Package Insert Labeling:
Satisfactory in draft as of April 28, 2000 submission.

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? Yes

What is the RLD on the 356(h) form: Tiazac®

NDA Number: 20-401

NDA Drug Name: Tiazac® (diltiazem hydrochloride) Extended-release Capsules

NDA Firm: Biovail

Date of Approval of NDA Insert and supplement #: *4/5/00 (S-015)*
~~3/24/00 (S-019)~~

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: side-by-sides

Other Comments: I spoke to Jackie Davis of the firm. She asked some questions:

1. What if firm wants to change the proposed trade name - (a) before approval - send in new name and labeling which would be sent to OPDRA for evaluation (b) after approval - send in prior approval supplement with new name and labeling which would be sent to OPDRA for evaluation
2. What if firm drops the proposed trade name and goes with the established name - (a) before approval - send in new labels and labeling without the trade name (b) after approval - send in the new labels and labeling with out the trade name in an annual report.
3. I told Ms. Davis that the print size in the two tables in the PI is too small and that before full approval the firm will need to send in revised PI's with this deficiency corrected. The firm has done this with the April 28, 2000 amendment.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? YES - SUBMITTED TO OPDRA - FOUND ACCEPTABLE	X		
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	

Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
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Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?	X		
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List C _{max} , T _{max} , T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD: (portions taken from previous review)

- This review was based on the labeling for Tiazac® (S-019 - Approved 3-24-00; Revised 10-99 [in draft]). There is an SE1-007 supplement approved 1-30-98 which I have asked the project manager, Dave Roeder, to send me or at least let me know what changes were approved. I received the labeling - SE1-007 provides for the use of Tiazac® for the treatment of chronic stable angina. This has exclusivity til 1/30/01.

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- Andrx has filed this ANDA under paragraph IV. The patent for the RLD does not expire until June 25, 2013. Applicant's labeling revised to carve out "management of chronic stable angina" protected until 1-30-01. The firm has certified to this.
- Storage/dispensing recommendations:

RLD - Store at CRT 20°-25°C
ANDA - Store at CRT 15°-30°C (59°-86°F)[see USP]

RLD - Dispense in well-closed containers with safety closures
ANDA - Dispense in tight containers with safety closures.
USP - Preserve in tight containers.
- The inactives are listed accurately in the DESCRIPTION section.

5. The firm has done single dose fasting, single dose food/fasting, and multiple dose steady state studies. The bio was found satisfactory. Waivers were granted for the 120 mg, 180 mg, 240 mg, and 300 mg capsules. The studies were done with the 360 mg capsule. Firm will have to do a bio sprinkle study however (see above).

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30s and 1000s - 120 mg, 180 mg, 240 mg, 300 mg, and 360 mg

The 120 mg, 180 mg, 240 mg, 300 mg and 360 mg 30s will have CRCs.

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8. The firm has distinguished its different strengths by contrasting colors.

Date of Review: 5-8-00

Date of Submission: 4-28-00

Primary Reviewer: Adolph Vezza

Date:

A. Vezza

5/9/00

Team Leader: Charlie Hoppes

Date:

CHoppes

5/9/00

cc:

ANDA: 75-401
DUP/DIVISION FILE
HFD-613/AVezza/CHoppes (no cc)
aev/5/8/00|V:\FIRMSAM\ANDRX\LTRS&REV\75401tap.l2
Review

APPEARS THIS WAY
ON ORIGINAL

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: **75-401**

Date of Submission: **January 14, 19, and 24, 2000**

Applicant's Name: **Andrx Pharmaceuticals, Inc.**

Established Name: **Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-Day Dosage), 120 mg, 180 mg, 240 mg, 300 mg, and 360 mg**

Labeling Deficiencies:

1. GENERAL COMMENT

Your proposed proprietary name, "Taztia XT" has been found acceptable by OPDRA.

2. INSERT

a. Increase the print size in the two tables.

b. DESCRIPTION

Revise the chemical name as follows:

... -5-[2-(dimethylamino ... -2-(4-methoxyphenyl ...

c. DOSAGE AND ADMINISTRATION

Add the following as the last subsection in this section. Your proprietary name may be substituted in the following passage where appropriate.

Sprinkling the Capsule Contents on Food

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

Please revise your insert labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes –

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling?

Container Labels: 30s and 1000s
Satisfactory in FPL as of January 14, 2000 submission (pending resolution of proposed trade name).

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? Yes

What is the RLD on the 356(h) form: Tiazac®

NDA Number: 20-401

NDA Drug Name: Tiazac® (diltiazem hydrochloride) Extended-release Capsules

NDA Firm: Biovail

Date of Approval of NDA Insert and supplement #: 3/24/00 (S-019)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: side-by-sides

Other Comments: I spoke to Jackie Davis of the firm. She asked some questions:

1. What if firm wants to change the proposed trade name - (a) before approval - send in new name and labeling which would be sent to OPDRA for evaluation (b) after approval - send in prior approval supplement with new name and labeling which would be sent to OPDRA for evaluation
2. What if firm drops the proposed trade name and goes with the established name - (a) before approval - send in new labels and labeling without the trade name (b) after approval - send in the new labels and labeling with out the trade name in an annual report.
3. I told Ms. Davis that the print size in the two tables in the PI is too small and that before full approval the firm will need to send in revised PI's with this deficiency corrected.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? YES - SUBMITTED TO OPDRA	X		
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	

Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?	X		
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List C _{max} , T _{max} , T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	

Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD: (portions taken from previous review)

1. This review was based on the labeling for Tiazac® (S-019 - Approved 3-24-00; Revised 10-99 [in draft]). There is an SE1-007 supplement approved 1-30-98 which I have asked the project manager, Dave Roeder, to send me or at least let me know what changes were approved. I received the labeling - SE1-007 provides for the use of Tiazac® for the treatment of chronic stable angina. This has exclusivity til 1/30/01.
The new labeling has 2 tables in the ADVERSE REACTIONS section, the second being adverse reaction rates which occurred in angina trials. Beneath the 2 tables is a listing of adverse reactions occurring in 2% or more than placebo-treated patients. The previous labeling has 1% table (S-006) and the 1% adverse reactions listing for this review. I have E-mailed Dave Roeder, the PM for this drug, and let him know our quandary. What do we do when another generic comes in and models after the SE1-007 labeling?
The latest labeling (S-019) allows for the sprinkling of the capsule contents on applesauce. I have asked the generic to add this information to the DOSAGE AND ADMINISTRATION section as in the innovator. As a result of this, the generic will have to do a bio sprinkle study per Vijay. This will hold up their approval/tentative approval. I checked with the PM in New Drug about the possibility of this getting exclusivity and was told that it would not.
2. Andrx has filed this ANDA under paragraph IV. The patent for the RLD does not expire until June 25, 2013.
3. Storage/dispensing recommendations:

RLD - Store at CRT 20°-25°C
ANDA - Store at CRT 15°-30°C (59°-86°F)[see USP]

RLD - Dispense in well-closed containers with safety closures
ANDA - Dispense in tight containers with safety closures.
USP - Preserve in tight containers.
4. The inactives are listed accurately in the DESCRIPTION section.
5. The firm has done single dose fasting, single dose food/fasting, and multiple dose steady state studies. The bio was found satisfactory. Waivers were granted for the 120 mg, 180 mg, 240 mg, and 300 mg capsules. The studies were done with the 360 mg capsule. Firm will have to do a bio sprinkle study however (see above).
6. Container/closure

30s and 1000s - 120 mg, 180 mg, 240 mg, 300 mg, and 360 mg

The 120 mg, 180 mg, 240 mg, 300 mg and 360 mg 30s will have CRCs.
7. The firm has submitted the proprietary name, "TAZTIA XT" and it has been sent to OPDRA. The firm is exploring possibilities of dropping the trade name and going with the established name or proposing a different trade name. See comments under "Other Comments" and telecon dated 1-28-00. OPDRA has found the proposed trade name acceptable.
8. The firm has distinguished its different strengths by contrasting colors.

Date of Review: 4-7-00

Date of Submission: 1-14-00, 1-19-00 and 1-24-00

Primary Reviewer: Adolph Vezza

Date:

Team Leader: Charlie Hoppes

Date:

As of 1-28-00 the proposed trade name has not been approved by OPDRA - final approval cannot take place until this has occurred unless firm drops the trade name and submits new labeling

**TENTATIVE APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: 75-401

Date of Submission: January 14 and 24, 2000

Applicant's Name: Andrx Pharmaceuticals, Inc.

Established Name: Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-Day Dosage), 120 mg, 180 mg, 240 mg, 300 mg, and 360 mg

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling?

Container Labels: 30s and 1000s

Satisfactory in FPL as of January 14, 2000 submission (pending resolution of proposed trade name).

Professional Package Insert Labeling:

Satisfactory in printers proof as of January 24, 2000 submission (pending resolution of proposed trade name).

Revisions needed post-approval: prior to full approval the firm needs to increase the print size in the two tables of the PI

BASIS OF APPROVAL:

Was this approval based upon a petition? Yes

What is the RLD on the 356(h) form: Tiazac®

NDA Number: 20-401

NDA Drug Name: Tiazac® (diltiazem hydrochloride) Extended-release Capsules

NDA Firm: Biovail

Date of Approval of NDA Insert and supplement #: 10/16/98 (S-013)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: side-by-sides

Other Comments: I spoke to Jackie Davis of the firm. She asked some questions:

1. What if firm wants to change the proposed trade name - (a) before approval - send in new name and labeling which would be sent to OPDRA for evaluation (b) after approval - send in prior approval supplement with new name and labeling which would be sent to OPDRA for evaluation
2. What if firm drops the proposed trade name and goes with the established name - (a) before approval - send in new labels and labeling without the trade name (b) after approval - send in the new labels and labeling with out the trade name in an annual report.
3. I told Ms. Davis that the print size in the two tables in the PI is too small and that before full approval the firm will need to send in revised PI's with this deficiency corrected.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? YES - SUBMITTED TO OPDRA	X		
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode,		X	

Opaspray?			
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?	X		
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List C _{max} , T _{max} , T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD: (portions taken from previous review)

1. This review was based on the labeling for Tiazac® (S-006 - Approved 10-1-97; Revised April 97). There is an SE1-007 supplement approved 1-30-98 which I have asked the project manager, Dave Roeder, to send me or at least let me know what changes were approved. I received the labeling - SE1-007 provides for the use of Tiazac® for the treatment of chronic stable angina. This has exclusivity til 1/30/01.
The new labeling has 2 tables in the ADVERSE REACTIONS section, the second being adverse reaction rates which occurred in angina trials. Beneath the 2 tables is a listing of adverse reactions occurring in 2% or more than placebo-treated patients. The previous labeling has 1% table (S-006) and the 1% adverse reactions listing for this review. I have E-mailed Dave Roeder, the PM for this drug, and let him know our quandary. What do we do when another generic comes in and models after the SE1-007 labeling?
2. Andrx has filed this ANDA under paragraph IV. The patent for the RLD does not expire until June 25, 2013.
3. Storage/dispensing recommendations:

RLD - Store at CRT 20°-25°C
ANDA - Store at CRT 15°-30°C (59°-86°F)[see USP]

RLD - Dispense in well-closed containers with safety closures
ANDA - Dispense in tight containers with safety closures.
USP - Preserve in tight containers.
4. The inactives are listed accurately in the DESCRIPTION section.
5. The firm has done single dose fasting, single dose food/fasting, and multiple dose steady state studies. The bio was found satisfactory. Waivers were granted for the 120 mg, 180 mg, 240 mg, and 300 mg capsules. The studies were done with the 360 mg capsule.
6. Container/closure

30s and 1000s - 120 mg, 180 mg, 240 mg, 300 mg, and 360 mg

The 120 mg, 180 mg, 240 mg, 300 mg and 360 mg 30s will have CRCs.

7. The firm has submitted the proprietary name, "TAZTIA XT" and it has been sent to OPDRA. The firm is exploring possibilities of dropping the trade name and going with the established name or proposing a different trade name. See comments under "Other Comments" and telecon dated 1-28-00.
8. The firm has distinguished its different strengths by contrasting colors.

Date of Review: 1-28-00

Date of Submission: 1-14-00 and 1-24-00

Primary Reviewer: Adolph Vezza

Date:

Team Leader: Charlie Hoppes

Date:

cc:

ANDA: 75-401
DUP/DIVISION FILE
HFD-613/AVezza/CHoppes (no cc)
aev/1/28/00|V:FIRMSAMANDRXLTTRS&REV75401TAP.L
Review

APPEARS THIS WAY
ON ORIGINAL

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: 75-401

Date of Submission: October 29 and November 1, 1999

Applicant's Name: Andrx Pharmaceuticals, Inc.

Established Name: Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-Day Dosage),
120 mg, 180 mg, 240 mg, 300 mg, and 360 mg

Labeling Deficiencies:

INSERT

1. GENERAL COMMENTS

- a. Please note that the labeling for the reference listed drug, Tiazac®, has been revised (Biovail Laboratories, Approved October 16, 1998; Revised August 1998).
- b. Delete "USP" from the established name except in the TITLE, DESCRIPTION, INDICATIONS AND USAGE, and HOW SUPPLIED sections.

2. PRECAUTIONS

Drug Interactions, first sentence - "careful" (spelling)

3. ADVERSE REACTIONS

- a. First paragraph
 - i. First sentence - ... as well as with other ... (add "with")
 - ii. Add the following as the third and fourth sentences - ... these studies. A total of 256 hypertensives were treated for between 4 and 8 weeks with doses of diltiazem hydrochloride extended-release capsules (once-a-day dosage) ranging from 120 to 540 mg once daily. Two patients experienced first-degree AV block at 540 mg dose. The following table ...
 - iii. Last sentence - The following table ... adverse reactions, whether or not drug-related, reported in ... up to 360 mg and up to 540 mg with rates ... comparison.
- b. Revise the table as follows:

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

Adverse Events (COSTART Term)	Placebo n=57 # pts (%)	Diltiazem Hydrochloride Extended-Release Capsules USP (Once-a- Day Dosage)	
		Up to 360 mg n=149 # pts (%)	480-540 mg n=48 # pts (%)

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling?

Container Labels: 30s and 1000s
Satisfactory in draft as of October 29, 1999 submission.

Professional Package Insert Labeling:

Revisions needed post-approval: NONE

BASIS OF APPROVAL:

Was this approval based upon a petition? Yes *

What is the RLD on the 356(h) form: Tiazac®

NDA Number: 20-401

NDA Drug Name: Tiazac® (diltiazem hydrochloride) Extended-release Capsules

NDA Firm: Biovail

Date of Approval of NDA Insert and supplement #: 10/16/98 (S-013)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: side-by-sides

Other Comments: The firm has plans to submit a proprietary name.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? NO - BUT THEY WILL BE		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the		X	

product?			
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?	X		
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD: (portions taken from previous review)

1. This review was based on the labeling for Tiazac® (S-006 - Approved 10-1-97; Revised April 97). There is an SE1-007 supplement approved 1-30-98 which I have asked the project manager, Dave Roeder, to send me or at least let me know what changes were approved. I received the labeling - SE1-007 provides for the use of Tiazac® for the treatment of chronic stable angina. This has exclusivity til 1/30/01.
The new labeling has 2 tables in the ADVERSE REACTIONS section, the second being adverse reaction rates which occurred in angina trials. Beneath the 2 tables is a listing of adverse reactions occurring in 2% or more than placebo-treated patients. The previous labeling has 1% table (S-006) and the 1% adverse reactions listing for this review. I have E-mailed Dave Roeder, the PM for this drug, and let him know our quandary. What do we do when another generic comes in and models after the SE1-007 labeling?
2. Andrx has filed this ANDA under paragraph IV. The patent for the RLD does not expire until June 25, 2013.
3. Storage/dispensing recommendations:

RLD - Store at CRT 20°-25°C
ANDA - Store at CRT 15°-30°C (59°-86°F)[see USP]

RLD - Dispense in well-closed containers with safety closures
ANDA - Dispense in tight containers with safety closures.
USP - Preserve in tight containers.
4. The inactives are listed accurately in the DESCRIPTION section.
5. The firm has done single dose fasting, single dose food/fasting, and multiple dose steady state studies. The bio was found satisfactory. Waivers were granted for the 120 mg, 180 mg, 240 mg, and 300 mg capsules. The studies were done with the 360 mg capsule.
6. Container/closure

30s and 1000s - 120 mg, 180 mg, 240 mg, 300 mg, and 360 mg

The 120 mg, 180 mg, 240 mg, 300 mg and 360 mg 30s will have CRCs.
7. The firm has plans to submit a proprietary name.
8. The firm will distinguish its different strengths by contrasting colors.

Date of Review: 11-8-99

Date of Submission: 10-29-99 and 11-1-99

Primary Reviewer: Adolph Vezza

Date:

11/17/99

Team Leader: Charlie Hoppes

Date:

cc:

ANDA: 75-401

DUP/DIVISION FILE

HFD-613/AVezza/CHoppes (no cc)

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Review

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-401 Date of Submission: May 4, 1999

Applicant's Name: Andrx Pharmaceuticals, Inc.

Established Name: Diltiazem Hydrochloride Extended-release
Capsules USP (Once-a-Day Dosage), 120 mg,
180 mg, 240 mg, 300 mg, and 360 mg

Labeling Deficiencies:

1. GENERAL COMMENT

Please add (see USP) to your storage temperature recommendation throughout your labels and labeling.

2. CONTAINER 30s and 1000s

- a. See GENERAL COMMENT above.
- b. We encourage you to differentiate your product strengths by boxing, contrasting colors, or some other means.

3. INSERT

a. DESCRIPTION

Second paragraph - Increase the size of the dot in the molecular formula.

b. PRECAUTIONS

Pediatric Use - "pediatric patients" rather than

c. HOW SUPPLIED

See GENERAL COMMENT above.

Please revise your container labels and insert labeling, as instructed above, and submit in draft. We acknowledge your comment that you will be proposing a proprietary name for this drug product. Until such time as that occurs and is reviewed we will not ask for labels and labeling in final print.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling?

Container Labels: 30s and 1000s

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? Yes

What is the RLD on the 356(h) form: Tiazac[®]

NDA Number: 20-401

NDA Drug Name: Tiazac[®] (diltiazem hydrochloride) Extended-release Capsules

NDA Firm: Biovail

Date of Approval of NDA Insert and supplement #: 10/1/97 (S-006)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: side-by-sides

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? NO - BUT THEY WILL BE		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	

Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?	X		
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?	X		
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD: (portions taken from previous review)

1. This review was based on the labeling for Tiazac® (S-006 - Approved 10-1-97; Revised April 97). There is an SE1-007 supplement approved 1-30-98 which I have asked the project manager, Dave Roeder, to send me or at least let me know what changes were approved. I received the labeling - SE1-007 provides for the use of Tiazac® for the treatment of chronic stable angina. This has exclusivity til 1/30/01. The new labeling has 2 tables in the ADVERSE REACTIONS section, the second being adverse reaction rates which occurred in angina trials. Beneath the 2 tables is a listing of adverse reactions occurring in 2% or more than placebo-treated patients. The previous labeling has 1% table (S-006) and the 1% adverse reactions listing for this review. I have E-mailed Dave Roeder, the PM for this drug, and let him know our quandary. What do we do when another generic comes in and models after the SE1-007 labeling?

2. Andrx has filed this ANDA under paragraph IV. The patent for the RLD does not expire until June 25, 2013.

3. Storage/dispensing recommendations:

RLD - Store at CRT 20°-25°C

ANDA - Store at CRT 15°-30°C (59°-86°F)

RLD - Dispense in well-closed containers with safety closures

ANDA - Dispense in tight containers with safety closures.

USP - Preserve in tight containers.

4. The inactives are listed accurately in the DESCRIPTION section.

5. The firm has done single dose fasting, single dose food/fasting, and multiple dose steady state studies. The bio was found satisfactory. Waivers were granted for the 120 mg, 180 mg, 240 mg, and 300 mg capsules. The studies were done with the 360 mg capsule.

6. Container/closure

30s and 1000s - 120 mg, 180 mg, 240 mg, 300 mg, and 360 mg

The 120 mg, 180 mg, 240 mg, 300 mg and 360 mg 30s will have CRCs.

Date of Review: 5-13-99

Date of Submission: 5-4-99

Primary Reviewer: Adolph Vezza

Date:

A. Vezza

5/17/99

Team Leader: Charlie Hoppes

Date:

Charlie Hoppes

5/17/99

CC:

ANDA: 75-401

DUP/DIVISION FILE

HFD-613/AVezza/CHoppes (no cc)

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Review

APPEARS THIS WAY
ON ORIGINAL

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: **75-401**

Date of Submission: **January 14, 19, and 24, 2000**

Applicant's Name: **Andrx Pharmaceuticals, Inc.**

Established Name: **Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-Day Dosage), 120 mg, 180 mg, 240 mg, 300 mg, and 360 mg**

Labeling Deficiencies:

1. GENERAL COMMENT

Your proposed proprietary name, "Taztia XT" has been found acceptable by OPDRA.

2. INSERT

a. Increase the print size in the two tables.

b. DESCRIPTION

Revise the chemical name as follows:

... -5-[2-(dimethylamino ... -2-(4-methoxyphenyl ...

c. DOSAGE AND ADMINISTRATION

Add the following as the last subsection in this section. Your proprietary name may be substituted in the following passage where appropriate.

Sprinkling the Capsule Contents on Food

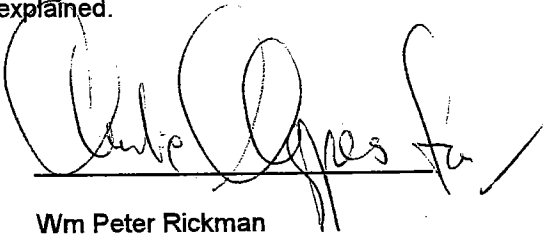
Diltiazem Hydrochloride Extended-release Capsules may also be administered by carefully opening the capsules and sprinkling the capsule contents on a spoonful of applesauce. The applesauce should be swallowed immediately without chewing, and followed with a glass of cool water to ensure complete swallowing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

Please revise your insert labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes –

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

A handwritten signature in black ink, appearing to read "Wm Peter Rickman", written over a horizontal line.

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

- c. Will the 30s container size for the 300 mg and 360 mg strength products be accompanied by a child resistant cap (CRC)? Page 860 of your July 29 submission implies that this container size for these two strengths will be available with CRC and non-CRC caps while on page 878 you indicate that they will be available with only non-CRC caps.

The Poison Prevention Packaging Act notes that special packaging (child-resistant closures) should be the responsibility of the manufacturer when the container is clearly intended to be utilized in dispensing (unit-of-use packaging). Your proposed containers of 30 appear to be in this category. Therefore, we believe that this package must comply with the Act. Please comment.

3. INSERT

a. GENERAL COMMENT

We prefer the abbreviation "mL" rather than "—"

b. DESCRIPTION

i. First paragraph - "structural formula" rather than "—"

ii. Second paragraph

A). Include the molecular formula.

B). Last sentence - ... capsules, for oral administration, contain ...

iii. Last paragraph

A). Replace "—" with "polyacrylic dispersion".

B). Please indicate the botanical source of the starch.

C). Please include "Aluminum Lake" with the names of the dyes.

D). You must include the USP drug release test with which this drug product complies.

c. CLINICAL PHARMACOLOGY

i. Pharmacodynamics - Leave a space between the number and the unit (e.g. "-3.7 mm Hg" and "90 mg").

ii. Pharmacokinetics and Metabolism, third paragraph - Delete "—"

d. WARNINGS

Delete " _____ " throughout this section.

e. PRECAUTIONS

- i. Delete " _____ " throughout this section.
- ii. Carcinogenesis, Mutagenesis, Impairment of Fertility - "Mutagenesis" (spelling)
- iii. Pediatric Use - "pediatric patients" rather than " _____ "

f. ADVERSE REACTIONS

- i. Delete " _____ " throughout this section except where it appears in association with the established name, diltiazem hydrochloride extended-release capsules.
- ii. Table - "paresthesia" (spelling)

g. OVERDOSAGE

Hypotension - "norepinephrine" rather than
" _____ "

h. DOSAGE AND ADMINISTRATION

Delete " _____ " throughout this section except where it appears in association with the established name, diltiazem hydrochloride extended-release capsules.

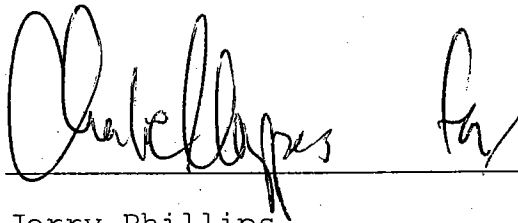
i. HOW SUPPLIED

- i. ... Capsules are available as follows:
- ii. See GENERAL COMMENT 1 (b).
- iii. We encourage you to relocate the symbol "Rx only" to immediately below the title of the insert.
- iv. We encourage you to include your dispensing statement in this section.

Please revise your container labels and insert labeling, as instructed above, and submit in draft. We acknowledge your comment that you will be proposing a proprietary name for this drug product. Until such time as that occurs and is reviewed we will not ask for labels and labeling in final print.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

A handwritten signature in black ink, appearing to read "Jerry Phillips", is written over a horizontal line. To the right of the signature is a small, stylized mark that looks like "for".

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes No
If no, list why:

Container Labels:

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? Yes

What is the RLD on the 356(h) form: Tiazac®

NDA Number: 20-401

NDA Drug Name: Tiazac® (diltiazem hydrochloride) Extended-release Capsules

NDA Firm: Biovail

Date of Approval of NDA Insert and supplement #: 10/1/97 (S-006)

Has this been verified by the MIS system for the NDA?
Yes No

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: side-by-sides

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? NO - But they have indicated that they will be submitting one.			

	Yes	No	N.A.
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?	X		
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement? See REVIEW, FTR and NOTE TO CHEMIST	X		
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	

	Yes	No	N.A.
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? Yes If any, does ANDA meet them? No See FTR			
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List C _{max} , T _{max} , T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST:

1. I have asked the firm to change their storage recommendations to read "Store at CRT 15° to 30°C (59° to 86°F) .
2. There are some irregularities in the DESCRIPTION section:
 - a. I have asked the firm to replace " ————" with "polyacrylic dispersion.
 - b. I have asked the firm to include the botanical source of the starch.
 - c. I have further asked the firm to include "Aluminum Lake" with the names for the dyes.
3. Do you concur with all of the above? *JK (AV) 12/30/98*
4. I was not able to verify the capsule descriptions as seen in the HOW SUPPLIED section.

FOR THE RECORD:

1. This review was based on the labeling for Tiazac® (S-006 - Approved 10-1-97; Revised April 97). There is an SE1-007 supplement approved 1-30-98 which I have asked the project manager, Dave Roeder, to send me or at least let me know what changes were approved. I received the labeling - SE1-007 provides for the use of Tiazac® for the treatment of chronic stable angina. This has exclusivity til 1/30/01. The new labeling has 2 tables in the ADVERSE REACTIONS section, the second being adverse reaction rates which occurred in angina trials. Beneath the 2 tables is a listing of adverse reactions occurring in 2% or more than placebo-treated patients. The previous labeling has 1% table (S-006) and the 1% adverse reactions listing for this review. I have E-mailed Dave Roeder, the PM for this drug, and let him know our quandary. What do we do when another generic comes in and models after the SE1-007 labeling?

2. Andrx has filed this ANDA under paragraph IV. The patent for the RLD does not expire until June 25, 2013.

3. Storage/dispensing recommendations:

RLD - Store at CRT 20°-25°C

ANDA - Store at CRT 20°-25°C (68°-77°F)

I have asked the firm to change to "Store at CRT 15° to 30°C (59° to 85°F)

RLD - Dispense in well-closed containers with safety closures

ANDA - same

USP - Preserve in tight containers.

I have asked the firm to revise to "Dispense in tight containers with safety closures.

4. I was not able to verify the accuracy of the markings on the capsules as seen in the HOW SUPPLIED section.
5. The inactives are listed accurately in the DESCRIPTION section save for the following: (a) ' — ' is a trade name - I asked them to revise to "polyacrylic dispersion" (b) I asked for the food source of the starch @ The dyes in this product are "Aluminum Lake" but the firm did not state this - I asked them to correct.
6. The firm has done single dose fasting, single dose food/fasting, and multiple dose steady state studies. The bio was found satisfactory. Waivers were granted for the 120 mg, 180 mg, 240 mg, and 300 mg capsules. The studies were done with the 360 mg capsule.

7. Container/closure

30s and 1000s - 120 mg, 180 mg, 240 mg, 300 mg, and 360 mg

The 120 mg, 180 mg, and 240 mg 30s will have CRCs. It is unclear at this time whether the 300 mg and 360 mg 30s will have CRCs or not.

Date of Review: 10-28-98 Dates of Submission: 6-22-98 & 7-29-98

Primary Reviewer: Adolph Vezza

Date:

A. Vezza

11/5/98

Team Leader: Charlie Hoppes

Date:

Charlie Hoppes

11/6/98

CC:

ANDA: 75-401

DUP/DIVISION FILE

HFD-613/AVezza/CHoppes (no cc)

aev/10/28/98|X:\NEW\FIRMSAM\ANDRX\LTRS&REV\75401NA1.L

Review

APPEARS THIS WAY
ON ORIGINAL

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75-401

CHEMISTRY REVIEW(S)

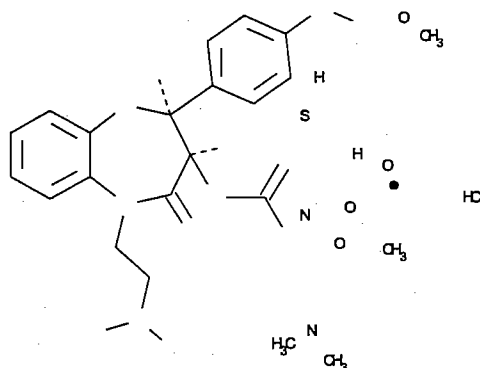
1. CHEMISTRY REVIEW NO. 1
2. ANDA # 75-401
3. NAME AND ADDRESS OF APPLICANT
Andrx Pharmaceuticals, Inc.
Attention: David A. Gardner
4001 S.W. 47th Avenue
Fort Lauderdale, Fl 33314
4. LEGAL BASIS FOR SUBMISSION
The basis for the submission is Tiazac ER Capsules
manufactured by Bio-vail Laboratories, Inc.
5. SUPPLEMENT(s)
N/A
6. PROPRIETARY NAME
N/A
7. NONPROPRIETARY NAME
Diltiazem HCl
8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A
9. AMENDMENTS AND OTHER DATES:
Orig. Sub. 06/22/98
Amendment 07/29/98
(4 Additional strengths)
Amendment 08/10/98
(Copy of AP LTR for CP that establishes Tiazac as RLD)
Ack Ltr 08/20/98
10. PHARMACOLOGICAL CATEGORY
Hypertensive
11. Rx or OTC
Rx
12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
ER Capsule
14. POTENCY
120 mg, 180, 240 mg, 300 mg, 360 mg

APPEARS THIS WAY
ON ORIGINAL

15. CHEMICAL NAME AND STRUCTURE
Diltiazem Hydrochloride USP

$C_{22}H_{26}N_2O_4S \cdot HCl$; M.W. = 450.98



(+)-5-[2-(Dimethylamino)ethyl]-*cis*-2,3-dihydro-3-hydroxy-2-(*p*-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one acetate (ester) monohydrochloride. CAS [33286-22-5]

Fine needles from ethanol-isopropanol, mp 207.5 - 212°C, optical rotation +98.3 ± 1.4° (c = 1.002 in methanol), 110 - 116 in a 1 to 100 solution in water. Freely soluble in water, methanol, chloroform: slightly soluble in absolute ethanol. Practically insoluble in benzene.

16. RECORDS AND REPORTS
 N/A

17. COMMENTS
 USP drug substance and drug product. First generic for 360 mg strength.

18. CONCLUSIONS AND RECOMMENDATIONS
 Not approvable.

19. REVIEWER:
 A. Langowski

DATE COMPLETED:
 12/31/98

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✓ 1. CHEMISTRY REVIEW NO. 2

2. ANDA # 75-401

3. NAME AND ADDRESS OF APPLICANT

Andrx Pharmaceuticals, Inc.
Attention: David A. Gardner
4001 S.W. 47th Avenue
Fort Lauderdale, Fl 33314

4. LEGAL BASIS FOR SUBMISSION

The basis for the submission is Tiazac ER Capsules
manufactured by Bio-vail Laboratories, Inc.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Diltiazem HCl

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Firm:

Orig. Sub. 06/22/98

Amendment 07/29/98

(4 Additional strengths)

Amendment 08/10/98

(Copy of AP LTR for CP that establishes Tiazac as RLD)

Ack Ltr 08/20/98

Amendment: May 4, 1999

FDA:

Bio. Letter: June 22, 1998

Chemistry & labeling letter: March 11, 1999

10. PHARMACOLOGICAL CATEGORY

Hypertensive

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

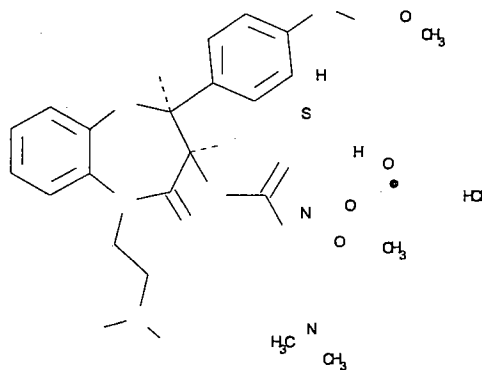
ER Capsule

14. POTENCY

120 mg, 180, 240 mg, 300 mg, 360 mg

15. CHEMICAL NAME AND STRUCTURE

Diltiazem Hydrochloride USP

 $C_{22}H_{26}N_2O_4S \cdot HCl$; M.W. = 450.98

(+)-5-[2-(Dimethylamino)ethyl]-cis-2,3-dihydro-3-hydroxy-2-(p-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one acetate (ester) monohydrochloride. CAS [33286-22-5]

Fine needles from ethanol-isopropanol, mp 207.5 - 212°C, optical rotation $+98.3 \pm 1.4^\circ$ (c = 1.002 in methanol), 110 - 116 in a 1 to 100 solution in water. Freely soluble in water, methanol, chloroform: slightly soluble in absolute ethanol. Practically insoluble in benzene.

16. RECORDS AND REPORTS

N/A

17. COMMENTS

USP drug substance and drug product. First generic for 360 mg strength.

-DMF was acceptable on 7-7-99

-Bioequivalency is acceptable on 10-9-98

- EER is acceptable on 8-30-99
- Dissolution specifications should be revised.
- Labeling is deficient

18. CONCLUSIONS AND RECOMMENDATIONS

This application is considered as not approvable. The amendment will be considered as a Facsimile.

19. REVIEWER:

S.Basaran, Ph.D.

DATE COMPLETED:

10-1-99

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ON ORIGINAL

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1. CHEMISTRY REVIEW NO. 3
2. ANDA # 75-401
3. NAME AND ADDRESS OF APPLICANT
Andrx Pharmaceuticals, Inc.
Attention: David A. Gardner
4001 S.W. 47th Avenue
Fort Lauderdale, Fl 33314
4. LEGAL BASIS FOR SUBMISSION
The basis for the submission is Tiazac ER Capsules
manufactured by Bio-vail Laboratories, Inc.
5. SUPPLEMENT(s)
N/A
6. PROPRIETARY NAME
N/A
7. NONPROPRIETARY NAME
Diltiazem HCl
8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A
9. AMENDMENTS AND OTHER DATES:
Firm:
Orig. Sub. 06/22/98
Amendment 07/29/98
(4 Additional strengths)
Amendment 08/10/98
(Copy of AP LTR for CP that establishes Tiazac as RLD)
Ack Ltr 08/20/98
Amendment: May 4, 1999
Telephone amendment: December 3, 1999

FDA:
Bio. Letter: June 22, 1998
Chemistry & labeling letter: March 11, 1999
Labeling deficiency letter: 11-18-1999
Telephone amendment: December 1, 1999
10. PHARMACOLOGICAL CATEGORY
Hypertensive
11. Rx or OTC
Rx
12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
ER Capsule
14. POTENCY
120 mg, 180, 240 mg, 300 mg, 360 mg

15. CHEMICAL NAME AND STRUCTURE

Diltiazem Hydrochloride USP
 $C_{22}H_{26}N_2O_4S.HCl$; M.W. = 450.98

(+)-5-[2-(Dimethylamino)ethyl]-cis-2,3-dihydro-3-hydroxy-2-(p-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one acetate (ester) monohydrochloride. CAS [33286-22-5]

Fine needles from ethanol-isopropanol, mp 207.5 - 212°C, optical rotation $+98.3 \pm 1.4^\circ$ (c = 1.002 in methanol), 110 - 116 in a 1 to 100 solution in water. Freely soluble in water, methanol, chloroform: slightly soluble in absolute ethanol. Practically insoluble in benzene.

16. RECORDS AND REPORTS

N/A

17. COMMENTS

USP drug substance and drug product. First generic for 360 mg strength.

-DMF was acceptable on 2-14-00
-Bioequivalency is acceptable on 11-16-98
-EER is acceptable on 8-30-99
-Dissolution specifications revised.
-Labeling is acceptable on 1-28-00.

18. CONCLUSIONS AND RECOMMENDATIONS

This application is considered as approvable. The approval letter will be issued.

19. REVIEWER:

S.Basaran, Ph.D.

DATE COMPLETED:

12-7-99; 2-14-00 (revised)

APPEARS THIS WAY
ON ORIGINAL

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- ✓ 1. CHEMISTRY REVIEW NO. 4
2. ANDA # 75-401
3. NAME AND ADDRESS OF APPLICANT
Andrx Pharmaceuticals, Inc.
Attention: David A. Gardner
4001 S.W. 47th Avenue
Fort Lauderdale, Fl 33314
4. LEGAL BASIS FOR SUBMISSION
The basis for the submission is Tiazac ER Capsules
manufactured by Bio-vail Laboratories, Inc.
5. SUPPLEMENT(s)
N/A
6. PROPRIETARY NAME
N/A
7. NONPROPRIETARY NAME
Diltiazem HCl ER Capsules, USP
8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A
9. AMENDMENTS AND OTHER DATES:
Firm:
Orig. Sub. 06/22/98
Amendment 07/29/98
(4 Additional strengths)
Amendment 08/10/98
(Copy of AP LTR for CP that establishes Tiazac as RLD)
Ack Ltr 08/20/98
Amendment: May 4, 1999
Labeling amendment: October 29, 1999
Chemistry amendment: November 1, 1999
Telephone amendment: December 3, 1999
Labeling amendment : January 14 and 19, 2000
Labeling telephone amendment : January 24, 2000
Facsimile amendment (withdraw _____ as a
_____ March 29, 2000
Major amendment for bio and labeling: April 28, 2000
Waiver of court decision: June 15, 2000
Bio. Amendment and request for classification to Minor
Amendment: June 26, 2000
Amendments: September 12 and 18, 2000

FDA:
Bio. Letter: June 22, 1998
Chemistry & labeling letter: March 11, 1999
Labeling and chemistry deficiency letter: October 25, 1999
Labeling deficiency letter: 11-18-1999
Bio.letter: 12-1-1999

Telephone amendment (for CMC): December 2, 1999
Labeling telephone conversation: January 19, 2000
Labeling deficiency letter: January 29, 2000
Labeling telephone conversation: March 29, 2000
Labeling deficiency letter: April 7, 2000
Major NA Bio. Deficiency letter: April 13, 2000
Labeling Facsimile deficiency letter: April 19, 2000
Labeling Facsimile deficiency letter: April 26, 2000
Bio. deficiency letter: June 9, 2000
Bio. AP letter: July 12, 2000
Memorandum (Request for reclassification to minor amendment
April 28 and June 26, 2000 denied): August 10, 2000

10. <u>PHARMACOLOGICAL CATEGORY</u> Hypertensive	11. <u>Rx or OTC</u> Rx
12. <u>RELATED IND/NDA/DMF(s)</u>	
13. <u>DOSAGE FORM</u> ER Capsule	14. <u>POTENCY</u> 120 mg, 180, 240 mg, 300 mg, 360 mg

**APPEARS THIS WAY
ON ORIGINAL**

15. CHEMICAL NAME AND STRUCTURE

Diltiazem Hydrochloride USP
 $C_{22}H_{26}N_2O_4S.HCl$; M.W. = 450.98

(+)-5-[2-(Dimethylamino)ethyl]-cis-2,3-dihydro-3-hydroxy-2-(p-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one acetate (ester) monohydrochloride. CAS [33286-22-5]

Fine needles from ethanol-isopropanol, mp 207.5 - 212°C, optical rotation $+98.3 \pm 1.4^\circ$ (c = 1.002 in methanol), 110 - 116 in a 1 to 100 solution in water. Freely soluble in water, methanol, chloroform: slightly soluble in absolute ethanol. Practically insoluble in benzene.

16. RECORDS AND REPORTS

N/A

17. COMMENTS

USP drug substance and drug product. First generic for 360 mg strength.

- DMF was acceptable on 2-14-2000
- Bioequivalency is acceptable on 7-12-2000
- EER is acceptable on 3-31-2000
- Dissolution specifications revised.
- Labeling is acceptable on 5-9-2000.

18. CONCLUSIONS AND RECOMMENDATIONS

The CMC issues was satisfactorily addressed on December 3, 1999. Firm's waiver request for sprinkling bioequivalence study on diltiazem ER 360 mg capsule was denied on June 9, 2000. Therefore NA Major letter was sent to the firm on April 13 2000.

The bio. Studies on diltiazem 120 mg, 180 mg, 240 mg, 300 mg and 360 mg are found acceptable by the Division of Bioequivalence on July 12, 2000. The labeling deficiencies are also found satisfactory on May 9, 2000. There is no change regarding CMC issues. Therefore this application is considered as approvable. The approval letter will be issued.

19. REVIEWER:

S.Basaran, Ph.D.

DATE COMPLETED:

8-17-2000

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- ✓ 1. CHEMISTRY REVIEW NO. 5
2. ANDA # 75-401
3. NAME AND ADDRESS OF APPLICANT
Andrx Pharmaceuticals, Inc.
Attention: David A. Gardner
4001 S.W. 47th Avenue
Fort Lauderdale, Fl 33314
4. LEGAL BASIS FOR SUBMISSION
The basis for the submission is Tiazac ER Capsules
manufactured by Bio-vail Laboratories, Inc.
5. SUPPLEMENT(s)
N/A
6. PROPRIETARY NAME
N/A
7. NONPROPRIETARY NAME
Diltiazem HCl ER Capsules, USP
8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A
9. AMENDMENTS AND OTHER DATES:
Firm:
Orig. Sub. 06/22/98
Amendment 07/29/98
(4 Additional strengths)
Amendment 08/10/98
(Copy of AP LTR for CP that establishes Tiazac as RLD)
Ack Ltr 08/20/98
Amendment: May 4, 1999
Labeling amendment: October 29, 1999
Chemistry amendment: November 1, 1999
Telephone amendment: December 3, 1999
Labeling amendment: January 14 and 19, 2000
Labeling telephone amendment: January 24, 2000
Facsimile amendment (withdraw _____ as a
_____: March 29, 2000
Major amendment for bio and labeling: April 28, 2000
Waiver of court decision: June 15, 2000
Bio. Amendment and request for classification to Minor
Amendment: June 26, 2000
Amendment: September 12, 2000
Facsimile Amendment: September 18, 2000
Minor amendment: December 12, 2000.

FDA:

Bio. Letter: June 22, 1998

Chemistry & labeling letter: March 11, 1999

Labeling and chemistry deficiency letter: October 25, 1999

Labeling deficiency letter: 11-18-1999

Bio.letter: 12-1-1999

Telephone amendment (for CMC): December 2, 1999

Labeling telephone conversation: January 19, 2000

Labeling deficiency letter: January 29, 2000

Labeling telephone conversation: March 29, 2000

Labeling deficiency letter: April 7, 2000

Major NA Bio. Deficiency letter: April 13, 2000

Labeling Facsimile deficiency letter: April 19, 2000

Labeling Facsimile deficiency letter: April 26, 2000

Bio. deficiency letter: June 9, 2000

Bio. AP letter: July 12, 2000

Memorandum (Request for reclassification to minor amendment April 28 and June 26, 2000 denied): August 10, 2000

Telephone call (CMC): September 11, 2000

Telephone call (CMC): September 14, 2000

Tentative approval letter: September 29, 2000

Telephone call (labeling): January 28, 2001

10. PHARMACOLOGICAL CATEGORY

Hypertensive

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)13. DOSAGE FORM

ER Capsule

14. POTENCY

120 mg, 180, 240 mg, 300 mg, 360 mg

15. CHEMICAL NAME AND STRUCTURE

Diltiazem Hydrochloride USP

 $C_{22}H_{26}N_2O_4S.HCl$; M.W. = 450.98

(+)-5-[2-(Dimethylamino)ethyl]-cis-2,3-dihydro-3-hydroxy-2-(p-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one acetate (ester) monohydrochloride. CAS [33286-22-5]

Fine needles from ethanol-isopropanol, mp 207.5 - 212°C, optical rotation $+98.3 \pm 1.4^\circ$ (c = 1.002 in methanol), 110 - 116 in a 1 to 100 solution in water. Freely soluble in water, methanol, chloroform: slightly soluble in absolute ethanol. Practically insoluble in benzene.

16. RECORDS AND REPORTS

Circumstances that may affect the date of final approval:

As required by 21 CFR 314.95(b), Andrx submitted patent notices to the patent holders and the NDA holder of the Reference listed product, Tiazac®. Based on the information contained in their October 16, 1998 patent amendment, Andrx believes that the thirty-month stay of final approval will expire on February 11, 2001. However on December 4, 2000, the Court of Appeals heard oral argument on the NDA holder's appeal of the lower court order stating that Andrx's ANDA product did not infringe the NDA holder's patent. Andrx believes that the appellate court's order will be issued within the month of December 2000, before the expiration of thirty-month stay of final approval in February 2001. A copy of the final order will be submitted to the Agency as soon as the court decision has been reached. We will not issue a final approval letter, before all this issues has been resolved.

17. COMMENTS

USP drug substance and drug product. First generic for 360 mg strength.

- DMF was acceptable on 2-14-2000
- Bioequivalency is acceptable on 12-21-2000
- EER is acceptable on 3-31-2000
- Dissolution method revised.
- Labeling is acceptable on 5-9-2000.

18. CONCLUSIONS AND RECOMMENDATIONS

The CMC issues were satisfactorily addressed on December 12, 2000.

The current dissolution method using _____
_____ for diltiazem 120 mg, 180 mg, 240 mg,

300 mg and 360 mg extended-release capsules are found acceptable by the Division of Bioequivalence on December 12, 2000. The labeling deficiencies are also found satisfactory on May 9, 2000. There is no change regarding CMC issues. Therefore this application is considered as approvable. However, a new formulation patent has been filed for Tiazac. This patent expires 4/28/18. A minor deficiency letter will be issued asking the firm to certify to this patent.

19. REVIEWER:

S.Basaran, Ph.D.

DATE COMPLETED:

12-27-2000

**APPEARS THIS WAY
ON ORIGINAL**

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38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-401

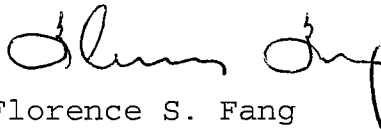
APPLICANT: Andrx Pharmaceuticals, Inc.

DRUG PRODUCT: Diltiazem Hydrochloride Extended-release
Capsules USP, 120 mg, 180 mg, 240 mg, 300 mg and
360 mg

The deficiency below represents a fax deficiency.

Please provide a patent certification to patent #6162463, which expires on April 28, 2018.

Sincerely yours,



Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

1. CHEMISTRY REVIEW NO. 6
2. ANDA # 75-401
3. NAME AND ADDRESS OF APPLICANT
Andrx Pharmaceuticals, Inc.
Attention: David A. Gardner
4001 S.W. 47th Avenue
Fort Lauderdale, Fl 33314
4. LEGAL BASIS FOR SUBMISSION
The basis for the submission is Tiazac ER Capsules
manufactured by Bio-vail Laboratories, Inc.
5. SUPPLEMENT(s)
N/A
6. PROPRIETARY NAME
N/A
7. NONPROPRIETARY NAME
Diltiazem HCl ER Capsules, USP
8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A
9. AMENDMENTS AND OTHER DATES:

Firm:

Orig. Sub. 06/22/98

Amendment 07/29/98 (4 Additional strengths)

Amendment 08/10/98

(Copy of AP LTR for CP that establishes Tiazac as RLD)

Acknowledgement Letter 08/20/98

Amendment: May 4, 1999

Labeling amendment: October 29, 1999

Chemistry amendment: November 1, 1999

Telephone amendment: December 3, 1999

Labeling amendment: January 14 and 19, 2000

Labeling telephone amendment: January 24, 2000

Facsimile amendment (withdraw _____ as a
_____ : March 29, 2000

Major amendment for bio and labeling: April 28, 2000

Waiver of court decision: June 15, 2000

Bio. Amendment and request for classification to Minor

Amendment: June 26, 2000

Amendment: September 12, 2000

Facsimile Amendment: September 18, 2000

Minor amendment: December 12, 2000.

New Bio. Correspondence: January 5, 2001

Fax amendment (patent certification: February 16, 2001

Labeling Amendment: February 28, 2001

Chemistry Correspondence: March 1, 2001

Labeling Amendment: March 8, 2001
 New Correspondence (Patent): March 13, 2001

FDA:

Bio. Letter: June 22, 1998
 Chemistry & labeling letter: March 11, 1999
 Labeling and chemistry deficiency letter: October 25, 1999
 Labeling deficiency letter: 11-18-1999
 Bio.letter: 12-1-1999
 Telephone amendment (for CMC): December 2, 1999
 Labeling telephone conversation: January 19, 2000
 Labeling deficiency letter: January 29, 2000
 Labeling telephone conversation: March 29, 2000
 Labeling deficiency letter: April 7, 2000
 Major NA Bio. Deficiency letter: April 13, 2000
 Labeling Facsimile deficiency letter: April 19, 2000
 Labeling Facsimile deficiency letter: April 26, 2000
 Bio. Deficiency letter: June 9, 2000
 Bio. AP letter: July 12, 2000
 Memorandum (Request for reclassification to minor amendment
 April 28 and June 26, 2000 denied): August 10, 2000
 Telephone call(CMC): September 11, 2000
 Telephone call (CMC): September 14, 2000
 Tentative approval letter: September 29, 2000
 Telephone call (labeling): January 28, 2001
 CMC Fax amendment (patent certification): February 2, 2000
 Telephone call (request FPL): February 27, 2001

10. PHARMACOLOGICAL CATEGORY
 Hypertensive

11. Rx or OTC
 Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
 ER Capsule

14. POTENCY
 120 mg, 180 mg, 240 mg, 300 mg, 360 mg

15. CHEMICAL NAME AND STRUCTURE

Diltiazem Hydrochloride USP
 $C_{22}H_{26}N_2O_4S.HCl$; M.W. = 450.98

(+)-5-[2-(Dimethylamino)ethyl]-cis-2,3-dihydro-3-hydroxy-2-(p-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one acetate (ester) monohydrochloride. CAS [33286-22-5]

Fine needles from ethanol-isopropanol, mp 207.5 - 212°C, optical rotation $+98.3 \pm 1.4^\circ$ (c = 1.002 in methanol), 110 - 116 in a 1 to 100 solution in water. Freely soluble in water, methanol, chloroform: slightly soluble in absolute ethanol. Practically insoluble in benzene.

16. RECORDS AND REPORTS

Circumstances that may affect the date of final approval:

Andrx is amending the application to provide a patent certification to patent#616263, which expires on April 28, 2018. See amendment submitted on February 16, 2001.

17. COMMENTS

USP drug substance and drug product. First generic for 360 mg strength.

- DMF was acceptable on 2-14-2000
- Bioequivalency is acceptable on 1-3-2001
- EER is acceptable on 3-31-2000
- Labeling is acceptable on 3-20-2001.

18. CONCLUSIONS AND RECOMMENDATIONS

The CMC issues were satisfactorily addressed on February 16, 2001.

The current dissolution method using _____ at 37°C, using USP _____ at _____ for diltiazem 120 mg, 180 mg, 240 mg, 300 mg and 360 mg extended-release capsules were found acceptable by the Division of Bioequivalence on 1-3-2001. The applicant has submitted a commitment, as requested by Dr. F. Holcombe, Associate Director of Chemistry, OGD, to study the effect of moisture on drug release and submit results post-approval. There are no other changes regarding CMC issues. The labeling review is satisfactory on March 20, 2001. Therefore, this application is considered as approvable.

19. REVIEWER:

S.Basaran, Ph.D.

DATE COMPLETED:

3-6-2001; 3-20-2001 (revised)

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1. CHEMISTRY REVIEW NO. 6 Addendum
2. ANDA # 75-401
3. NAME AND ADDRESS OF APPLICANT
Andrx Pharmaceuticals, Inc.
Attention: David A. Gardner
4001 S.W. 47th Avenue
Fort Lauderdale, Fl 33314
4. LEGAL BASIS FOR SUBMISSION
The basis for the submission is Tiazac ER Capsules
manufactured by Bio-vail Laboratories, Inc.
5. SUPPLEMENT(s)
N/A
6. PROPRIETARY NAME
N/A
7. NONPROPRIETARY NAME
Diltiazem HCl ER Capsules, USP
8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A
9. AMENDMENTS AND OTHER DATES:
Firm:
Orig. Sub. 06/22/98
Amendment 07/29/98
(4 Additional strengths)
Amendment 08/10/98
(Copy of AP LTR for CP that establishes Tiazac as RLD)
Ack Ltr 08/20/98
Amendment: May 4, 1999
Labeling amendment: October 29, 1999
Chemistry amendment: November 1, 1999
Telephone amendment: December 3, 1999
Labeling amendment: January 14 and 19, 2000
Labeling telephone amendment: January 24, 2000
Facsimile amendment (withdraw _____ as a
_____ March 29, 2000
Major amendment for bio and labeling: April 28, 2000
Waiver of court decision: June 15, 2000
Bio. Amendment and request for classification to Minor
Amendment: June 26, 2000
Amendment: September 12, 2000
Facsimile Amendment: September 18, 2000
Minor amendment: December 12, 2000.
New Correspondence: Jan. 5, 2001, Add. Information for
CMC/Bio
Patent Certification: Feb. 16, 2001
Labeling Amendment: Feb. 28, 2001
New Correspondence: Mar. 1, 2001 _____ Study
Commitment)

Labeling Amendment: Mar. 8, 2001 (Revised Package Insert)
 Patent Amendment: Mar. 13, 2001
 New Correspondence: Mar. 14, 2001
 Patent amendment: April 13, 2001

FDA:

Bio. Letter: June 22, 1998
 Chemistry & labeling letter: March 11, 1999
 Labeling and chemistry deficiency letter: October 25, 1999
 Labeling deficiency letter: 11-18-1999
 Bio.letter: 12-1-1999
 Telephone amendment (for CMC): December 2, 1999
 Labeling telephone conversation: January 19, 2000
 Labeling deficiency letter: January 29, 2000
 Labeling telephone conversation: March 29, 2000
 Labeling deficiency letter: April 7, 2000
 Major NA Bio. Deficiency letter: April 13, 2000
 Labeling Facsimile deficiency letter: April 19, 2000
 Labeling Facsimile deficiency letter: April 26, 2000
 Bio. deficiency letter: June 9, 2000
 Bio. AP letter: July 12, 2000
 Memorandum (Request for reclassification to minor amendment
 April 28 and June 26, 2000 denied): August 10, 2000
 Telephone call (CMC): September 11, 2000
 Telephone call (CMC): September 14, 2000
 Tentative approval letter: September 29, 2000
 Telephone call (labeling): January 28, 2001

10. PHARMACOLOGICAL CATEGORY
 Hypertensive

11. Rx or OTC
 Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
 ER Capsule

14. POTENCY
 120 mg, 180, 240 mg, 300 mg, 360 mg

15. CHEMICAL NAME AND STRUCTURE

Diltiazem Hydrochloride USP
 $C_{22}H_{26}N_2O_4S \cdot HCl$; M.W. = 450.98

(+)-5-[2-(Dimethylamino)ethyl]-cis-2,3-dihydro-3-hydroxy-2-(p-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one acetate (ester) monohydrochloride. CAS [33286-22-5]

Fine needles from ethanol-isopropanol, mp 207.5 - 212°C,

optical rotation $+98.3 \pm 1.4^\circ$ ($c = 1.002$ in methanol), 110 - 116 in a 1 to 100 solution in water. Freely soluble in water, methanol, chloroform: slightly soluble in absolute ethanol. Practically insoluble in benzene.

16. RECORDS AND REPORTS

Circumstances that may affect the date of final approval:

As required by 21 CFR 314.95(b), Andrx submitted patent notices to the patent holders and the NDA holder of the Reference listed product, Tiazac®. Based on the information contained in their October 16, 1998 patent amendment, Andrx believes that the thirty-month stay of final approval will expire on February 11, 2001. However on December 4, 2000, the Court of Appeals heard oral argument on the NDA holder's appeal of the lower court order stating that Andrx's ANDA product did not infringe the NDA holder's patent. Andrx believes that the appellate court's order will be issued within the month of December 2000, before the expiration of thirty-month stay of final approval in February 2001. A copy of the final order will be submitted to the Agency as soon as the court decision has been reached. We will not issue a final approval letter, before all this issues has been resolved.

17. COMMENTS

USP drug substance and drug product. First generic for 360 mg strength.

- DMF was acceptable on 2-14-2000
- Bioequivalency is acceptable on 12-21-2000 and 1-3-2001
- EER is acceptable on 3-31-2000
- Dissolution method revised.
- Labeling is acceptable on 5-9-2000 and 3-20-2001.

18. CONCLUSIONS AND RECOMMENDATIONS

The CMC issues were satisfactorily addressed on December 12, 2000.

The current dissolution method using _____ for diltiazem 120 mg, 180 mg, 240 mg, 300 mg and 360 mg extended-release capsules are found acceptable by the Division of Bioequivalence on 1-3-2001. The labeling deficiencies are also found satisfactory on 3-20-2001. There is no change regarding CMC issues. Since the patent issues are resolved by Greg Davis on April 20, 2001, therefore this application is considered as approvable.

19. REVIEWER:
S.Basaran, Ph.D.

DATE COMPLETED:
4-6-2001/4-27-01

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The records indicate no Chemistry Review #7. The reviews appeared to be numbered incorrectly.

1. CHEMISTRY REVIEW NO. ~~8~~ ~~10~~
2. ANDA # 75-401
3. NAME AND ADDRESS OF APPLICANT
Andrx Pharmaceuticals, Inc.
Attention: David A. Gardner
4001 S.W. 47th Avenue
Fort Lauderdale, FL 33314
4. LEGAL BASIS FOR SUBMISSION
The basis for the submission is Tiazac ER Capsules
manufactured by Bio-vail Laboratories, Inc.
5. SUPPLEMENT(s)
N/A
6. PROPRIETARY NAME
N/A
7. NONPROPRIETARY NAME 8. SUPPLEMENT(s) PROVIDE(s) FOR:
Diltiazem HCl ER Capsules, USP N/A
9. AMENDMENTS AND OTHER DATES:
Firm:
Orig. Sub. 06/22/98
Amendment 07/29/98
(4 Additional strengths)
Amendment 08/10/98
(Copy of AP LTR for CP that establishes Tiazac as RLD)
Ack Ltr 08/20/98
Amendment: May 4, 1999
Labeling amendment: October 29, 1999
Chemistry amendment: November 1, 1999
Telephone amendment: December 3, 1999
Labeling amendment: January 14 and 19, 2000
Labeling telephone amendment: January 24, 2000
Facsimile amendment (withdraw _____ as a
_____ March 29, 2000
Major amendment for bio and labeling: April 28, 2000
Waiver of court decision: June 15, 2000
Bio. Amendment and request for classification to Minor
Amendment: June 26, 2000
Amendment: September 12, 2000
Facsimile Amendment: September 18, 2000
Minor amendment: December 12, 2000.
New Correspondence: Jan. 5, 2001, Add. Information for
CMC/Bio
Patent Certification: Feb. 16, 2001
Labeling Amendment: Feb. 28, 2001

New Correspondence: Mar. 1, 2001 (Study Commitment)
 Labeling Amendment: Mar. 8, 2001 (Revised Package Insert)
 Patent Amendment: Mar. 13, 2001
 New Correspondence: Mar. 14, 2001
 Patent amendment: April 13, 2001
 New Correspondence: May 10, 2001
 New Correspondence: May 14, 2001
 Minor amendment for FA: September 21, 2001.
 Control Correspondence: October 5, 2001.
 Control Correspondence: October 9, 2001
 Control Correspondence: November 16, 2001
 Control Correspondence: December 11, 2001
 Control Correspondence: January 15, 2002
 New Correspondence: February 1, 2002
 Control Correspondence: March 5, 2002

FDA:

Bio. Letter: June 22, 1998
 Chemistry & labeling letter: March 11, 1999
 Labeling and chemistry deficiency letter: October 25, 1999
 Labeling deficiency letter: 11-18-1999
 Bio. letter: 12-1-1999
 Telephone amendment (for CMC): December 2, 1999
 Labeling telephone conversation: January 19, 2000
 Labeling deficiency letter: January 29, 2000
 Labeling telephone conversation: March 29, 2000
 Labeling deficiency letter: April 7, 2000
 Major NA Bio. Deficiency letter: April 13, 2000
 Labeling Facsimile deficiency letter: April 19, 2000
 Labeling Facsimile deficiency letter: April 26, 2000
 Bio. deficiency letter: June 9, 2000
 Bio. AP letter: July 12, 2000
 Memorandum (Request for reclassification to minor amendment April 28 and June 26, 2000 denied): August 10, 2000
 Telephone call (CMC): September 11, 2000
 Telephone call (CMC): September 14, 2000
 Tentative approval letter: September 29, 2000
 Requested additional information regarding the lot submitted in the control correspondence 01-507 November 16, 2001
 Telephone call (labeling): January 28, 2001
 Tentative Approval letter: May 14, 2001
 Teleconference : December 05, 2001

10. PHARMACOLOGICAL CATEGORY
Hypertensive

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
ER Capsule

14. POTENCY
120 mg, 180, 240 mg, 300 mg, 360 mg

15. CHEMICAL NAME AND STRUCTURE

Diltiazem Hydrochloride USP
 $C_{22}H_{26}N_2O_4S.HCl$; M.W. = 450.98

(+)-5-[2-(Dimethylamino)ethyl]-cis-2,3-dihydro-3-hydroxy-2-(p-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one acetate (ester) monohydrochloride. CAS [33286-22-5]

Fine needles from ethanol-isopropanol, mp 207.5 - 212°C, optical rotation $+98.3 \pm 1.4^\circ$ ($c = 1.002$ in methanol), 110 - 116 in a 1 to 100 solution in water. Freely soluble in water, methanol, chloroform: slightly soluble in absolute ethanol. Practically insoluble in benzene.

16. RECORDS AND REPORTS

Circumstances that may affect the date of final approval:

See new correspondences submitted by Keller and Heckman LLP. on May 10, 2001 and May 14, 2001.

17. COMMENTS

USP drug substance and drug product. First generic for 360 mg strength.

- DMF was acceptable on 2-14-2000
- New Bioequivalency studies will be performed
- EER is acceptable on 3-31-2000
- Dissolution method to be evaluated
- Labeling is acceptable on 5-9-2000 and 3-20-2001.

18. CONCLUSIONS AND RECOMMENDATIONS

The ANDA was tentatively approved on May 14, 2001. Biovail Corporation, the holder of the RLD, obtained samples from Andrx during their litigation and found that the 240 mg

product did not meet bioequivalence criteria. However, the 120 mg strength product met the bioequivalence criteria. Andrx noted that the 240 mg product failed CRT stability studies at 3 months (failed dissolution specification). We requested batch data to assess the reasons for the stability failure. Andrx was also requested to submit information on their optimized process, comparing it with their non-optimized and ANDA processes. The assessments of this information may be found under review element #25, Manufacturing and Processing and review element #28, Laboratory Controls. The conclusions are as follows:

a.

[]

b. The optimized process provides for better controls with tighter ranges for the manufacturing process; however, these process parameters may not be the only ones that affect the process

c.

d.

e. f

[]

f. BA/BE studies should be conducted to qualify the optimized process that will be used for future production.

19. REVIEWER:
S.Basaran, Ph.D.

DATE COMPLETED:
2-19-02/3-4-02

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✓ 1. CHEMISTRY REVIEW NO. 9

2. ANDA # 75-401

3. NAME AND ADDRESS OF APPLICANT

Andrx Pharmaceuticals, Inc.
Attention: David A. Gardner
4001 S.W. 47th Avenue
Fort Lauderdale, FL 33314 •

4. LEGAL BASIS FOR SUBMISSION

The basis for the submission is Tiazac ER Capsules
manufactured by Bio-vail Laboratories, Inc.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Diltiazem HCl ER Capsules, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Firm:

Orig. Sub. 06/22/98

Amendment 07/29/98

(4 Additional strengths)

Amendment 08/10/98

(Copy of AP LTR for CP that establishes Tiazac as RLD)

Ack Ltr 08/20/98

Amendment: May 4, 1999

Labeling amendment: October 29, 1999

Chemistry amendment: November 1, 1999

Telephone amendment: December 3, 1999

Labeling amendment: January 14 and 19, 2000

Labeling telephone amendment: January 24, 2000

Facsimile amendment (withdraw _____ as a
March 29, 2000

Major amendment for bio and labeling: April 28, 2000

Waiver of court decision: June 15, 2000

Bio. Amendment and request for classification to Minor
Amendment: June 26, 2000

Amendment: September 12, 2000

Facsimile Amendment: September 18, 2000

Minor amendment: December 12, 2000.

New Correspondence: Jan. 5, 2001, Add. Information for
CMC/Bio

Patent Certification: Feb. 16, 2001

Labeling Amendment: Feb. 28, 2001

New Correspondence: Mar. 1, 2001 _____ Study
Commitment)
Labeling Amendment: Mar. 8, 2001 (Revised Package Insert)
Patent Amendment: Mar. 13, 2001
New Correspondence: Mar. 14, 2001
Patent amendment: April 13, 2001
New Correspondence: May 10, 2001
New Correspondence: May 14, 2001
Minor amendment for FA: September 21, 2001.
Control Correspondence: October 5, 2001.
Control Correspondence: October 9, 2001
Control Correspondence: November 16, 2001
Control Correspondence: December 11, 2001
Control Correspondence: January 15, 2002
New Correspondence: February 1, 2002
Control Correspondence: March 5, 2002
Major Amendment (CMC and Bio.): May 22, 2002
New Correspondence: June 7, 2002
Bioequivalency amendment: September 30, 2002

FDA:

Bio. Letter: June 22, 1998
Chemistry & labeling letter: March 11, 1999
Labeling and chemistry deficiency letter: October 25, 1999
Labeling deficiency letter: 11-18-1999
Bio. letter: 12-1-1999
Telephone amendment (for CMC): December 2, 1999
Labeling telephone conversation: January 19, 2000
Labeling deficiency letter: January 29, 2000
Labeling telephone conversation: March 29, 2000
Labeling deficiency letter: April 7, 2000
Major NA Bio. Deficiency letter: April 13, 2000
Labeling Facsimile deficiency letter: April 19, 2000
Labeling Facsimile deficiency letter: April 26, 2000
Bio. deficiency letter: June 9, 2000
Bio. AP letter: July 12, 2000
Memorandum (Request for reclassification to minor amendment
April 28 and June 26, 2000 denied): August 10, 2000
Telephone call(CMC): September 11, 2000
Telephone call (CMC): September 14, 2000
Tentative approval letter: September 29, 2000
Requested additional information regarding the lot
submitted in the control correspondence 01-507 November 16,
2001
Telephone call (labeling): January 28, 2001

Tentative Approval letter: May 14, 2001

Teleconference : December 05, 2001

Bioequivalency deficiency letter: March 5, 2002

Bioequivalency deficiency letter: March 12, 2002

Bioequivalency deficiency letter: September 11, 2002

10. <u>PHARMACOLOGICAL CATEGORY</u>	.11. <u>Rx or OTC</u>
Hypertensive	Rx

12. RELATED IND/NDA/DMF(s)

13. <u>DOSAGE FORM</u>	14. <u>POTENCY</u>
ER Capsule	120 mg, 180, 240 mg, 300 mg, 360 mg

- 15.
- CHEMICAL NAME AND STRUCTURE

Diltiazem Hydrochloride USP

$$\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_4\text{S} \cdot \text{HCl}; \text{ M.W. } = 450.98$$

(+)-5-[2-(Dimethylamino)ethyl]-cis-2,3-dihydro-3-hydroxy-2-(p-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one acetate (ester) monohydrochloride. CAS [33286-22-5]

Fine needles from ethanol-isopropanol, mp 207.5 - 212°C, optical rotation $+98.3 \pm 1.4^\circ$ ($c = 1.002$ in methanol), 110 - 116 in a 1 to 100 solution in water. Freely soluble in water, methanol, chloroform: slightly soluble in absolute ethanol. Practically insoluble in benzene.

- ## 16. RECORDS AND REPORTS

Control Document # 01-507 was submitted by ANDRX in support of their request for final approval of this ANDA. At the completion of the review of this CD, however, the Division converted it to an amendment and Review #8 was generated. This amendment is in response to the NA letter sent at that time.

- 17.
- COMMENTS

USP drug substance and drug product. First generic for 360 mg strength.

-DMF was acceptable on 10-17-2002

- New Bioequivalency studies deficient
- EER is acceptable on 3-31-2000, update requested on 10-9-02
- Dissolution method to be evaluated by Division of Bio.
- Labeling is acceptable on 5-9-2000 and 3-20-2001.

18. CONCLUSIONS AND RECOMMENDATIONS

The ANDA was tentatively approved on May 14, 2001. Biovail Corporation, the holder of the RLD, obtained samples from Andrx during their litigation and found that the 240 mg product did not meet bioequivalence criteria. However, the 120 mg strength product met the bioequivalence criteria. Andrx noted that the 240 mg product failed CRT stability studies at 3 months (failed dissolution specification). We requested batch data to assess the reasons for the stability failure. Andrx was also requested to submit information on their optimized process, comparing it with their non-optimized and ANDA processes. After reviewing the room temperature stability data in the Major amendment dated May 22, 2002, I am not convinced that Andrx is solved their dissolution failures changing the curing time and equilibration period in their new optimized manufacturing process. We need more solid dissolution test results on the validation batches.

19. REVIEWER:

DATE COMPLETED:

S.Basaran, Ph.D.

10-17-02; revised 10-31-02

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1. CHEMISTRY REVIEW NO. 10

2. ANDA # 75-401

3. NAME AND ADDRESS OF APPLICANT

Andrx Pharmaceuticals, Inc.

Attention: Janet Vaughn

4955 Orange Avenue

Fort Lauderdale, FL 33314

4. LEGAL BASIS FOR SUBMISSION

The basis for the submission is Tiazac ER Capsules manufactured by Bio-Vail Laboratories, Inc.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME N/A

7. NONPROPRIETARY NAME Diltiazem HCl ER Capsules, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

Firm:

Orig. Sub. June 22, 1998

Amendment July 29, 1998

(4 Additional strengths)

Amendment August 10, 1998

(Copy of AP LTR for CP that establishes Tiazac as RLD)

Ack Ltr August 20, 1998

Amendment: May 4, 1999

Bio amendment October 24, 2001

Labeling amendment: October 29, 1999

Chemistry amendment: November 1, 1999

Bio amendment November 8, 2001

Telephone amendment: December 3, 1999

Labeling amendment: January 14 and 19, 2000

Labeling telephone amendment: January 24, 2000

Facsimile amendment (withdraw ~~as a~~ as a

March 29, 2000

Major amendment for bio and labeling: April 28, 2000

Waiver of court decision: June 15, 2000

Bio. Amendment and request for classification to Minor

Amendment: June 26, 2000

Amendment: September 12, 2000

Facsimile Amendment: September 18, 2000

Minor amendment:	December 12, 2000.
New Correspondence:	January 5, 2001, Add. Information for CMC/Bio
Patent Certification:	February 16, 2001
Labeling Amendment:	February 28, 2001
New Correspondence:	March 1, 2001 (————— , Study
Commitment)	
Labeling Amendment:	March 8, 2001 (Revised Package Insert)
Patent Amendment:	March 13, 2001
New Correspondence:	March 14, 2001
Patent amendment:	April 13, 2001
New Correspondence:	May 10, 2001
New Correspondence:	May 14, 2001
Minor amendment for FA:	September 21, 2001.
Control Correspondence:	October 5, 2001.
Control Correspondence:	October 9, 2001
Control Correspondence:	November 16, 2001
Control Correspondence:	December 11, 2001
Control Correspondence:	January 15, 2002
New Correspondence:	February 1, 2002
Control Correspondence:	March 5, 2002
Major Amendment (CMC and Bio.):	May 22, 2002
New Correspondence:	June 7, 2002
Bioequivalency amendment:	September 30, 2002
Bioequivalency amendment:	October 29, 2002
CMC, labeling minor amendment:	November 22, 2002.
Labeling amendment:	December 10, 2002.
Labeling amendment	January 14, 2003
Labeling amendment	March 18, 2003
FDA:	
Bio. Letter:	June 22, 1998
Chemistry & labeling letter:	March 11, 1999
Labeling and chemistry deficiency letter:	October 25, 1999
Labeling deficiency letter:	November 18, 1999
Bio. letter:	December 1, 1999
Telephone amendment (for CMC):	December 2, 1999
Labeling telephone conversation:	January 19, 2000
Labeling deficiency letter:	January 29, 2000
Labeling telephone conversation:	March 29, 2000
Labeling deficiency letter:	April 7, 2000
Major NA Bio. Deficiency letter:	April 13, 2000
Labeling Facsimile deficiency letter:	April 19, 2000
Labeling Facsimile deficiency letter:	April 26, 2000
Bio. deficiency letter:	June 9, 2000
Bio. AP letter:	July 12, 2000
Memorandum (Request for reclassification to minor amendment	April 28 and June 26,

2000 denied): August 10, 2000
 Telephone call(CMC): September 11, 2000
 Telephone call (CMC): September 14, 2000
 Tentative approval letter: September 29, 2000
 Requested additional information regarding the lot submitted in the control
 correspondence 01-507 November 16, 2001
 Telephone call (labeling): January 28, 2001
 Tentative Approval letter: May 14, 2001
 Teleconference: December 05, 2001
 Bioequivalency deficiency letter: March 5, 2002
 Bioequivalency deficiency letter: March 12, 2002
 CMC Defecency letter March 20, 2002
 Bioequivalency deficiency letter: September 11, 2002
 CMC Minor deficiency letter: November 6, 2002

10. PHARMACOLOGICAL CATEGORY 11. Rx or OTC
 Hypertensive Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM 14. POTENCY
 ER Capsule 120 mg, 180, 240 mg, 300 mg, 360 mg

15. CHEMICAL NAME AND STRUCTURE

Diltiazem Hydrochloride USP
 $C_{22}H_{26}N_2O_4S.HCl$; M.W. = 450.98

(+)-5-[2-(Dimethylamino)ethyl]-cis-2,3-dihydro-3-hydroxy-2-(p-
 methoxyphenyl) -1,5-benzothiazepin-4(5H)-one acetate (ester)
 monohydrochloride. CAS [33286-22-5]

Fine needles from ethanol-isopropanol, mp 207.5 - 212°C, optical rotation $+98.3 \pm 1.4^\circ$
 (c = 1.002 in methanol), 110 - 116 in a 1 to 100 solution in water. Freely soluble in
 water, methanol, and chloroform: slightly soluble in absolute ethanol. Practically
 insoluble in benzene.

16. RECORDS AND REPORTS

Control Document # 01-507 was submitted by ANDRX in support of their request for final approval of this ANDA.

17. COMMENTS

- USP drug substance and drug product; First generic for 360 mg strength.
- DMF was acceptable on 10-17-2002; CMC satisfactory in the amendment
- New Bioequivalency studies acceptable 11-26-02; dissolution specification needs to be finalized
- EER is acceptable on 3-31-2000, update requested on 10-9-02; Updated EER is for ABIC and is pending, but other facilities are OK
- Labeling was acceptable on 5-9-2000 and 3-20-2001. The new update labeling is acceptable as of 3-26-03.

18. CONCLUSIONS AND RECOMMENDATIONS

This application is approved (Note: this will be final approval; the ANDA was TA twice before).

19. REVIEWER: DATE COMPLETED:

S.Basaran, Ph.D.

1-15-03

**APPEARS THIS WAY
ON ORIGINAL**

Redacted

9

Page(s) of trade

secret and /or

confidential

commercial

information

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75-401

**BIOEQUIVALENCE
REVIEW(S)**

APR 11 3 1987

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-401

APPLICANT: Andrx Pharmaceuticals

DRUG PRODUCT: Diltiazem HCl Extended Release Capsules, 360mg, 300mg, 240mg, 180mg, and 120mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. The reference listed drug labeling has been amended to incorporate dosage administration by sprinkling the contents of a capsule on applesauce. The Division of Bioequivalence current practice is to request an additional sprinkling bioequivalence study when the dosage and administration section of the labeling describes administration of the product sprinkled on food.
2. A single dose, two-way crossover sprinkling study on the 360mg ER capsule should be conducted comparing your 360mg ER capsule to the 360mg ER Tiazac capsule by sprinkling both on applesauce.
3. The bioequivalence of the two treatments will be determined using the 90% confidence interval criterion.
4. Sprinkling studies on your ER capsules of the lower strengths are not necessary if the sprinkling study on your 360mg ER capsule is acceptable.
5. You may submit a protocol for this study or may select the conventional two-way crossover design with particular attention to the dosage and administration section of the amended labeling.

Sincerely yours,



Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

6

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75401

APPLICANT: Andrx Pharmaceuticals

DRUG PRODUCT: Diltiazem Hydrochloride ER Capsules
120 mg, 180 mg, 240 mg, 300 mg, 360 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23, Supplement 8, Test 6.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,



Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #75-401

SPONSOR: Andrx Pharmaceuticals

DRUG: Diltiazem Hydrochloride ER

DOSAGE FORM: Capsules

STRENGTHS/(s): 120 mg, 180 mg, 240 mg, 300 mg, 360 mg

TYPE OF STUDY: Single/Multiple

STUDY SITE: _____

STUDY SUMMARY: Fasting, non-fasting, and multi-dose studies are acceptable.

DISSOLUTION: The dissolution testing was conducted using USP 23, supplement 8, test 6 method. The formulation of 120, 180, 240, and 300 mg capsules is proportionally similar to 360 mg capsules which underwent bioequivalency testing. The dissolution testing results on 120, 180, 240, 300, and 360 mg capsules are acceptable. The waiver of *in vivo* bioequivalence requirements for 120, 180, 240, and 300 mg capsules is granted.

PRIMARY REVIEWER: Kuldeep R. Dhariwal, Ph.D, BRANCH: II

INITIAL: K. Dhariwal DATE 10/9/98

BRANCH CHIEF: Shriniwas Nerurkar, Ph.D., BRANCH: II

INITIAL: S. Nerurkar DATE 10/9/1998

DIRECTOR

DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm. D.

INITIAL: DP DATE 10/16/98

DIRECTOR

OFFICE OF GENERIC DRUGS:

INITIAL: _____ DATE _____

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-401

APPLICANT: Andrx

DRUG PRODUCT: Diltiazem Hydrochloride ER Capsules, USP
120 mg, 180 mg, 240 mg, 300 mg, 360 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

The dissolution testing should be conducted in _____
_____, using _____

The test product should meet the following specifications:

2h	NMT
4h	_____
8h	_____
12h	NLT
16h	NLT

During the developmental stages of the dissolution testing, you used _____ for _____ testing. Please note that in future, you should use _____ for _____ dissolution testing as recommended in the _____. The pH range of the _____ is _____.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,



Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 75401
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)

HFD-655/Dhariwal *AND* 1/21/03

HFD-655/Nerurkar .

HFD-617/Nwaba

HFD-650/Dale Conner

PR 1/29/03

[Signature] 1/21/2003

BIOEQUIVALENCY

Submission Dates: 11/22/02

1. **STUDY AMENDMENT (STA)**
11/22/02

Strengths: All
✓ Outcome: AC

Outcome Decisions:
AC - Acceptable

APPEARS THIS WAY
ON ORIGINAL

8

OFFICE OF GENERIC DRUGS DIVISION OF BIOEQUIVALENCE

ANDA # : 75401

SPONSOR : Andrx

DRUG AND DOSAGE FORM : Diltiazem HCl ER Capsules, USP

STRENGTH(S) : 120 mg, 180 mg, 240 mg, 300 mg, 360 mg

TYPES OF STUDIES : Fasting, fed and sprinkling on 360 mg.
Fasting on 240 mg

CLINICAL STUDY SITE(S) : _____

ANALYTICAL SITE(S) : _____

STUDY SUMMARY : All bioequivalence studies are acceptable.

DISSOLUTION : Acceptable. The dissolution testing should be conducted in _____
 _____ using apparatus ? _____ The test product
 should meet the following specifications: 2h: NMT _____ 4h: _____, 8h: _____ 12h:
 NLT _____ 16h: NLT _____ The waiver is granted for 120, 180, and 300 mg capsules.

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic <u>Yes</u> New facility _____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Kuldeep R. Dhariwal, Ph.D.

BRANCH : II

INITIAL : MD DATE : 1/27/03

TEAM LEADER : S. Nerurkar, Ph.D.

BRANCH : II

INITIAL : [Signature] DATE : 1/27/2003

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : DP DATE : 1/29/03

JAN 29 2003

Diltiazem Hydrochloride
Extended Release Capsules, USP
120, 180, 240, 300, 360 mg
ANDA #75-401

Reviewer: Kuldeep R. Dhariwal
V:\Firmsam\Andrx\Ltrs&rev\75401A1102.doc

Andrx Pharmaceuticals
4955 Orange Drive
Fort Lauderdale
Florida 33314
Submission Date:
November 22, 2002

Review of an Amendment

The fasting, fed, and sprinkling studies submitted in amendments dated May 22, September 30, and October 29, 2002 were acceptable to the Division of Bioequivalence (75401A0902.doc). The dissolution data were reviewed but the dissolution method and specifications were not finalized pending Chemistry review.

Andrx proposed to use _____ as dissolution medium. The Division of Chemistry recommended Andrx to use _____ because Andrx earlier indicated that _____ obscures the effect caused by the _____ equilibrium phenomenon. In its response to the Division of Chemistry, Andrx stated that their earlier statement was incorrect. The firm submitted the supporting data for Chemistry review. The Division of Chemistry has reviewed the data and found that the firm's justification for using _____ in place of _____ as the dissolution medium is acceptable. The Division of Chemistry has recommended the Division of Bioequivalence (DBE) to accept firm's proposal (Chemistry review #10 and attached ANDA approval summary).

Comments:

1. The firm conducted the dissolution testing in _____. The dissolution results were submitted in an earlier amendment (review 75401A0902). The firm used _____ for dissolution testing at _____ but the pH range of the _____ is _____. The firm was not asked to repeat the dissolution testing at _____ using _____ because the OGD was considering the data in _____ and at _____. However, the firm should be informed that in future, _____ should be used for _____.

2. Firm's proposed dissolution method and specifications are acceptable. The dissolution testing should be conducted in _____ using _____ at _____. The test product should meet the following specifications:

2h	NMT _____
4h	_____
8h	_____
12h	NLT _____
16h	NLT _____

Recommendations:

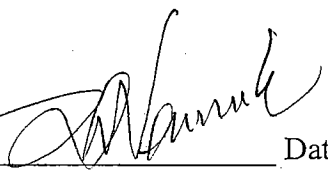
1. The *in vivo* bioequivalence study conducted under fasting conditions by Andrx on its diltiazem hydrochloride 360 mg ER capsules, lot #700B006A comparing it to the reference product Tiazac 360 mg ER capsules, lot #010912 manufactured by Biovail is acceptable to the Division of Bioequivalence.
2. The *in vivo* bioequivalence study conducted under non-fasting conditions by Andrx on its diltiazem hydrochloride 360 mg ER capsules, lot #700B006A comparing it to the reference product Tiazac 360 mg ER capsules, lot #010912 manufactured by Biovail is acceptable to the Division of Bioequivalence.
3. The *in vivo* bioequivalence study conducted under fasting conditions by Andrx on its diltiazem hydrochloride 240 mg ER capsules, lot #698B006B comparing it to the reference product Tiazac 240 mg ER capsules, lot #010807 manufactured by Biovail is acceptable to the Division of Bioequivalence.
4. The sprinkling bioequivalence study conducted by Andrx on its diltiazem hydrochloride 360 mg ER capsules, lot #700B006A comparing it to the reference product Tiazac 360 mg ER capsules, lot #010912 manufactured by Biovail is acceptable to the Division of Bioequivalence.
5. The dissolution testing conducted by the firm on its test products is acceptable. The formulation of 120, 180, 240 and 300 mg capsules is proportionally similar to the 360 mg capsules. The waiver of *in vivo* bioequivalence study requirements for 120 mg, 180 mg, and 300 mg capsules of the test product is granted.
6. The dissolution testing should be incorporated into firm's manufacturing controls and stability programs. The dissolution testing should be conducted in _____, using apparatus _____. The test product should meet the following specifications:

2h	NMT	_____
4h		_____
8h		_____
12h	NLT	_____
16h	NLT	_____

Moharawal

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR

 Date 1/27/2003

Concur:



Date 1/29/03

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence

Attachment

ANDA APPROVAL SUMMARY

ANDA: 75-401 DRUG PRODUCT: Diltiazem Hydrochloride ER Capsule, USP
FIRM: Andrx Pharmaceuticals Inc. DOSAGE FORM: Capsule
STRENGTH: 120 mg, 180 mg, 240 mg, 300 mg and 360 mg

CGMP STATEMENT/EIR UPDATE STATUS:
CGMP certification is satisfactory (See Page 9162).
EIR update: EER acceptable on 10-9-02.

BIO STUDY: Satisfactory; Reviewed by K.R. Dhariwal

- ◆ Bio study conducted under fasting conditions for 360 mg EXC, lot # 700B006A is satisfactory
- ◆ Bio study conducted under non- fasting conditions for 360 mg EXC, lot # 700B006A is satisfactory.
- ◆ Bio study conducted under fasting conditions for 240 mg EXC, lot # 698B006B is satisfactory.
- ◆ The sprinkling biostudy for the 360 mg EXC, lot# 700B006A is satisfactory
- ◆ Currently, the DOB is withholding their comments on the proposed dissolution specification _____, pending our review of the dissolution data. We have found the firm's justification for using _____ in place of _____ as the dissolution medium acceptable. We will be recommending to DOB that they accept firm's proposal for the dissolution specifications. The formulation of 120, 180, 240 and 300 mg capsules is proportionally similar to 360 mg (lot#700B006) capsules that was used to establish bioequivalency. The dissolution testing results on 120, 180, 240, 340 and 360 mg capsules are acceptable. The waiver of in vivo bioequivalence requirements for 120(lot#696B006), 180 (lot#696B007), 240 (lot#149B042)and 300 (lot#699B005)mg capsules are granted.

Dissolution specifications:

<u>Time</u>	<u>Specification</u>
2hr	NMT : _____
4hr	_____
8hr	_____
12hr	NLT _____
16hr	NLT _____

The DOB has recommended that the firm should use : _____ for _____ dissolution studies and not _____

VALIDATION -(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
Not required, USP product.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN
CONTAINER SECTION?:

Containers used in the stability testing are the same as described in the container section. The package size is 30's, and 1000's counts.. Stability data and protocol are acceptable. Expiration date is granted for 24 months and is supported by stability data.

LABELING:

Satisfactory on 3-20-2001. Update labeling is pending for review

STERILIZATION VALIDATION (IF APPLICABLE):

NA

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):

Diltiazem Hydrochloride ER Capsules, 360 mg, batch # 700B006 is compared to the listed drug Tiazac. A waiver of in vivo bioavailability testing for the Diltiazem Hydrochloride ER Capsules USP, 120 mg, 180 mg, 240 mg and 300 mg was requested and granted.

The size of the bio batch 360 mg, lot #700B006, was _____ capsules

Firm's source of NDS OK: Yes (_____), DMF# _____, DMF# _____ reviewed by S.Basaran on 10-17-02 and found satisfactory.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY
MANUFACTURED VIA THE SAME PROCESS?):

For 120 mg Capsules: _____ Capsules lot # 696B006
For 180 mg Capsules: _____ Capsules lot # 697B007
For 240 mg Capsules: _____ Capsules lot # 698B006
For 300 mg Capsules: _____ Capsules lot # 699B005
For 360 mg Capsules: _____ Capsules lot # 700B006

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS
BIO/STABILITY?:

For 120 mg Capsules: _____ Capsules
For 180 mg Capsules: _____ Capsules
For 240 mg Capsules: _____ Capsules
For 300 mg Capsules: _____ Capsules
For 360 mg Capsules: _____ Capsules

The proposed manufacturing process is the same as that used for the bio and stability batches.

CHEMIST: S. Basaran, Ph.D.

DATE:1-15-2003

Team Leader: U. Venkataram, Ph.D.

DATE:1-17-2003

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10.1

NOV 26 2002

Diltiazem Hydrochloride

Extended Release Capsules, USP

120, 180, 240, 300, 360 mg

ANDA #75-401

Reviewer: Kuldeep R. Dhariwal

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Andrx Pharmaceuticals

4955 Orange Drive

Fort Lauderdale

Florida 33314

Submission Date:

September 30, 2002

October 29, 2002

Review of an amendment

Andrx has responded to the deficiencies communicated to the firm on the bio-studies submitted on May 22, 2002.

Fasting study on the 360 mg capsules:

1. Sample numbers 6.07.4, 6.08.4, 10.05.1, 12.04.3, 12.05.3, 16.08.1, 16.09.1 were coded IA and were reassayed for diltiazem, desacetyldiltiazem, and desmethyldiltiazem. However, these samples do not seem to meet the definition of 'IA' given in SOP DH 8.2 (vol.10.3, page 0433). Please provide the justification for reassaying these samples and using the reassay values.

Response: An error in one step of the extraction procedure occurred for the eight listed samples, requiring a re-extraction of the plasma samples. Because of this error, although the samples were analyzed, the concentrations were never calculated and thus, no 'initial' values were reported.

According to terminology given in SOP DH 8.2, a result obtained when a plasma sample is re-extracted is referred to as a 'reassay' value, regardless of whether a first value was obtained or not. As there were no initial values, the reassayed values are the only values that were obtained for these samples.

Reviewer's comments: The firm states that during the first analysis, an error in the extraction procedure (two vials were mistakenly pooled) occurred and though these samples were analyzed but *the concentrations were never calculated and thus, no 'initial' values were reported.* However, table on page 462 (vol.10.3) reports values obtained during the first analysis for all these samples. For example, sample numbers 6.07.4 and 6.08.4 had diltiazem concentrations of 120 ng/mL and 129 ng/mL in the first analysis (batch #04AAO) and 107 ng/mL and 149 ng/mL respectively in the second analysis (reassay, batch #20-1AAO). The samples were reassayed once and the reassay values were used in the data analysis. On October 22, the firm was asked to explain the initial values.

In the amendment dated October 29, the firm explained that even though the sample processing errors were noted *a priori* to analysis, the samples were processed as if they were legitimate samples. The software program calculates a value despite the fact that *a priori* result is already known to be not reliable. Therefore legitimate meaningful initial concentration values did not

exist for the samples in question, in other words, meaningful concentrations were never calculated.

The firm admits that the initial values were reported but were not used since they were not reliable. The response is satisfactory.

2. Please provide potency and content uniformity data of the reference product.

Response: Tiazac 360 mg capsules, lot #010912: Assay 100.1%, Content uniformity 100.6%.

Reviewer's comments: The response is satisfactory.

3. The size of the bio batch and that of the largest lot planned for full production is not given.

Response: Theoretical bio-batch size: _____ capsules, theoretical commercial batch size: _____ capsules.

Reviewer's comments: The response is satisfactory.

Fasting study on the 240 mg capsules:

1. Please clarify if the clinical study was conducted in _____ (page 4, vol. 10.13; page 1518, vol. 10.15) or in _____ (page 1523, vol. 10.15).

Response: The clinical portion of the study was done at the _____ facility.

Reviewer's comments: The response is satisfactory.

2. Please provide potency and content uniformity data of the test and reference products.

Response: Tiazac 240 mg capsules, lot #010807: Assay 99.9%, Content uniformity 100.1%.

Reviewer's comments: The response is satisfactory.

3. The size of the bio batch and that of the largest lot planned for full production is not given. The manufacture date of the test product should be provided.

Response: Theoretical bio batch size: _____ capsules, theoretical commercial batch size: _____ capsules, date of manufacture: September 11, 2001.

Reviewer's comments: The response is satisfactory.

Sprinkling study:

- 1. In the fed study, one subject (#22) had diltiazem C_{max} T/R ratio of 0.362 but the results were not considered enigmatic. Please explain why these results were not considered enigmatic whereas the similar results obtained in the sprinkling study (subject #21) were considered enigmatic.**

Response: In the fed study, although the results from subject #22 after reference dosing appear enigmatic, the subject presented no apparent clinical reasons and was not deemed an outlier. Therefore subject #22 in the fed study was not removed from the final data set. Whereas in the sprinkling study, clinical reasons were presented (viral illness/medication ingestion prior to and/or during period 2) to consider the results for subject #21 to be enigmatic and therefore a repeat study with this subject and 3 control subjects was performed. The results of the repeat study confirmed that the results for subject #21 in the sprinkling study were enigmatic, and subject #21 was subsequently removed from the final data set.

Reviewer's comments: Subject #21 had a viral illness (sore throat, coughing, headache and nasal congestion) during second period of the sprinkling study. The subject admitted to ingesting at least two doses of ibuprofen preceding period 2 dosing. The firm states that this illness could account for the enigmatic results obtained for this subject. In contrast to firm's statement that subject #22 in the fed study presented no apparent clinical reasons, this subject experienced following adverse events during the study: AV block (first degree), AV block (second degree), headache, Mobitz type 1, sore throat and stuffy nose. Since both subjects (#21 in the sprinkling study and #22 in the fed study) experienced adverse events, the firm was asked on October 22 to explain why only subject #21 in the sprinkling study was considered an outlier.

In an amendment dated October 29, the firm stated that based on the mean $\pm$ SD C_{max} values (test: 297.18 ± 113.71 ; reference: 323.73 ± 212.80) obtained from the fed study, it is clear that the apparent enigmatic values observed from subject #22 relate to the period 2 dosing of the reference product (C_{max} 1222.0) and not following period 1 dosing of the test product (C_{max} 442.0). The adverse events of pharyngitis and rhinitis observed with subject 22 occurred during period 1 dosing. Therefore, although the results from subject #22 after period 2 dosing appear enigmatic, the subject presented no clinical reasons during period 2 dosing to explain the enigmatic value and was not deemed an outlier.

It is true that subject #22 in the fed study experienced headache, AV block (first degree), AV block (second degree), pharyngitis and rhinitis during period 2 dosing but this subject also experienced headache, Mobitz type 1 and AV block (first degree) during period 1 dosing. The diltiazem C_{max} test/reference ratio for subject #22 in the fed study (0.362) was as bad as for subject #21 in the original sprinkling study (0.368). Subject #21 in the sprinkling study was removed from the data set after a repeat study but subject #22 in the fed study was not removed from the data set and a repeat study was not conducted. The reviewer reanalyzed the fed study data after dropping subject #22. The study remains acceptable.

2. Please clarify if the clinical study was conducted in _____ (page 3, vol. 10.19; page 1433, vol. 10.22) or in _____ age 478, vol. 10.20).

Response: The clinical portion of the study was done at the _____ facility.

Reviewer's comments: The response is satisfactory.

Dissolution:

Please provide volumes, compositions and molarities of the dissolution media used in the dissolution testing.

Response:

[]

Formulation:

[]

Reviewer's comments: The response is satisfactory.

General Comments:

The Division of Chemistry has not completed the review of firm's amendment dated May 22, 2002. The Division of Chemistry needs to review the dissolution data before the DBE can make recommendation regarding the medium and the specification for the finished drug product. Andrx proposes to use _____ as dissolution medium. The Division of Chemistry recommended Andrx to use _____ because Andrx earlier indicated that _____ obscures the effect caused by the moisture equilibrium phenomenon. In its response to the Division of Chemistry, Andrx now states that their earlier statement was incorrect. The firm has submitted the data for Chemistry review.

This reviewer discussed the dissolution data with the Chemistry team leader, U.Venkataram on October 25, 2002. The Division of Chemistry needs clarifications from the firm and therefore is not able to take a decision about the dissolution medium and specifications at this time.

The firm has satisfactorily responded to all the deficiencies to the Division of Bioequivalence. Therefore, bioequivalence portion of this ANDA is acceptable. The dissolution conditions for the test product will be established after completion of the Chemistry review.

Recommendation:

1. The in vivo bioequivalence study conducted under fasting conditions by Andrx on its diltiazem hydrochloride 360 mg ER capsules, lot #700B006A comparing it to the reference product Tiazac 360 mg ER capsules, lot #010912 manufactured by Biovail is acceptable to the Division of Bioequivalence.
2. The in vivo bioequivalence study conducted under non-fasting conditions by Andrx on its diltiazem hydrochloride 360 mg ER capsules, lot #700B006A comparing it to the reference product Tiazac 360 mg ER capsules, lot #010912 manufactured by Biovail is acceptable to the Division of Bioequivalence.
3. The in vivo bioequivalence study conducted under fasting conditions by Andrx on its diltiazem hydrochloride 240 mg ER capsules, lot #698B006B comparing it to the reference product Tiazac 240 mg ER capsules, lot #010807 manufactured by Biovail is acceptable to the Division of Bioequivalence.
4. The sprinkling bioequivalence study conducted by Andrx on its diltiazem hydrochloride 360 mg ER capsules, lot #700B006A comparing it to the reference product Tiazac 360 mg ER capsules, lot #010912 manufactured by Biovail is acceptable to the Division of Bioequivalence.

5. The Division of Chemistry will make a decision about the dissolution medium after review of the data to be submitted by the firm. The dissolution conditions for the test product will be established by the DBE after completion of the Chemistry review.

Mohariwal 11/7/02

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR

[Signature] Date 11/8/2002

Concur: [Signature] Date 11/26/02
Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-401

APPLICANT: Andrx

DRUG PRODUCT: Diltiazem Hydrochloride ER Capsules, USP
120 mg, 180 mg, 240 mg, 300 mg, 360 mg

The Division of Bioequivalence has completed its review and has no further questions at this time. •

The dissolution conditions for your drug product have not yet been established and therefore will be communicated to you later.

In future, you should use acetate buffer instead of _____
_____ for _____ dissolution testing as recommended in _____
The pH range of the _____ is _____

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,



Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 75401
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DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)

HFD-655/Dhariwal *ME 11/7/02*

HFD-655/Nerurkar

HFD-617/Nwaba

HFD-650/Dale Conner *ME 11/26/02*

EW 11/8/02

BIOEQUIVALENCY

Submission Dates: 9/30/02
10/29/02

1. **STUDY AMENDMENT (STA)**
9/30/02

Strengths: All
✓ Outcome: AC

2. **STUDY AMENDMENT (STA)**
10/29/02

Strengths: All
✓ Outcome: AC

Outcome Decisions:
AC - Acceptable

APPEARS THIS WAY
ON ORIGINAL

SEP - 6 2002

Diltiazem Hydrochloride

Extended Release Capsules, USP

120, 180, 240, 300, 360 mg

ANDA #75-401

Reviewer: Kuldeep R. Dhariwal

V:\firmsam\Andrx\Ltrs&rev\75401A0502.doc

Andrx Pharmaceuticals

4955 Orange Drive

Fort Lauderdale

Florida 33314

Submission Date:

May 22, 2002

Review of Bioequivalence Studies and Dissolution Data

The reference listed drug is Tiazac® by Biovail. Tiazac® is currently marketed in six strengths: 120 mg, 180 mg, 240 mg, 300 mg, 360 mg and 420 mg. All strengths are marked '+' in the Orange Book.

History of Andrx submissions:

June 22, 1998:

Andrx submitted ANDA for diltiazem hydrochloride ER capsules. The firm conducted fasting, non-fasting and multiple-dose studies on 360 mg strength. Diltiazem and the two metabolites, desmethyldiltiazem and desacetyldiltiazem were measured and subjected to 90% confidence interval approach.

July 29, 1998:

Dissolution data on 120, 180, 240, and 300 mg strengths and waiver requests for these strengths.

October 16, 1998:

Studies acceptable. Waivers granted. The firm was told that the dissolution testing should be conducted using USP test 6 method and the test product should meet the following interim specifications:

2h	NMT	_____
4h		_____
8h		_____
12h	NLT	_____
16h	NLT	_____

Note: The firm had proposed specifications of _____ for the 4h time interval.

October 29, 1999:

Andrx submitted an amendment to request that _____ range at 4h as suggested in the original application be retained.

November 1, 1999:

Study amendment with more supporting data to change the suggested dissolution specifications.

November 16, 1999:

The DBE revised the 4h specifications from _____

April 11, 2000:

The Agency requested the firm to conduct a single dose, two-way crossover sprinkling study on its 360 mg capsule because the reference listed drug labeling was amended to incorporate dosage administration by sprinkling the contents of a capsule on applesauce.

April 28, 2000: Amendment requesting a waiver of the *in vivo* bioequivalence sprinkling study.

June 9, 2000: The waiver was denied. The firm was requested to conduct *in vivo* bioequivalence sprinkling study.

June 26, 2000: Firm submitted sprinkling study.

July 12, 2000: Sprinkling study acceptable.

December 12, 2000: Andrx requested that _____ should be replaced with _____ as it is not a good medium for its product. The firm also requested that paddle speed should be changed from _____. A change in specification was not requested.

January 3, 2001: The DBE accepted to change the dissolution medium and paddle speed.

September 29, 2000: ANDA was tentatively approved by the OGD.

Biovail submissions challenging Andrx:

Biovail submitted biostudies conducted under fasting conditions comparing Andrx's 120 mg capsules with Biovail's 120 mg capsules and Andrx's 240 mg capsules with Biovail's 240 mg capsules. These studies were conducted at Biovail. The 120 mg study passed but the 240 mg capsule failed bioequivalence criteria. Another study on the 240 mg capsule was conducted by _____ which also did not meet the bioequivalence criteria. The clinical and analytical sites used by Andrx (studies submitted in ANDA 75401) and Biovail were inspected by the DSI. The DSI did not find any significant objectionable findings at these facilities. The DSI has also completed the inspection of _____ facility and the findings do not change the outcome of the study. However, during the _____ inspection, the DSI found that _____ also conducted a fasting study comparing Andrx's 360 mg capsules with Biovail's Tiazac 360 mg capsules. The results of this study showed that the two products are bioequivalent. Biovail had not revealed this study to the FDA. This bioequivalence study has not been submitted to the FDA.

Biovail argued that Andrx is unable to manufacture a product that is consistently bioequivalent to Tiazac[®], and therefore the Andrx ANDA should not be approved. Biovail questioned the manufacturing process used by the Andrx.

Andrx's arguments:

On October 5, 2001, Andrx submitted an amendment stating that the FDA should reject Biovail's data on both scientific and policy grounds for various reasons (see earlier reviews).

The Division of Chemistry reviewed CMC data and concluded that the Andrx cannot produce a product of consistent quality and performance.

[]

Controlled Correspondence from Andrx: March 5, 2002

On March 5, 2002 Andrx informed the OGD that Andrx and Biovail are settling all pending litigation between them. Andrx further stated that the firm has already initiated three bioequivalence studies as follows:

1. Diltiazem hydrochloride 360 mg capsules (Andrx) vs. Tiazac® 360 mg capsules (Biovail).
Single dose fasting in 40 healthy subjects
Randomized, 4 period, 2 sequence, crossover, replicate design
Measurement of diltiazem, desmethyldiltiazem and desacetyldiltiazem to 48 h
2. Diltiazem hydrochloride 360 mg capsules (Andrx) vs. Tiazac® 360 mg capsules (Biovail).
Single dose fed in 24 healthy subjects
Randomized, 2 period, 2 sequence, crossover design
Measurement of diltiazem, desmethyldiltiazem and desacetyldiltiazem to 48 h
3. Diltiazem hydrochloride 240 mg capsules (Andrx) vs. Tiazac® 240 mg capsules (Biovail).
Single dose fasting in 40 healthy subjects
Randomized, 4 period, 2 sequence, crossover, replicate design
Measurement of diltiazem, desmethyldiltiazem and desacetyldiltiazem to 48 h

In addition to the bioequivalence studies, Andrx planned to submit the following information:

1. Dissolution profiles for all five strengths of the test and reference products, using _____ dissolution media, as well as _____. The F_2 factors comparing each of the four lower strengths of the test product to the highest strength (360 mg).
2. Results of ongoing room temperature stability studies (up to 6 months) on batches produced with the scaled-up process in October 2001.

The above proposal for bioequivalence studies and the dissolution testing was acceptable to the DBE. The DBE requested that a sprinkling study on the proposed highest strength should also be conducted.

This submission:

Andrx acknowledges DBE's comments concerning _____ and withdraws _____ data submitted earlier. The firm accepts reviewer's arguments that the two strengths used to develop _____ cannot be called medium and fast formulations.

Andrx has submitted the necessary bioequivalence studies and the dissolution data.

Protocol # R02-045: A relative bioavailability study of 360 mg diltiazem extended-release capsules under fasting conditions.

STUDY INFORMATION

STUDY FACILITY INFORMATION

Clinical Facility:	
Principal Investigator:	
Clinical Study Dates:	Period 1 February 10, 2002 Period 2 February 17, 2002 Period 3 February 24, 2002 Period 4 March 3, 2002
Analytical Facility	
Analytical Director:	
Analytical Study Dates:	March 7-26, 2002
Storage Period:	44 days

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Diltiazem HCl capsules	Tiazac® capsules
Manufacturer:	Andrx	Biovail
Manufacture Date:	9/01	N/A
Expiration Date:	N/A	9/05
ANDA Batch Size:	Not provided	N/A
Batch/Lot Number:	700B006A	010912
Potency:	102.2%	Not provided
Content Uniformity:	100.0%	Not provided
Strength:	360 mg	360 mg
Dosage Form:	Extended release capsule	Extended release capsule
Dose Administered:	1x360 mg	1x360 mg
Study Condition:	Fasting	Fasting
Length of Fasting:	Overnight	Overnight

RANDOMIZATION

DESIGN

Randomized:	Y	Design Type:	Crossover
No. of Sequences:	2	Replicated Treatment Design:	Y
No. of Periods:	4	Balanced:	N
No. of Treatments:	2	Washout Period:	7 days

ABAB: 1,2,3,4,5,12,13,15,17,18,19,20,24,27,28,29,31,33,36,38

BABA: 6,7,8,9,10,11,14,16,21,22,23,25,26,30,32,34,35,37,39,40

SUBJECT DEMOGRAPHICS

Race:	Caucasian 36, Asian 2, American Indian 1, Hispanic 1
Height:	Mean 177.5 cm, range 152.4-193 cm
Weight:	Mean 79.6 kg, range 58.4-101.0 kg
Sex:	Male 34, Female 6
Age group:	<18 0 18-40 38 41-64 2 65-75 0 >75 0 Mean age 24.1 years, range 18-46 years

DOSING

SUBJECTS

Single or Multiple Dose:	Single	IRB Approval:	Y
Steady State:	N	Informed Consent Obtained:	Y
Volume of Liquid Intake:	240 mL	No. of Subjects Enrolled:	40
Route of Administration:	Oral	No. of Subjects Completing:	37
Dosing Interval:	N/A	No. of Subjects Plasma Analyzed:	37
Number of Doses:	N/A	No. of Dropouts:	3
Loading Dose:	N/A	Sex(es) Included:	Both
Steady State Dose Time:	N/A	Healthy Volunteers Only:	Y
Length of Infusion:	N/A	No. of Adverse Events:	Total 105

Dietary Restrictions:	Subjects were instructed to abstain from caffeine, grapefruit products, or xanthine containing food during the confinement period of the study. No fluid was allowed from 1 h prior to dose until 2 h after dosing.
Activity Restrictions:	For their personal safety, subjects were required to remain in a seated or semi-seated position for initial 4 hours after dosing avoiding complete rest.
Drug Restrictions:	No prescription drugs 14 days prior to study and during the study. No OTC drugs 3 days prior to study.
Blood Sampling Time:	Blood samples (10 mL) were collected in EDTA Vacutainers before dosing (0 h) and at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 20, 24, 36 and 48 hrs post-dose.

1) Clinical

Adverse Events: The most common event was headache and was comparable on the test and reference drugs. Subject #37 fainted at study hour 3 (period 1) secondary to difficult phlebotomy. The subject was placed in a supine position for about 10 minutes. First degree AV blocks were recorded for subjects 18, 25 and 38 during study periods 3 and 4. A second degree SA block was recorded for subject 9 during period 3. The subjects were asymptomatic with vital signs within normal limits.

Protocol Deviations: There were a few sampling time deviations. Actual sampling times were used for calculations of pharmacokinetic parameters. Several subjects took ibuprofen during the study. Some subjects took Tylenol during the study.

Redacted _____

Page(s) of trade

secret and /or

confidential

commercial

information

3) Pharmacokinetics:

Diltiazem:

Mean Plasma Concentrations:	Table 1, Figure 1	
PK Parameters:	Table 1	
90% Confidence Intervals:	LAUC _{0-t}	97.40-105.57%
	LAUC _{0-inf}	96.98-105.00%
	LC _{max}	92.81-103.43%

Desacetyldiltiazem:

Mean Plasma Concentrations:	Table 2, Figure 2	
PK Parameters:	Table 2	
90% Confidence Intervals:	LAUC _{0-t}	96.39-103.43%
	LAUC _{0-inf}	96.56-102.74%
	LC _{max}	96.28-105.10%

Desmethyldiltiazem:

Mean Plasma Concentrations:	Table 3, Figure 3	
PK Parameters:	Table 3	
90% Confidence Intervals:	LAUC _{0-t}	98.41-103.39%
	LAUC _{0-inf}	95.63-102.56%
	LC _{max}	95.20-102.10%

Comments:

1. The reviewer repeated statistical analyses of the data. The reported values are in good agreement with those obtained by the reviewer. The 90% confidence intervals for log transformed AUC_{0-t}, AUC_{0-inf} and C_{max} for diltiazem, desacetyldiltiazem, and desmethyldiltiazem are within acceptable limits.
2. One diltiazem sample was reassayed for pharmacokinetic reasons and the reassayed value was used for statistical analysis. This value was not a C_{max} value and therefore use of original value in stead of reassay value would not change the 90% CI for LC_{max}.
3. Sample numbers 6.07.4, 6.08.4, 10.05.1, 12.04.3, 12.05.3, 16.08.1, 16.09.1 were coded IA and were reassayed for diltiazem, desacetyldiltiazem, and desmethyldiltiazem. However, these samples do not seem to meet the definition of 'IA' given in SOP DH 8.2 (vol.10.3, page 0433). The firm should provide the justification for reassaying these samples and using the reassay values.
4. The firm should provide potency and content uniformity data of the reference product.
5. The size of the bio batch and that of the largest lot planned for full production is not given.
6. The fasting study is incomplete.

Protocol # R02-046: A relative bioavailability study of 360 mg diltiazem extended-release capsules under non-fasting conditions.

STUDY INFORMATION

STUDY FACILITY INFORMATION

Clinical Facility:	
Principal Investigator:	
Clinical Study Dates:	Period 1 March 2, 2002 Period 2 March 9, 2002
Analytical Facility	
Analytical Director:	
Analytical Study Dates:	March 19 to April 19, 2002
Storage Period:	47 days

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Diltiazem HCl capsules	Tiazac capsules
Manufacturer:	Andrx	Biovail
Manufacture Date:	9/01	N/A
Expiration Date:	N/A	9/05
ANDA Batch Size:	Not provided	N/A
Batch/Lot Number:	700B006A	010912
Potency:	102.2%	Not provided
Content Uniformity:	100.0%	Not provided
Strength:	360 mg	360 mg
Dosage Form:	Extended release capsule	Extended release capsule
Dose Administered:	1x360 mg	1x360 mg
Study Condition:	Non-fasting	Non-fasting
Length of Fasting:	Overnight	Overnight
Standard Breakfast:	Yes	Yes

RANDOMIZATION

DESIGN

Randomized:	Y	Design Type:	Crossover
No. of Sequences:	2	Replicated Treatment Design:	N
No. of Periods:	2	Balanced:	N
No. of Treatments:	2	Washout Period:	7 days

AB: 1,9,10,11,12,13,14,17,18,21,22,24

BA: 2,3,4,5,6,7,8,15,16,19,20,23

SUBJECT DEMOGRAPHICS

Race:	Caucasian 20, Asian 1, African American 2, Hispanic 1
Height:	Mean 173.2 cm, range 154.9-195.6 cm

Weight:	Mean 74.9 kg, range 48.0-101.5 kg
Sex:	Male 16, Female 8
Age group:	<18 0 19-40 21 41-64 3 65-75 0 >75 0 Mean age 26.1 years, range 18-47 years

DOSING

SUBJECTS

Single or Multiple Dose:	Single	IRB Approval:	Y
Steady State:	N	Informed Consent Obtained:	Y
Volume of Liquid Intake:	240 mL	No. of Subjects Enrolled:	24
Route of Administration:	Oral	No. of Subjects Completing:	22
Dosing Interval:	N/A	No. of Subjects Plasma Analyzed:	22
Number of Doses:	N/A	No. of Dropouts:	2
Loading Dose:	N/A	Sex(es) Included:	Both
Steady State Dose Time:	N/A	Healthy Volunteers Only:	Y
Length of Infusion:	N/A	No. of Adverse Events:	Total 56

Dietary Restrictions:	Subjects were instructed to abstain from caffeine, grapefruit products, or xanthine containing food during the confinement period of the study. No fluid was allowed from 1 h prior to dose until 2 h after dosing.
Activity Restrictions:	For their personal safety, subjects were required to remain in a seated or semi-seated position for initial 4 hours after dosing avoiding complete rest.
Drug Restrictions:	No prescription drugs 14 days prior to study and during the study. No OTC drugs 3 days prior to study.
Blood Sampling Time:	Blood samples (10 mL) were collected in EDTA Vacutainers before dosing (0 h) and at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 20, 24, 36 and 48 hrs post-dose.

1) Clinical

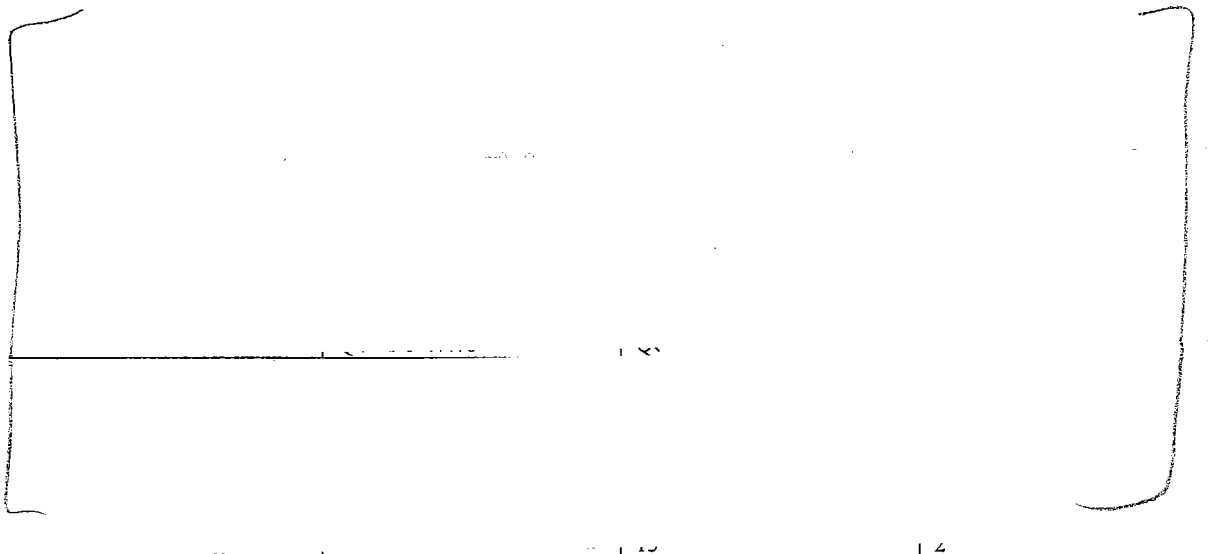
Adverse Events: The most common event was headache and was comparable on the test and reference drugs. First degree AV blocks were recorded for subjects 3, 4, 8, 19, 22 and 23.

Protocol Deviations: There were a few sampling time deviations. Actual sampling times were used for calculations of pharmacokinetic parameters. One subject took ibuprofen during the study.

Drop-outs: The strep throat was reported by subject #1 between study periods 1 and 2 and was treated with erythromycin. Subject #1 was therefore dropped prior to period 2 dosing. Subject #21 was dropped by the medical investigator prior to period 2 dosing secondary to ECG changes (Wolff-Parkinson-White Pattern) observed during period 1 (test drug).

2) Analytical (Not to be released Under FOI):

Within-study results:



3) Pharmacokinetics:

Diltiazem:

Mean Plasma Concentrations: Table 4, Figure 4

PK Parameters: Table 4

90% Confidence Intervals:

LAUC _{0-t}	97.23-121.42%
LAUC _{0-inf}	97.16-121.15%
LC _{max}	85.82-110.04%

Desacetyldiltiazem:

Mean Plasma Concentrations: Table 5, Figure 5

PK Parameters: Table 5

90% Confidence Intervals:

LAUC _{0-t}	100.56-112.65%
LAUC _{0-inf}	99.47-111.69%
LC _{max}	99.54-115.24%

Desmethyldiltiazem:

Mean Plasma Concentrations: Table 6, Figure 6

PK Parameters: Table 6

90% Confidence Intervals:

LAUC _{0-t}	100.10-110.87%
LAUC _{0-inf}	99.96-110.70%
LC _{max}	93.80-104.84%

Comments:

1. The pharmacokinetic parameters were recalculated using the plasma data provided by the firm. The statistical analyses were repeated using the recalculated pharmacokinetic

parameters. The ratios of means for log transformed AUC_{0-t} , AUC_{0-inf} and C_{max} were within acceptable limits in all analyses.

2. The firm should provide potency and content uniformity data of the reference product.
3. The size of bio batch and that of the largest lot planned for full production is not given.
4. The non-fasting study is incomplete.

Protocol # R02-206: A relative bioavailability study of 240 mg diltiazem extended-release capsules under fasting conditions.

STUDY INFORMATION

STUDY FACILITY INFORMATION

Clinical Facility:	
Principal Investigator:	
Clinical Study Dates:	Period 1 February 24, 2002 Period 2 March 3, 2002 Period 3 March 10, 2002 Period 4 March 17, 2002
Analytical Facility	
Analytical Director:	
Analytical Study Dates:	March 27 to April 24, 2002
Storage Period:	59 days

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Diltiazem HCl capsules	Tiazac [®] capsules
Manufacturer:	Andrx	Biovail
Manufacture Date:	Not provided	N/A
Expiration Date:	N/A	6/05
ANDA Batch Size:	Not provided	N/A
Batch/Lot Number:	698B006B	010807
Potency:	Not provided	Not provided
Content Uniformity:	Not provided	Not provided
Strength:	240 mg	240 mg
Dosage Form:	Extended release capsule	Extended release capsule
Dose Administered:	1x240 mg	1x240 mg
Study Condition:	Fasting	Fasting
Length of Fasting:	Overnight	Overnight

RANDOMIZATION

DESIGN

Randomized:	Y	Design Type:	Crossover
No. of Sequences:	2	Replicated Treatment Design:	Y
No. of Periods:	4	Balanced:	N

No. of Treatments:	2	Washout Period:	7 days
ABAB: 2,3,4,6,7,11,12,16,17,18,19,21,27,28,29,30,33,34,38,40			
BABA: 1,5,8,9,10,13,14,15,20,22,23,24,25,26,31,32,35,36,37,39			

SUBJECT DEMOGRAPHICS

Race:	Caucasian 39, Hispanic 1												
Height:	Mean 175.4 cm, range 152.4-190.5 cm												
Weight:	Mean 75.7 kg, range 54.8-96.0 kg												
Sex:	Male 30, Female 10												
Age group:	<table> <tr><td><18</td><td>0</td></tr> <tr><td>18-40</td><td>34</td></tr> <tr><td>41-64</td><td>6</td></tr> <tr><td>65-75</td><td>0</td></tr> <tr><td>>75</td><td>0</td></tr> <tr><td colspan="2">Mean age 26.1 years, range 18-46 years</td></tr> </table>	<18	0	18-40	34	41-64	6	65-75	0	>75	0	Mean age 26.1 years, range 18-46 years	
<18	0												
18-40	34												
41-64	6												
65-75	0												
>75	0												
Mean age 26.1 years, range 18-46 years													

DOSING

SUBJECTS

Single or Multiple Dose:	Single	IRB Approval:	Y
Steady State:	N	Informed Consent Obtained:	Y
Volume of Liquid Intake:	240 mL	No. of Subjects Enrolled:	40
Route of Administration:	Oral	No. of Subjects Completing:	37
Dosing Interval:	N/A	No. of Subjects Plasma Analyzed:	37
Number of Doses:	N/A	No. of Dropouts:	3
Loading Dose:	N/A	Sex(es) Included:	Both
Steady State Dose Time:	N/A	Healthy Volunteers Only:	Y
Length of Infusion:	N/A	No. of Adverse Events:	Total 84

Dietary Restrictions:	Subjects were instructed to abstain from caffeine, grapefruit products, or xanthine containing food during the confinement period of the study. No fluid was allowed from 1 h prior to dose until 2 h after dosing.
Activity Restrictions:	For their personal safety, subjects were required to remain in a seated or semi-seated position for initial 4 hours after dosing avoiding complete rest.
Drug Restrictions:	No prescription drugs 14 days prior to study and during the study. No OTC drugs 3 days prior to study.
Blood Sampling Time:	Blood samples (10 mL) were collected in EDTA Vacutainers before dosing (0 h) and at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 20, 24, 36 and 48 hrs post-dose.

1) Clinical

Adverse Events: The most common event was headache and was comparable on the test and reference drugs. First degree AV blocks were recorded for subjects 8,13 and 30. A left anterior fascicular block was recorded for subject #23. A second degree SA block was recorded for subject #9 and 27. The subjects were asymptomatic with vital signs within normal limits.

Protocol Deviations: There were a few sampling time deviations. Actual sampling times were used for calculations of pharmacokinetic parameters. Several subjects took ibuprofen, acetaminophen, pseudoephedrine during the study.

Drop-outs: Subject #40 failed to return for period 2 check-in. Subject #20 elected to withdraw following completion of period 2. Subject #19 was dropped by the medical investigator prior to period 4 dosing secondary to phlebitis of the arms and legs.

2) Analytical (Not to be released Under FOI):

Within-study results:

3) Pharmacokinetics:

Diltiazem:

Mean Plasma Concentrations: Table 7, Figure 7

PK Parameters: Table 7

90% Confidence Intervals:	LAUC _{0-t}	93.63-101.06%
	LAUC _{0-inf}	93.89-101.15%
	LC _{max}	88.36-100.32%

Desacetyldiltiazem:

Mean Plasma Concentrations: Table 8, Figure 8

PK Parameters: Table 8

90% Confidence Intervals:	LAUC _{0-t}	97.50-105.86%
	LAUC _{0-inf}	95.75-104.31%
	LC _{max}	98.31-108.03%

Desmethyldiltiazem:

Mean Plasma Concentrations:	Table 9, Figure 9	
PK Parameters:	Table 9	
90% Confidence Intervals:	LAUC _{0-t}	96.57-100.88%
	LAUC _{0-inf}	96.35-100.86%
	LC _{max}	93.42-101.40%

Comments:

1. The reviewer repeated statistical analyses of the data. The reported values are in good agreement with those obtained by the reviewer. The 90% confidence intervals for log transformed AUC_{0-t}, AUC_{0-inf} and C_{max} for diltiazem, desacetyldiltiazem, and desmethyldiltiazem are within acceptable limits.
2. The firm should clarify if the clinical study was conducted in _____ (page 4, vol. 10.13; page 1518, vol. 10.15) or in _____ (page 1523, vol. 10.15).
3. The firm should provide potency and content uniformity data of the test and reference products.
4. The size of the bio batch and that of the largest lot planned for full production is not given. The manufacture date of the test product should be provided.
5. The fasting study is incomplete.

Protocol # R02-048: A relative bioavailability study of 360 mg diltiazem extended-release capsules administered with applesauce.

STUDY INFORMATION**STUDY FACILITY INFORMATION**

Clinical Facility:	_____
Principal Investigator:	_____
Clinical Study Dates:	Period 1 March 31, 2002 Period 2 April 7, 2002 Repeat (re-dosing) study Period 1 April 27, 2002 Period 2 May 4, 2002
Analytical Facility	_____
Analytical Director:	_____
Analytical Study Dates:	April 11 to April 22, 2002 Repeat study: May 9 to May 10, 2002
Storage Period:	Less than 34 days

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	T	R

Product Name:	Diltiazem HCl capsules	Tiazac [®] capsules
Manufacturer:	Andrx	Biovail
Manufacture Date:	9/01	N/A
Expiration Date:	N/A	9/05
ANDA Batch Size:	Not provided	N/A
Batch/Lot Number:	700B006A	010912
Potency:	102.2%	Not provided
Content Uniformity:	100.0%	Not provided
Strength:	360 mg	360 mg
Dosage Form:	Extended release capsule	Extended release capsule
Dose Administered:	1x360 mg*	1x360 mg*
Study Condition:	Fasting	Fasting
Length of Fasting:	Overnight	Overnight

* The contents of capsules were sprinkled on a tablespoon of applesauce, swallowed without chewing, followed by 240 mL of water.

RANDOMIZATION

DESIGN

Randomized:	Y	Design Type:	Crossover
No. of Sequences:	2	Replicated Treatment Design:	N
No. of Periods:	2	Balanced:	N
No. of Treatments:	2	Washout Period:	7 days

AB: 7,8,11,13,16,17,18,20,21,22,23,25,27,29,31,34,35,36

BA: 1,2,3,4,5,6,9,10,12,14,15,19,24,26,28,30,32,33

SUBJECT DEMOGRAPHICS

Race:	Caucasian 34, Hispanic 2
Height:	Mean 174.1 cm, range 157.5-188 cm
Weight:	Mean 74.3 kg, range 60.2-94.2 kg
Sex:	Male 30, Female 6
Age group:	<18 0 18-40 35 41-64 1 65-75 0 >75 0 Mean age 22.1 years, range 18-46 years

DOSING

SUBJECTS

Single or Multiple Dose:	Single	IRB Approval:	Y
Steady State:	N	Informed Consent Obtained:	Y
Volume of Liquid Intake:	240 mL	No. of Subjects Enrolled:	36
Route of Administration:	Oral	No. of Subjects Completing:	34
Dosing Interval:	N/A	No. of Subjects Plasma Analyzed:	34
Number of Doses:	N/A	No. of Dropouts:	2

Loading Dose:	N/A	Sex(es) Included:	Both
Steady State Dose Time:	N/A	Healthy Volunteers Only:	Y
Length of Infusion:	N/A	No. of Adverse Events:	Total 66

Dietary Restrictions:	Subjects were instructed to abstain from caffeine, grapefruit products, or xanthine containing food during the confinement period of the study. No fluid was allowed from 1 h prior to dose until 2 h after dosing.
Activity Restrictions:	For their personal safety, subjects were required to remain in a seated or semi-seated position for initial 4 hours after dosing avoiding complete rest.
Drug Restrictions:	No prescription drugs 14 days prior to study and during the study. No OTC drugs 3 days prior to study.
Blood Sampling Time:	Blood samples (10 mL) were collected in EDTA Vacutainers before dosing (0 h) and at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 20, 24, 36 and 48 hrs post-dose.

1) Clinical

Adverse Events: Subject #6, 24 and 25 reported dizziness between study hours 1 and 2 in period 1 secondary to difficult phlebotomy. The subjects were placed in a supine position until the event resolved. The most common event was headache and was comparable on the test and reference drugs. First degree AV blocks were recorded for subjects 1, 14, 19, 23, 25, 30 and 32. The subjects were asymptomatic with vital signs within normal limits.

Protocol Deviations: There were a few sampling time deviations. Actual sampling times were used for calculations of pharmacokinetic parameters. Several subjects took ibuprofen during the study.

Drop-outs: Subject #1 was dropped prior to period 2 dosing due to positive drug screen. Subject #30 was dropped prior to period 2 dosing due to a PR interval of 176 ms on the pre-dose ECG. Subject #30 was given the reference drug in period 1.

2) Analytical (Not to be released Under FOI):

Within-study results:

3) Pharmacokinetics:

Diltiazem:

Mean Plasma Concentrations:	Table 10, Figure 10	
PK Parameters:	Table 10	
90% Confidence Intervals:	LAUC _{0-t}	92.98-104.97%
	LAUC _{0-inf}	93.29-105.13%
	LC _{max}	78.71-92.90%

Desacetyldiltiazem:

Mean Plasma Concentrations:	Table 11, Figure 11	
PK Parameters:	Table 11	
90% Confidence Intervals:	LAUC _{0-t}	98.50-108.73%
	LAUC _{0-inf}	98.62-108.90%
	LC _{max}	92.89-104.87%

Desmethyldiltiazem:

Mean Plasma Concentrations:	Table 12, Figure 12	
PK Parameters:	Table 12	
90% Confidence Intervals:	LAUC _{0-t}	96.56-103.64%
	LAUC _{0-inf}	97.05-104.10%
	LC _{max}	87.66-97.21%

Excluding subject #21

Diltiazem:

Mean Plasma Concentrations:	Table 13, Figure 13	
PK Parameters:	Table 13	
90% Confidence Intervals:	LAUC _{0-t}	95.99-105.96%
	LAUC _{0-inf}	96.23-106.12%
	LC _{max}	81.75-94.18%

Desacetyldiltiazem:

Mean Plasma Concentrations:	Table 14, Figure 14	
PK Parameters:	Table 14	
90% Confidence Intervals:	LAUC _{0-t}	99.63-109.59%
	LAUC _{0-inf}	99.47-109.70%
	LC _{max}	95.20-105.96%

Desmethyldiltiazem:

Mean Plasma Concentrations: Table 15, Figure 15

PK Parameters: Table 15

90% Confidence Intervals: LAUC_{0-t} 97.92-104.27%
 LAUC_{0-inf} 98.24-104.73%
 LC_{max} 89.45-98.06%

Comments:

1. The firm states that subject #21 data should not be used in statistical analysis because his results appear enigmatic. The enigmatic result was the diltiazem C_{max} value of 443 ng/mL on the reference product in period 2. The test/reference C_{max} ratio in this subject was 0.368. At period 2 check-in, this subject reported viral illness (pharyngitis, coughing, headache and nasal congestion). The 90% CI for LC_{max} are outside the acceptable limits (78.71-92.90%) including the data from subject #21 but are within the acceptable limits if the data from this subject are excluded. To confirm that subject #21 data are enigmatic, the firm redosed this subject along with three other subjects originally dosed as #7, 12 and 15.
2. The repeat study was a randomized, single-dose, one sequence (BA), two-way crossover design. Upon redosing, subject #21 had a C_{max} of 188 ng/mL on the reference drug and a test/reference ratio of 0.984. The firm concluded that the data from subject #21 in the original study were enigmatic and therefore this subject should be dropped from the statistical analyses. The following values were obtained for these subjects in the original and redosing studies:

Original study: Diltiazem

Subj #	AUC _{0-t} ng.h/mL		AUC _{0-inf} ng.h/mL		C _{max} ng/mL		
	Test	Reference	Test	Reference	Test	Reference	T/R Ratio
21	2932.78	5775.80	3001.39	5786.00	163.00	443.00	0.368
7	3255.43	3238.46	3302.36	3271.41	204.00	187.00	1.091
12	3696.00	3901.53	3716.86	3931.60	462.00	397.00	1.164
15	2157.83	2448.48	2201.71	2536.14	102.00	127.00	0.803

Redosing study: Diltiazem

Subj #	AUC _{0-t} ng.h/mL		AUC _{0-inf} ng.h/mL		C _{max} ng/mL		
	Test	Reference	Test	Reference	Test	Reference	T/R Ratio
21	2621.30	3420.97	2736.13	3446.58	185.00	188.00	0.984
7	3223.36	4073.68	3252.04	4094.16	158.00	216.00	0.731
12	3824.84	3952.54	3842.98	3966.74	364.00	375.00	0.971
15	2329.83	2425.22	2417.74	2462.11	128.00	113.00	1.133

3. The reviewer repeated statistical analyses of the data. The reported values are in good agreement with those obtained by the reviewer. The 90% confidence intervals for log transformed AUC_{0-t} , AUC_{0-inf} and C_{max} for diltiazem, desacetyldiltiazem, and desmethyl diltiazem are within acceptable limits excluding subject #21.
4. The firm should provide potency and content uniformity data of the reference product.
5. The size of the bio batch and that of the largest lot planned for full production is not given.
6. In the fed study, one subject (#22) had diltiazem C_{max} T/R ratio of 0.362 but the results were not considered enigmatic. The firm should explain why these results were not considered enigmatic whereas the similar results obtained in the sprinkling study were considered enigmatic.
7. The firm should clarify if the clinical study was conducted in _____ (page 3, vol. 10.19; page 1433, vol. 10.22) or in _____ (page 478, vol.10.20).
8. The sprinkling study is incomplete.

Formulation: The quantities of active pellets' ingredients given in the master formula on page 75 vol. 9.1 differ from that given in the original application. The firm should provide comparative quantitative composition of all strengths of the test capsules.

Dissolution (Not to be released under FOI)

Dissolution Method:

Medium:

Volume: Not given

Dissolution Apparatus:

Mean Dissolution Data

Test				Reference		
Lot No.: 696B006C				Lot No.: 010433		
Strength: 120 mg				Strength: 120 mg		
No. of Units: 12				No. of Units: 12		
Time(h)	Mean	Range	%CV	Mean	Range	%CV
0	-3	_____	-32	-1	_____	-171
2	10	_____	14	17	_____	30
4	24	_____	7	45	_____	10
8	53	_____	3	72	_____	4
12	68	_____	2	83	_____	3
16	77	_____	2	88	_____	3

Mean Dissolution Data

Test				Reference		
Lot No.: 697B007C				Lot No.: 010717		
Strength: 180 mg				Strength: 180 mg		
No. of Units: 12				No. of Units: 12		
Time(h)	Mean	Range	%CV	Mean	Range	%CV
0	0	_____	-	-2	_____	-62.9

2	14	11.7	12	9.8
4	34	5.6	40	3.9
8	60	2.9	72	2.5
12	76	2.6	84	2.0
16	86	2.1	91	2.2

Mean Dissolution Data

Test				Reference		
Lot No.: 698B006B				Lot No.: 010807		
Strength: 240 mg				Strength: 240 mg		
No. of Units: 12				No. of Units: 12		
Time(h)	Mean	Range	%CV	Mean	Range	%CV
0	-1		-62	-1		-98.2
2	10		15	14		9
4	24		7	42		4
8	55		3	72		2.9
12	70		2	84		2.6
16	79		2	90		2.6

Mean Dissolution Data

Test				Reference		
Lot No.: 699B005C				Lot No.: 010901		
Strength: 300 mg				Strength: 300 mg		
No. of Units: 12				No. of Units: 6*		
Time(h)	Mean	Range	%CV	Mean	Range	%CV
0	0		-	0		-
2	12		9	12		9
4	28		6	39		5
8	60		3	70		3
12	74		3	83		3
16	84		3	90		2

* A set-up error occurred causing 6 vessels to be invalid. The firm repeated the test on 12 capsules of lot #010902. Results were similar to lot #010901.

Mean Dissolution Data

Test				Reference		
Lot No.: 700B006A				Lot No.: 010912		
Strength: 360 mg				Strength: 360 mg		
No. of Units: 12				No. of Units: 12		
Time(h)	Mean	Range	%CV	Mean	Range	%CV
0	-1		-46.7	-1		-74
2	13		6.3	13		8.0
4	27		4.1	39		12.6
8	57		1.6	72		1.9
12	72		1.5	84		1.7
16	81		1.4	90		1.7

Dissolution Method:

Medium: _____

Volume: Not given

Dissolution Apparatus: _____

Mean Dissolution Data

Test				Reference		
Lot No.: 696B006C				Lot No.: 010433		
Strength: 120 mg				Strength: 120 mg		
No. of Units: 12				No. of Units: 12		
Time(h)	Mean	Range	%CV	Mean	Range	%CV
0	0	_____	-	0	_____	-
2	14	_____	20	15	_____	7.3
4	28	_____	11	42	_____	5.0
8	69	_____	3	71	_____	2.9
12	88	_____	2	83	_____	2.2
16	96	_____	2	89	_____	1.9

Mean Dissolution Data

Test				Reference		
Lot No.: 697B007C				Lot No.: 010717		
Strength: 180 mg				Strength: 180 mg		
No. of Units: 12				No. of Units: 12		
Time(h)	Mean	Range	%CV	Mean	Range	%CV
0	0	_____	-	0	_____	-
2	15	_____	14.2	11	_____	10.3
4	28	_____	6.8	39	_____	5.2
8	73	_____	2.1	75	_____	2.6
12	92	_____	1.9	90	_____	2.1
16	101	_____	1.9	97	_____	1.9

Mean Dissolution Data

Test				Reference		
Lot No.: 698B006B				Lot No.: 010807		
Strength: 240 mg				Strength: 240 mg		
No. of Units: 12				No. of Units: 12		
Time(h)	Mean	Range	%CV	Mean	Range	%CV
0	0	_____	-	-1	_____	-171
2	13	_____	12	12	_____	19.5
4	27	_____	6	38	_____	9.5
8	71	_____	1	70	_____	3.9
12	91	_____	1	84	_____	3.4
16	100	_____	1	90	_____	3.1

Mean Dissolution Data

Test				Reference		
Lot No.: 699B005C				Lot No.: 010901		
Strength: 300 mg				Strength: 300 mg		
No. of Units: 12				No. of Units: 12		
Time(h)	Mean	Range	%CV	Mean	Range	%CV
0	0		-148	0		-5
2	13		10	9		9
4	27		6	35		3
8	68		2	71		2
12	87		1	87		1
16	95		1	94		1

Mean Dissolution Data

Test				Reference		
Lot No.: 700B006A				Lot No.: 010912		
Strength: 360 mg				Strength: 360 mg		
No. of Units: 12				No. of Units: 12		
Time(h)	Mean	Range	%CV	Mean	Range	%CV
0	0		-4.6	0		-
2	16		6.8	9		6.3
4	29		2.9	36		3.0
8	70		1.3	69		1.9
12	89		1.2	83		1.3
16	98		1.2	88		1.3

Dissolution Method:

Medium:

Volume: Not given

Dissolution Apparatus:

Mean Dissolution Data

Test				Reference		
Lot No.: 696B006C				Lot No.: 010433		
Strength: 120 mg				Strength: 120 mg		
No. of Units: 12				No. of Units: 12		
Time(h)	Mean	Range	%CV	Mean	Range	%CV
0	-3		-40	-1		-151
2	13		21	12		17
4	33		8	35		7
8	71		2	64		4
12	86		2	78		3
16	92		2	86		3

Mean Dissolution Data

Test				Reference		
Lot No.: 697B007C				Lot No.: 010717		
Strength: 180 mg				Strength: 180 mg		
No. of Units: 12				No. of Units: 12		
Time(h)	Mean	Range	%CV	Mean	Range	%CV
0	0	—	-	-1	—	-133.8
2	16	—	14.0	9	—	18.3
4	34	—	6.3	32	—	7.2
8	73	—	2.4	62	—	5.1
12	88	—	2.3	77	—	5.0
16	94	—	2.2	85	—	4.5

Mean Dissolution Data

Test				Reference		
Lot No.: 698B006B				Lot No.: 010807		
Strength: 240 mg				Strength: 240 mg		
No. of Units: 12				No. of Units: 12		
Time(h)	Mean	Range	%CV	Mean	Range	%CV
0	0	—	-	0	—	-
2	15	—	9	11	—	6.1
4	34	—	4	33	—	3.3
8	72	—	2	63	—	2.0
12	88	—	2	78	—	3.4
16	94	—	2	85	—	3.1

Mean Dissolution Data

Test				Reference		
Lot No.: 699B005C				Lot No.: 010901		
Strength: 300 mg				Strength: 300 mg		
No. of Units: 12				No. of Units: 12		
Time(h)	Mean	Range	%CV	Mean	Range	%CV
0	0	—	-	0	—	-
2	15	—	8	7	—	12
4	33	—	3	28	—	4
8	71	—	1	58	—	2
12	87	—	1	73	—	3
16	93	—	1	82	—	3

Mean Dissolution Data

Test				Reference		
Lot No.: 700B006A				Lot No.: 010912		
Strength: 360 mg				Strength: 360 mg		
No. of Units: 12				No. of Units: 12		

Time(h)	Mean	Range	%CV	Mean	Range	%CV
0	0		-	0		-
2	15		10.1	7		10.4
4	32		4.9	30		4.0
8	68		1.8	59		2.1
12	83		1.4	73		2.4
16	89		1.1	81		2.5

Dissolution Method:

Medium: _____

Volume: Not given

Dissolution Apparatus: _____

Mean Dissolution Data

Test				Reference		
Lot No.: 696B006C				Lot No.: 010433		
Strength: 120 mg				Strength: 120 mg		
No. of Units: 12				No. of Units: 12		
Time(h)	Mean	Range	%CV	Mean	Range	%CV
0	-3		-39	-2		-128.8
2	13		28	9		33.2
4	33		9	30		11.1
8	71		3	57		4.7
12	82		3	72		3.8
16	87		2	82		3.4

Mean Dissolution Data

Test				Reference		
Lot No.: 697B007C				Lot No.: 010717		
Strength: 180 mg				Strength: 180 mg		
No. of Units: 12				No. of Units: 12		
Time(h)	Mean	Range	%CV	Mean	Range	%CV
0	0		-	0		-3.8
2	14		10.3	7		8.6
4	34		4.1	28		4.4
8	75		2.8	56		3.3
12	87		2.5	70		1.9
16	92		2.6	78		2.1

Mean Dissolution Data

Test				Reference		
Lot No.: 698B006B				Lot No.: 010807		
Strength: 240 mg				Strength: 240 mg		
No. of Units: 12				No. of Units: 12		

Time(h)	Mean	Range	%CV	Mean	Range	%CV
0	-1		-200	0		-
2	14		19	14		8.3
4	25		11	39		3.8
8	67		4	69		2.7
12	85		3	82		2.5
16	93		3	89		2.3

Mean Dissolution Data

Test				Reference		
Lot No.: 697B007C				Lot No.: 010717		
Strength: 180 mg				Strength: 180 mg		
No. of Units: 12				No. of Units: 12		
Time(h)	Mean	Range	%CV	Mean	Range	%CV
0	0		-49.7	-3		-40.2
2	15		16.1	6		29.8
4	25		11.5	30		8.0
8	68		3.5	62		4.1
12	85		2.7	77		3.2
16	93		2.5	86		3.0

Mean Dissolution Data

Test				Reference		
Lot No.: 698B006B				Lot No.: 010807		
Strength: 240 mg				Strength: 240 mg		
No. of Units: 12				No. of Units: 12		
Time(h)	Mean	Range	%CV	Mean	Range	%CV
0	-1		-	-1		-104.4
2	13		13.7	11		9.2
4	25		8.9	38		2.3
8	67		2.6	69		1.3
12	85		2.3	83		1.4
16	92		2.3	91		1.1

Mean Dissolution Data

Test				Reference		
Lot No.: 699B005C				Lot No.: 010901		
Strength: 300 mg				Strength: 300 mg		
No. of Units: 12				No. of Units: 12		
Time(h)	Mean	Range	%CV	Mean	Range	%CV
0	-1		0	-1		-13
2	15		10	9		8
4	25		6	33		4
8	67		1	66		3

12	85	1	82	2
16	92	1	91	2

Mean Dissolution Data

Test				Reference		
Lot No.: 700B006A				Lot No.: 010912		
Strength: 360 mg				Strength: 360 mg		
No. of Units: 12				No. of Units: 12		
Time(h)	Mean	Range	%CV	Mean	Range	%CV
0	0		-	0		-
2	16		6.4	9		7.8
4	26		4.8	34		3.2
8	68		2.4	67		2.1
12	86		1.9	82		1.6
16	93		1.8	90		1.5

F₂ values:

Test product	Dissolution medium
360 mg vs. 300 mg	[]
360 mg vs. 240 mg	
360 mg vs. 180 mg	
360 mg vs. 120 mg	

Comments:

1. The firm has not provided volumes, compositions and molarities of the dissolution media used in the dissolution testing.
2. Andrx proposes to use _____ as dissolution medium. The Division of Chemistry recommended Andrx to use _____ for the dissolution test because Andrx earlier indicated that using _____ as the dissolution medium obscures the effect caused by the _____ equilibrium phenomenon. In its response the firm states, "we believe that our original statement was incorrect. Our current data show that the _____ does not obscure the _____ equilibrium phenomenon. Indeed, the onset of the equilibrium process is clearly evident equally in both _____ and _____ after _____." To demonstrate this fact, the firm has submitted dissolution data for the 360 mg capsules. In this study, dissolution testing was conducted at weekly intervals using both _____ . The results show that the dissolution behavior in both media is almost identical. However, a greater increase in the 4th hour dissolution value is seen with the _____. Therefore, Andrx proposes to continue use of _____ as the dissolution medium for product release and stability monitoring.
3. Andrx states that the extended release _____ will be released for _____ using dissolution specifications that are slightly different from the specifications for the finished drug product:

Time	For ER	For finished drug product
2 h	NMT	NMT
4 h		
8 h		
12 h	NLT	NLT
16 h	NLT	NLT

Andrx argues that the use of a different specification for the extended release will permit them to release the _____ for _____, after which the equilibration process will be allowed to occur.

- The dissolution medium _____ and the specifications for the finished drug product are the same as the DBE had accepted earlier for the test product. However, the reference product uses _____ as medium and has different specifications.
- The DBE will wait for the Division of Chemistry to review the dissolution data before making recommendation regarding the medium and the specifications for the finished drug product. In the interim, the firm should be asked to provide the volumes, compositions, and molarities of the dissolution media used in the dissolution testing.

Deficiencies:

Fasting study on the 360 mg capsules:

- Sample numbers 6.07.4, 6.08.4, 10.05.1, 12.04.3, 12.05.3, 16.08.1, 16.09.1 were coded IA and were reassayed for diltiazem, desacetyldiltiazem, and desmethyldiltiazem. However, these samples do not seem to meet the definition of 'IA' given in SOP DH 8.2 (vol.10.3, page 0433). The firm should provide the justification for reassaying these samples and using the reassay values.
- The firm should provide potency and content uniformity data of the reference product.
- The size of the bio batch and that of the largest lot planned for full production is not given.

Fasting study on the 240 mg capsules:

- The firm should clarify if the clinical study was conducted in _____ (page 4, vol. 10.13; page 1518, vol. 10.15) or in _____ (page 1523, vol. 10.15).
- The firm should provide potency and content uniformity data of the test and reference products.
- The size of the bio batch and that of the largest lot planned for full production is not given. The manufacture date of the test product should be provided.

Sprinkling study:

- In the fed study, one subject (#22) had diltiazem C_{max} T/R ratio of 0.362 but the results were not considered enigmatic. The firm should explain why these results were not considered enigmatic whereas the similar results obtained in the sprinkling study (subject #21) were considered enigmatic.
- The firm should clarify if the clinical study was conducted in _____ (page 3, vol. 10.19; page 1433, vol. 10.22) or in _____ (page 478, vol.10.20).

Dissolution:

1. The firm has not provided volumes, compositions and molarities of the dissolution media used in the dissolution testing.

Formulation:

The quantities of active — ingredients given in the master formula on page 75 vol. 9.1 differ from that given in the original application. The firm should provide comparative quantitative composition of all strengths of the test capsules.

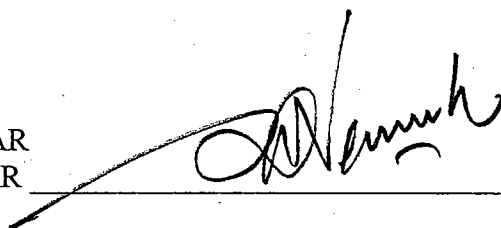
Recommendation:

1. The in vivo bioequivalence study conducted under fasting conditions by Andrx on its diltiazem hydrochloride 360 mg ER capsules, lot #700B006A comparing it to the reference product Tiazac® 360 mg ER capsules, lot #010912 manufactured by Biovail is incomplete.
2. The in vivo bioequivalence study conducted under non-fasting conditions by Andrx on its diltiazem hydrochloride 360 mg ER capsules, lot #700B006A comparing it to the reference product Tiazac® 360 mg ER capsules, lot #010912 manufactured by Biovail is incomplete.
3. The in vivo bioequivalence study conducted under fasting conditions by Andrx on its diltiazem hydrochloride 240 mg ER capsules, lot #698B006B comparing it to the reference product Tiazac® 360 mg ER capsules, lot #010807 manufactured by Biovail is incomplete.
4. The sprinkling bioequivalence study conducted by Andrx on its diltiazem hydrochloride 360 mg ER capsules, lot #700B006A comparing it to the reference product Tiazac® 360 mg ER capsules, lot #010912 manufactured by Biovail is incomplete.
5. The dissolution testing data are incomplete.

Mohariwal 7/18/02

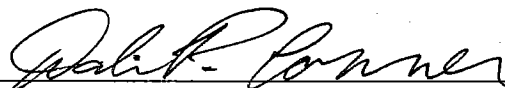
Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR



Date 7/23/2002

Concur:



Date

9/6/02

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

Table 1

MEAN PLASMA DILTIAZEM LEVELS FOR TEST (1) AND REFERENCE (2) PRODUCTS IN FASTING STUDY
DOSE= 1X360 MG, n=37

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	17.27	14.79	0.51	1.44	34.13
2	47.86	23.82	13.02	7.08	3.68
3	59.37	23.88	63.02	30.16	0.94
4	85.78	39.49	110.08	48.13	0.78
5	146.48	63.02	163.08	63.05	0.90
6	166.00	64.19	170.48	56.74	0.97
7	173.38	66.61	174.17	58.56	1.00
8	181.31	78.78	176.89	68.66	1.03
10	161.69	64.51	156.62	61.43	1.03
12	149.08	56.66	143.83	47.36	1.04
16	109.15	38.02	104.37	35.02	1.05
20	70.17	25.33	69.41	25.90	1.01
24	58.22	23.82	58.45	23.90	1.00
36	16.67	9.68	16.20	8.58	1.03
48	4.69	3.50	4.78	3.84	0.98

DILTIAZEM ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	3205.53	1042.34	3162.84	972.01	1.01
AUCT	3144.11	1020.99	3092.50	942.36	1.02
CMAx	199.49	79.02	200.15	69.55	1.00
KE	0.10	0.02	0.10	0.02	1.00
LAUCI	3058.03	0.31	3025.90	0.30	1.01
LAUCT	2999.08	0.31	2959.98	0.30	1.01
LCMAx	186.51	0.36	189.96	0.32	0.98
THALF	6.98	1.44	7.08	1.77	0.99
TMAx	8.03	2.21	6.92	1.94	1.16

Geometric means based on least squares means of log transformed values

	Test	Reference
LAUCT	2987.43	2946.00
LAUCI	3046.19	3018.78
LCMAx	186.04	189.86

Table 2

MEAN PLASMA DESACETYLDILTIAZEM LEVELS (NG/ML) FOR TEST (1) AND REFERENCE (2)
PRODUCTS IN FASTING STUDY, N=37, DOSE 1X360 MG

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	0.16	0.19	0.00	0.00	.
2	0.93	0.46	0.15	0.15	6.07
3	1.68	0.67	1.22	0.57	1.38
4	2.75	1.12	2.85	1.30	0.96
5	4.67	2.37	5.15	2.61	0.91
6	6.67	3.28	7.12	3.21	0.94
7	8.37	3.94	8.89	3.69	0.94
8	10.10	4.60	10.27	4.02	0.98
10	12.41	5.97	12.44	4.99	1.00
12	13.51	7.48	13.31	6.14	1.02
16	14.17	9.64	13.58	7.63	1.04
20	12.97	8.36	12.71	7.54	1.02
24	11.83	9.38	11.84	8.36	1.00
36	5.15	6.30	5.14	5.90	1.00
48	2.23	3.27	2.18	2.95	1.02

ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	425.05	360.28	428.26	323.33	0.99
AUCT	382.67	277.41	379.15	240.26	1.01
C _{MAX}	15.25	9.97	14.94	8.21	1.02
KE	0.08	0.02	0.08	0.02	1.02
LAUCI	360.26	0.50	365.75	0.50	0.98
LAUCT	333.73	0.46	334.70	0.46	1.00
LC _{MAX}	13.50	0.45	13.43	0.43	1.01
THALF	9.87	3.09	10.31	3.94	0.96
T _{MAX}	15.11	4.16	15.14	4.49	1.00

Geometric means based on least squares means of log transformed values

	Test	Reference
LAUCT	332.30	332.79
LAUCI	359.65	361.06
LC _{MAX}	13.50	13.42

Table 3

MEAN PLASMA DESMETHYLDILTIAZEM LEVELS (NG/ML) FOR TEST (1) AND REFERENCE (2)
PRODUCTS IN FASTING STUDY, N=37, DOSE 1X360 MG

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	4.60	3.38	0.19	0.39	24.28
2	12.47	4.49	3.53	1.45	3.53
3	17.35	4.07	14.85	5.12	1.17
4	23.64	6.41	25.63	7.62	0.92
5	34.01	9.72	36.07	10.06	0.94
6	39.51	11.05	42.35	10.28	0.93
7	43.50	10.99	45.49	10.59	0.96
8	46.01	12.04	47.46	12.15	0.97
10	46.65	12.06	47.24	12.49	0.99
12	47.78	12.34	47.47	11.86	1.01
16	42.97	10.63	41.56	11.18	1.03
20	32.21	8.46	31.98	8.13	1.01
24	27.12	7.30	27.41	7.63	0.99
36	11.61	4.42	11.45	4.36	1.01
48	4.48	2.24	4.41	2.21	1.01

ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	1230.63	285.68	1226.59	287.40	1.00
AUCT	1162.63	258.54	1154.21	258.56	1.01
CMAX	51.32	12.23	52.06	13.01	0.99
KE	0.08	0.02	0.07	0.02	1.01
LAUCI	1199.07	0.23	1195.18	0.23	1.00
LAUCT	1135.24	0.22	1127.09	0.22	1.01
LCMAX	50.00	0.23	50.66	0.23	0.99
THALF	9.60	1.94	9.71	2.11	0.99
TMAX	10.38	2.71	9.58	2.76	1.08

Geometric means based on least squares means of log transformed values

	Test	Reference
LAUCT	1130.47	1120.69
LAUCI	1192.51	1204.16
LCMAX	49.92	50.63

Table 4

MEAN PLASMA DILTIAZEM LEVELS (ng/mL) FOR TEST (1) AND REFERENCE (2) PRODUCTS
IN FED STUDY, N=22, Dose= 1x360 mg

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	1.47	2.86	0.15	0.72	9.63
2	27.33	19.54	5.88	6.96	4.65
3	71.75	34.39	45.64	32.90	1.57
4	109.95	48.39	128.86	58.93	0.85
5	233.64	116.84	299.86	192.99	0.78
6	269.23	113.28	302.64	212.22	0.89
7	275.18	120.92	263.64	116.91	1.04
8	266.77	80.16	264.50	113.44	1.01
10	229.73	58.48	213.86	106.16	1.07
12	207.73	60.48	181.27	81.86	1.15
16	147.40	44.98	133.19	56.23	1.11
20	97.65	31.89	87.76	36.91	1.11
24	78.28	25.83	69.15	26.68	1.13
36	19.34	8.69	17.69	7.54	1.09
48	5.26	3.83	5.44	4.37	0.97

ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	4396.50	1269.88	4155.68	1820.41	1.06
AUCT	4336.44	1258.52	4093.57	1806.52	1.06
CMAX	297.18	113.71	323.73	212.80	0.92
KE	0.11	0.02	0.11	0.02	1.01
LAUCI	4228.03	0.29	3889.49	0.35	1.09
LAUCT	4169.68	0.29	3831.28	0.35	1.09
LCMAX	282.82	0.30	291.32	0.41	0.97
THALF	6.42	1.07	6.50	1.21	0.99
TMAX	7.23	1.60	6.05	1.13	1.20

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	4377.99	4167.07	1.05	90.09	120.04
AUCT	4317.64	4103.50	1.05	90.02	120.42
CMAX	295.39	324.69	0.91	69.29	112.67
LAUCI	4212.48	3882.73	1.08	97.16	121.15
LAUCT	4153.80	3823.09	1.09	97.23	121.42
LCMAX	281.63	289.80	0.97	85.82	110.04

Table 5

MEAN PLASMA DESACETYLDILTIAZEM LEVELS (ng/mL) FOR TEST (1) AND REFERENCE (2)
PRODUCTS IN FED STUDY, N=22, Dose= 1x360 mg

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	0.00	0.00	0.00	0.00	.
2	0.28	0.28	0.03	0.08	9.87
3	1.26	0.63	0.63	0.44	2.00
4	2.52	1.01	2.38	1.41	1.06
5	5.21	2.23	6.26	3.51	0.83
6	8.34	3.34	9.30	4.90	0.90
7	10.79	4.30	11.16	4.89	0.97
8	13.21	5.12	13.63	6.14	0.97
10	15.47	5.56	15.45	6.99	1.00
12	16.00	6.37	14.94	6.71	1.07
16	15.49	8.05	14.68	8.24	1.06
20	14.25	8.42	13.43	8.15	1.06
24	13.61	13.23	11.63	8.07	1.17
36	5.18	7.70	4.78	5.63	1.08
48	2.30	4.42	2.09	2.86	1.10

UNIT: PLASMA LEVEL=NG/ML TIME=HRS

ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	467.79	408.35	435.65	315.58	1.07
AUCT	430.92	319.77	401.23	257.87	1.07
CMAx	18.42	12.74	16.54	8.55	1.11
KE	0.09	0.02	0.08	0.02	1.06
LAUCI	401.76	0.47	380.55	0.47	1.06
LAUCT	380.92	0.43	357.32	0.44	1.07
LCMAx	16.42	0.42	15.24	0.37	1.08
THALF	8.46	2.02	9.13	2.51	0.93
TMAx	12.55	4.15	11.91	3.05	1.05

UNIT: AUC=NG HR/ML CMAx=NG/ML TMAx=HR

LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	459.59	430.27	1.07	95.85	117.78
AUCT	424.26	396.89	1.07	97.33	116.46
CMAx	18.16	16.47	1.10	96.18	124.32
LAUCI	397.19	376.83	1.05	99.47	111.69
LAUCT	376.73	353.96	1.06	100.56	112.65
LCMAx	16.25	15.17	1.07	99.54	115.24

Table 6

MEAN PLASMA DESMETHYLDILTIAZEM LEVELS (ng/mL) FOR TEST (1) AND REFERENCE (2)
PRODUCTS IN FED STUDY, N=22, Dose= 1x360 mg

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	0.26	0.46	0.00	0.00	.
2	5.62	3.63	1.24	1.24	4.55
3	16.40	7.28	9.96	5.27	1.65
4	26.82	9.25	28.62	10.42	0.94
5	47.85	17.15	58.47	21.41	0.82
6	60.89	23.31	69.54	34.86	0.88
7	67.98	24.69	69.94	23.60	0.97
8	69.96	25.11	72.79	26.60	0.96
10	68.97	24.53	65.52	23.59	1.05
12	64.09	15.87	63.04	25.19	1.02
16	52.59	10.72	50.91	18.36	1.03
20	40.56	9.86	37.56	11.31	1.08
24	33.25	7.94	29.58	8.84	1.12
36	13.03	4.41	12.06	3.99	1.08
48	4.64	1.93	4.48	2.04	1.04

UNIT: PLASMA LEVEL=NG/ML TIME=HRS
ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	1548.17	362.81	1489.89	471.73	1.04
AUCT	1487.15	348.04	1429.11	456.16	1.04
C _{MAX}	74.97	25.65	76.35	32.79	0.98
K _E	0.08	0.01	0.08	0.01	1.03
LAUCI	1507.98	0.24	1433.85	0.27	1.05
LAUCT	1449.87	0.23	1376.81	0.27	1.05
LC _{MAX}	72.07	0.27	72.59	0.29	0.99
THALF	8.64	1.34	8.87	1.37	0.97
T _{MAX}	8.91	2.22	7.59	1.05	1.17

UNIT: AUC=NG HR/ML C_{MAX}=NG/ML T_{MAX}=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	1548.64	1492.29	1.04	97.50	110.05
AUCT	1488.05	1431.69	1.04	97.51	110.36
C _{MAX}	75.04	76.68	0.98	90.37	105.33
LAUCI	1507.39	1433.00	1.05	99.96	110.70
LAUCT	1449.68	1376.15	1.05	100.10	110.87
LC _{MAX}	72.03	72.63	0.99	93.80	104.84

Table 7

MEAN PLASMA DILTIAZEM LEVELS (ng/mL) FOR TEST (1) AND REFERENCE (2)
PRODUCTS IN FASTING STUDY, N=37, Dose= 1x240 mg

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	7.57	9.57	2.05	5.82	3.69
2	28.65	18.66	17.92	18.83	1.60
3	41.24	20.09	59.34	47.17	0.70
4	58.32	28.99	96.87	60.70	0.60
5	99.60	46.05	128.17	71.29	0.78
6	119.80	65.22	133.09	67.73	0.90
7	126.26	77.30	127.77	59.82	0.99
8	127.59	80.78	125.22	58.25	1.02
10	112.95	74.21	106.17	52.32	1.06
12	101.46	55.16	97.63	47.55	1.04
16	73.81	35.76	72.26	37.78	1.02
20	47.39	22.73	47.64	24.81	0.99
24	39.55	19.41	38.58	19.32	1.03
36	10.57	6.38	11.31	6.83	0.93
48	3.05	2.74	3.08	2.65	0.99

UNIT: PLASMA LEVEL=NG/ML TIME=HRS

ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	2188.25	1043.02	2236.58	1019.61	0.98
AUCT	2133.33	1023.64	2188.57	1014.70	0.97
C _{MAX}	142.28	83.19	148.95	70.58	0.96
K _E	0.10	0.02	0.10	0.02	1.00
LAUCI	2010.60	0.39	2063.99	0.39	0.97
LAUCT	1958.94	0.39	2014.39	0.39	0.97
LC _{MAX}	127.18	0.44	135.03	0.44	0.94
THALF	6.96	1.44	6.98	1.41	1.00
T _{MAX}	7.50	1.90	6.82	1.99	1.10

UNIT: AUC=NG HR/ML C_{MAX}=NG/ML T_{MAX}=HR

LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

LSMEANS

	LSM1	LSM2	RLSM12		
PARAMETER					
AUCI	2194.44	2241.85	0.98		
AUCT	2139.39	2193.92	0.98		
C _{MAX}	142.49	149.21	0.95		
LAUCI	2016.32	2068.94	0.97		
LAUCT	1964.48	2019.45	0.97		
LC _{MAX}	127.37	135.28	0.94		

Table 8

MEAN PLASMA DESACETYLDILTIAZEM LEVELS (ng/mL) FOR TEST (1) AND REFERENCE (2)
PRODUCTS IN FASTING STUDY, N=37, Dose= 1x240 mg

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	0.03	0.08	0.01	0.07	3.71
2	0.51	0.34	0.25	0.24	2.04
3	1.08	0.57	1.21	0.75	0.89
4	1.84	0.89	2.63	1.39	0.70
5	3.42	1.67	4.33	2.15	0.79
6	5.02	2.46	5.88	2.87	0.85
7	6.35	3.18	7.14	3.61	0.89
8	7.55	4.08	8.01	3.98	0.94
10	9.28	5.23	9.12	4.71	1.02
12	10.18	6.06	10.08	6.45	1.01
16	10.82	7.69	10.38	7.77	1.04
20	9.86	7.39	9.73	7.93	1.01
24	9.80	9.18	9.29	9.10	1.05
36	4.66	6.92	4.84	7.29	0.96
48	2.43	4.70	2.47	4.98	0.99

UNIT: PLASMA LEVEL=NG/ML TIME=HRS

ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	373.66	430.91	378.45	460.38	0.99
AUCT	309.63	272.23	306.93	281.57	1.01
C _{MAX}	12.17	9.14	11.74	9.01	1.04
KE	0.08	0.02	0.07	0.03	1.05
LAUCI	268.88	0.71	269.27	0.71	1.00
LAUCT	243.75	0.63	239.92	0.63	1.02
LC _{MAX}	9.94	0.60	9.64	0.59	1.03
THALF	10.18	4.60	11.00	5.23	0.93
T _{MAX}	15.72	4.89	14.14	4.64	1.11

UNIT: AUC=NG HR/ML C_{MAX}=NG/ML T_{MAX}=HR

LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

LSMEANS

	LSM1	LSM2	RLSM12		
PARAMETER					
AUCI	371.59	377.13	0.99		
AUCT	309.37	306.50	1.01		
C _{MAX}	12.16	11.73	1.04		
LAUCI	269.22	269.34	1.00		
LAUCT	244.02	240.18	1.02		
LC _{MAX}	9.94	9.65	1.03		

Table 9

MEAN PLASMA DESMETHYLDILTIAZEM LEVELS (ng/mL) FOR TEST (1) AND REFERENCE (2)
PRODUCTS IN FASTING STUDY, N=37, Dose= 1x240 mg

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	1.44	1.22	0.36	0.59	3.98
2	6.16	2.80	3.59	2.36	1.71
3	10.26	3.60	11.83	5.74	0.87
4	14.70	5.10	20.11	8.66	0.73
5	22.32	7.15	27.05	9.89	0.82
6	27.80	9.02	31.56	11.05	0.88
7	31.08	10.84	33.27	10.87	0.93
8	32.80	11.53	33.74	10.50	0.97
10	32.51	12.95	32.49	10.55	1.00
12	33.09	11.75	32.50	10.13	1.02
16	29.37	9.79	28.77	8.96	1.02
20	21.88	7.31	21.62	6.64	1.01
24	18.43	6.19	18.21	5.92	1.01
36	7.76	3.39	7.99	3.32	0.97
48	3.11	1.62	3.13	1.54	0.99

UNIT: PLASMA LEVEL=NG/ML TIME=HRS

ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	841.65	262.90	849.28	247.31	0.99
AUCT	789.26	243.77	799.21	235.05	0.99
C _{MAX}	36.57	12.31	37.39	11.48	0.98
K _E	0.07	0.02	0.07	0.02	1.00
LAUCI	806.33	0.29	818.49	0.27	0.99
LAUCT	757.97	0.28	770.07	0.27	0.98
LC _{MAX}	34.91	0.30	35.86	0.29	0.97
THALF	9.71	2.21	9.70	2.00	1.00
T _{MAX}	10.16	3.14	9.05	3.16	1.12

UNIT: AUC=NG HR/ML C_{MAX}=NG/ML T_{MAX}=HR

LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

LSMEANS

	LSM1	LSM2	RLSM12		
PARAMETER					
AUCI	842.96	849.94	0.99		
AUCT	790.46	799.91	0.99		
C _{MAX}	36.58	37.41	0.98		
LAUCI	807.62	819.22	0.99		
LAUCT	759.13	770.85	0.98		
LC _{MAX}	34.92	35.88	0.97		

Table 10

MEAN PLASMA DILTIAZEM LEVELS (ng/mL) FOR TEST (1) AND REFERENCE (2)
PRODUCTS IN SPRINKLING STUDY, N=34, Dose= 1x360 mg

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	21.58	13.94	0.81	1.70	26.65
2	52.39	25.90	14.47	8.98	3.62
3	60.01	29.13	70.77	48.09	0.85
4	78.80	44.91	115.80	58.24	0.68
5	129.67	60.25	169.46	62.62	0.77
6	152.01	64.87	190.19	70.06	0.80
7	163.64	68.43	190.08	76.17	0.86
8	174.93	78.00	194.05	82.54	0.90
10	169.04	66.86	171.72	65.28	0.98
12	157.43	55.17	154.89	51.71	1.02
16	114.75	37.39	113.77	41.20	1.01
20	76.49	25.84	71.00	25.96	1.08
24	62.46	24.52	54.16	22.14	1.15
36	16.68	8.49	15.05	8.52	1.11
48	3.96	2.68	3.56	2.52	1.11

UNIT: PLASMA LEVEL=NG/ML TIME=HRS

ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	3258.18	1075.45	3259.68	1047.52	1.00
AUCT	3210.22	1069.85	3217.39	1040.66	1.00
CMAX	191.65	79.62	219.35	78.95	0.87
KE	0.11	0.02	0.11	0.02	1.02
LAUCI	3078.70	0.35	3101.53	0.32	0.99
LAUCT	3029.06	0.36	3059.49	0.32	0.99
LCMAX	177.25	0.40	206.85	0.34	0.86
THALF	6.20	0.95	6.36	1.29	0.98
TMAX	8.35	2.10	7.62	2.52	1.10

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	3245.30	3253.38	1.00	93.01	106.49
AUCT	3197.70	3210.78	1.00	92.74	106.45
CMAX	191.25	219.05	0.87	78.14	96.49
LAUCI	3063.06	3092.97	0.99	93.29	105.13
LAUCT	3013.77	3050.65	0.99	92.98	104.97
LCMAX	176.55	206.47	0.86	78.71	92.90

Table 11

MEAN PLASMA DESACETYLDILTIAZEM LEVELS (ng/mL) FOR TEST (1) AND REFERENCE (2)
PRODUCTS IN SPRINKLING STUDY, N=34, Dose= 1x360 mg

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	0.25	0.19	0.00	0.00	.
2	1.04	0.48	0.17	0.17	5.96
3	1.80	0.87	1.23	0.64	1.46
4	2.75	1.45	2.80	1.57	0.98
5	4.28	2.39	4.99	2.57	0.86
6	6.29	3.72	7.52	4.33	0.84
7	7.88	4.47	9.27	5.39	0.85
8	9.74	6.26	11.20	6.46	0.87
10	12.07	7.59	13.36	9.30	0.90
12	14.05	11.42	14.22	11.34	0.99
16	15.43	15.41	15.00	14.22	1.03
20	14.74	16.08	13.98	15.02	1.05
24	14.23	19.26	12.35	16.49	1.15
36	7.28	16.16	6.21	13.31	1.17
48	3.24	8.78	2.73	6.93	1.18

UNIT: PLASMA LEVEL=NG/ML TIME=HRS

ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	518.85	837.13	478.07	705.79	1.09
AUCT	446.27	587.00	417.49	518.34	1.07
CMAx	16.93	18.91	16.45	16.63	1.03
KE	0.09	0.02	0.09	0.02	1.00
LAUCI	354.47	0.66	341.48	0.63	1.04
LAUCT	333.19	0.61	321.54	0.57	1.04
LCMAx	13.24	0.59	13.43	0.53	0.99
THALF	8.66	2.99	8.82	3.42	0.98
TMAx	15.76	3.37	13.74	3.89	1.15

UNIT: AUC=NG HR/ML CMAx=NG/ML TMAx=HR

LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	508.57	469.84	1.08	98.51	117.98
AUCT	439.23	411.71	1.07	100.37	113.00
CMAx	16.74	16.27	1.03	96.00	109.74
LAUCI	352.55	340.19	1.04	98.62	108.90
LAUCT	331.71	320.53	1.03	98.50	108.73
LCMAx	13.21	13.39	0.99	92.89	104.87

Table 12

MEAN PLASMA DESMETHYLDILTIAZEM LEVELS (ng/mL) FOR TEST (1) AND REFERENCE (2)
PRODUCTS IN SPRINKLING STUDY, N=34, Dose= 1x360 mg

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	5.50	2.79	0.24	0.35	22.47
2	13.45	4.70	3.63	1.70	3.70
3	17.21	4.66	16.05	7.33	1.07
4	22.16	6.92	26.51	10.15	0.84
5	29.96	9.34	36.59	10.16	0.82
6	37.12	11.28	43.51	10.49	0.85
7	40.91	11.85	47.42	11.45	0.86
8	43.82	13.43	49.68	13.16	0.88
10	46.29	12.91	47.87	12.71	0.97
12	47.99	12.44	48.76	11.59	0.98
16	43.21	9.06	43.25	8.44	1.00
20	32.88	7.63	31.37	7.23	1.05
24	27.26	7.05	25.81	6.65	1.06
36	11.50	4.85	10.50	4.22	1.10
48	4.03	2.03	3.62	1.82	1.11

UNIT: PLASMA LEVEL=NG/ML TIME=HRS

ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	1208.19	282.85	1191.17	246.68	1.01
AUCT	1152.50	257.04	1143.06	229.27	1.01
CMAx	50.39	13.72	54.09	13.36	0.93
KE	0.08	0.02	0.08	0.02	0.96
LAUCI	1175.63	0.24	1166.21	0.21	1.01
LAUCT	1123.91	0.23	1120.63	0.20	1.00
LCMAx	48.68	0.27	52.63	0.23	0.92
THALF	8.93	1.61	8.59	1.61	1.04
TMAx	11.24	2.73	9.53	2.84	1.18

UNIT: AUC=NG HR/ML CMAx=NG/ML TMAx=HR

LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	1202.96	1189.46	1.01	97.58	104.69
AUCT	1148.06	1141.48	1.01	96.98	104.17
CMAx	50.29	54.08	0.93	87.54	98.46
LAUCI	1170.50	1164.53	1.01	97.05	104.10
LAUCT	1119.51	1119.05	1.00	96.56	103.64
LCMAx	48.56	52.61	0.92	87.66	97.21

Table 13

MEAN PLASMA DILTIAZEM LEVELS (ng/mL) FOR TEST (1) AND REFERENCE (2)
 PRODUCTS IN SPRINKLING STUDY, N=33, Dose= 1x360 mg
 EXCLUDING SUBJECT #21

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	21.87	14.06	0.65	1.44	33.71
2	52.22	26.28	14.09	8.84	3.71
3	59.68	29.52	64.76	33.46	0.92
4	78.34	45.52	110.00	48.18	0.71
5	129.06	61.08	163.78	53.96	0.79
6	151.67	65.84	185.19	64.71	0.82
7	163.93	69.47	182.42	62.64	0.90
8	175.66	79.09	186.31	70.63	0.94
10	169.98	67.66	166.28	57.97	1.02
12	158.29	55.80	151.31	48.04	1.05
16	115.21	37.87	111.70	40.01	1.03
20	76.56	26.24	70.00	25.69	1.09
24	62.85	24.80	53.71	22.32	1.17
36	16.65	8.62	15.21	8.60	1.09
48	3.89	2.69	3.61	2.54	1.08

UNIT: PLASMA LEVEL=NG/ML TIME=HRS

ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	3265.96	1091.15	3183.12	962.34	1.03
AUCT	3218.63	1085.29	3139.86	951.88	1.03
CMAx	192.52	80.69	212.58	69.41	0.91
KE	0.12	0.02	0.11	0.02	1.04
LAUCI	3081.07	0.36	3043.48	0.31	1.01
LAUCT	3032.03	0.36	3001.14	0.31	1.01
LCMAx	177.70	0.41	202.14	0.32	0.88
THALF	6.15	0.92	6.42	1.26	0.96
TMAx	8.42	2.09	7.64	2.56	1.10

UNIT: AUC=NG HR/ML CMAx=NG/ML TMAx=HR

LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	3258.91	3182.04	1.02	97.32	107.51
AUCT	3211.75	3138.65	1.02	97.20	107.46
CMAx	192.28	212.61	0.90	83.19	97.69
LAUCI	3072.71	3040.72	1.01	96.23	106.12
LAUCT	3023.83	2998.25	1.01	95.99	105.96
LCMAx	177.31	202.07	0.88	81.75	94.18

Table 14

MEAN PLASMA DESACETYLDILTIAZEM LEVELS (ng/mL) FOR TEST (1) AND REFERENCE (2)
 PRODUCTS IN SPRINKLING STUDY, N=33, Dose= 1x360 mg
 EXCLUDING SUBJECT #21

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	0.25	0.19	0.00	0.00	.
2	1.03	0.49	0.17	0.16	6.18
3	1.78	0.88	1.18	0.57	1.51
4	2.72	1.47	2.70	1.49	1.01
5	4.24	2.42	4.85	2.49	0.87
6	6.25	3.77	7.35	4.28	0.85
7	7.84	4.54	9.04	5.31	0.87
8	9.71	6.36	10.95	6.39	0.89
10	12.10	7.70	13.07	9.29	0.93
12	14.11	11.59	14.00	11.44	1.01
16	15.54	15.64	14.89	14.42	1.04
20	14.85	16.32	13.97	15.25	1.06
24	14.37	19.54	12.40	16.75	1.16
36	7.39	16.40	6.34	13.49	1.16
48	3.28	8.91	2.80	7.03	1.17

UNIT: PLASMA LEVEL=NG/ML TIME=HRS

ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	523.81	849.61	479.31	716.70	1.09
AUCT	449.78	595.74	417.02	526.37	1.08
CMAX	17.07	19.19	16.25	16.85	1.05
KE	0.09	0.02	0.09	0.02	1.02
LAUCI	354.44	0.67	338.93	0.64	1.05
LAUCT	333.28	0.62	318.65	0.58	1.05
LCMAX	13.27	0.60	13.21	0.53	1.00
THALF	8.62	3.02	8.92	3.42	0.97
TMAX	15.88	3.35	13.85	3.89	1.15

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	518.22	474.92	1.09	99.35	118.88
AUCT	445.96	413.97	1.08	101.56	113.89
CMAX	16.96	16.16	1.05	98.90	110.97
LAUCI	353.42	338.33	1.04	99.47	109.70
LAUCT	332.49	318.21	1.04	99.63	109.59
LCMAX	13.26	13.20	1.00	95.20	105.96

Table 15

MEAN PLASMA DESMETHYLDILTIAZEM LEVELS (ng/mL) FOR TEST (1) AND REFERENCE (2)
 PRODUCTS IN SPRINKLING STUDY, N=33, Dose= 1x360 mg
 EXCLUDING SUBJECT #21

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	5.56	2.81	0.23	0.35	24.06
2	13.40	4.76	3.59	1.71	3.73
3	17.06	4.64	15.38	6.27	1.11
4	21.95	6.92	25.87	9.58	0.85
5	29.73	9.39	36.01	9.72	0.83
6	36.90	11.38	42.94	10.11	0.86
7	40.77	12.01	46.61	10.58	0.87
8	43.94	13.62	49.06	12.88	0.90
10	46.34	13.11	46.96	11.74	0.99
12	48.12	12.61	48.23	11.35	1.00
16	43.27	9.20	42.78	8.09	1.01
20	32.95	7.74	31.19	7.27	1.06
24	27.33	7.15	25.66	6.70	1.06
36	11.55	4.91	10.55	4.27	1.09
48	4.02	2.06	3.66	1.83	1.10

UNIT: PLASMA LEVEL=NG/ML TIME=HRS

ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	1209.30	287.16	1181.46	243.81	1.02
AUCT	1153.80	260.91	1132.48	224.23	1.02
CMAx	50.55	13.90	53.37	12.88	0.95
KE	0.08	0.02	0.08	0.02	0.97
LAUCI	1175.75	0.24	1157.08	0.21	1.02
LAUCT	1124.34	0.23	1110.95	0.20	1.01
LCMAx	48.79	0.27	52.01	0.23	0.94
THALF	8.90	1.63	8.66	1.59	1.03
TMAx	11.36	2.67	9.52	2.88	1.19

UNIT: AUC=NG HR/ML CMAx=NG/ML TMAx=HR

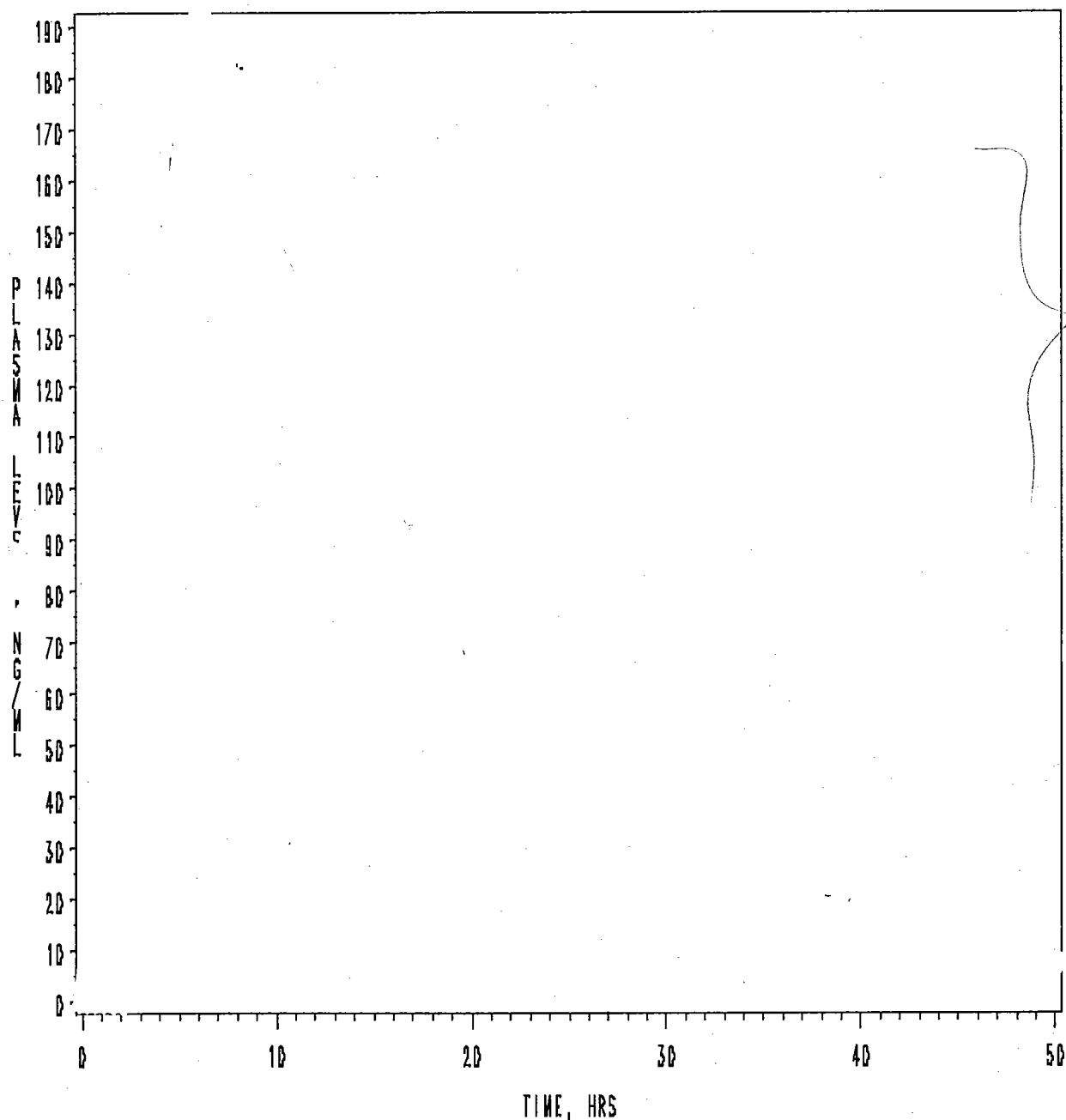
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	1206.50	1180.84	1.02	99.02	105.33
AUCT	1151.40	1131.95	1.02	98.63	104.80
CMAx	50.49	53.39	0.95	89.78	99.37
LAUCI	1173.03	1156.46	1.01	98.24	104.73
LAUCT	1121.99	1110.40	1.01	97.92	104.27
LCMAx	48.72	52.02	0.94	89.45	98.06

FIG 1. PLASMA DILTIAZEM LEVELS

DILTIAZEM HCL CAPSULES, 360 MG, ANDA #75-401
UNDER FASTING CONDITIONS
DOSE=1 X 360 MG

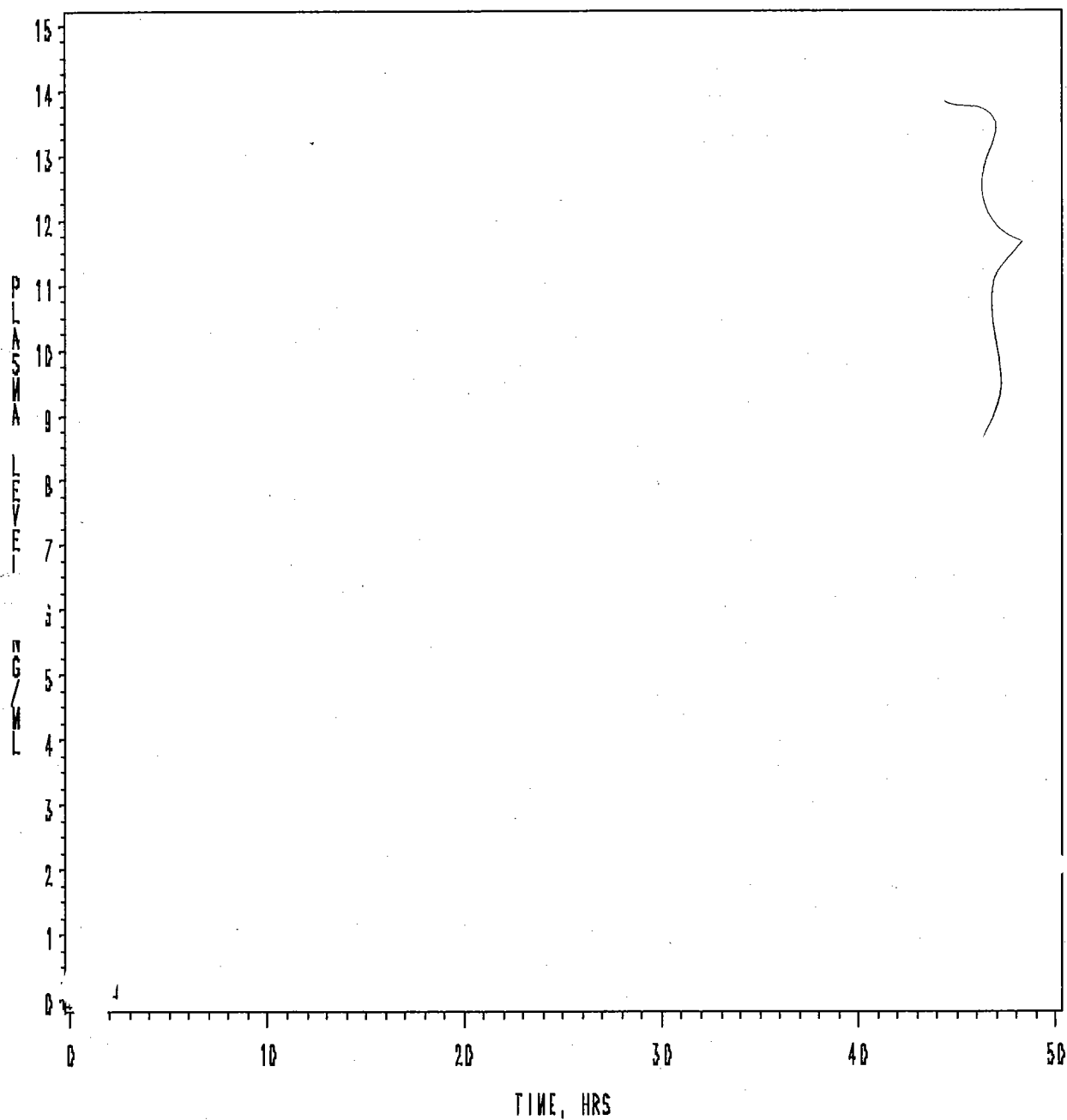


TRT **** 1 □□□ 2

1=TEST(ANDRX) 2=REF(BIDVAIL)

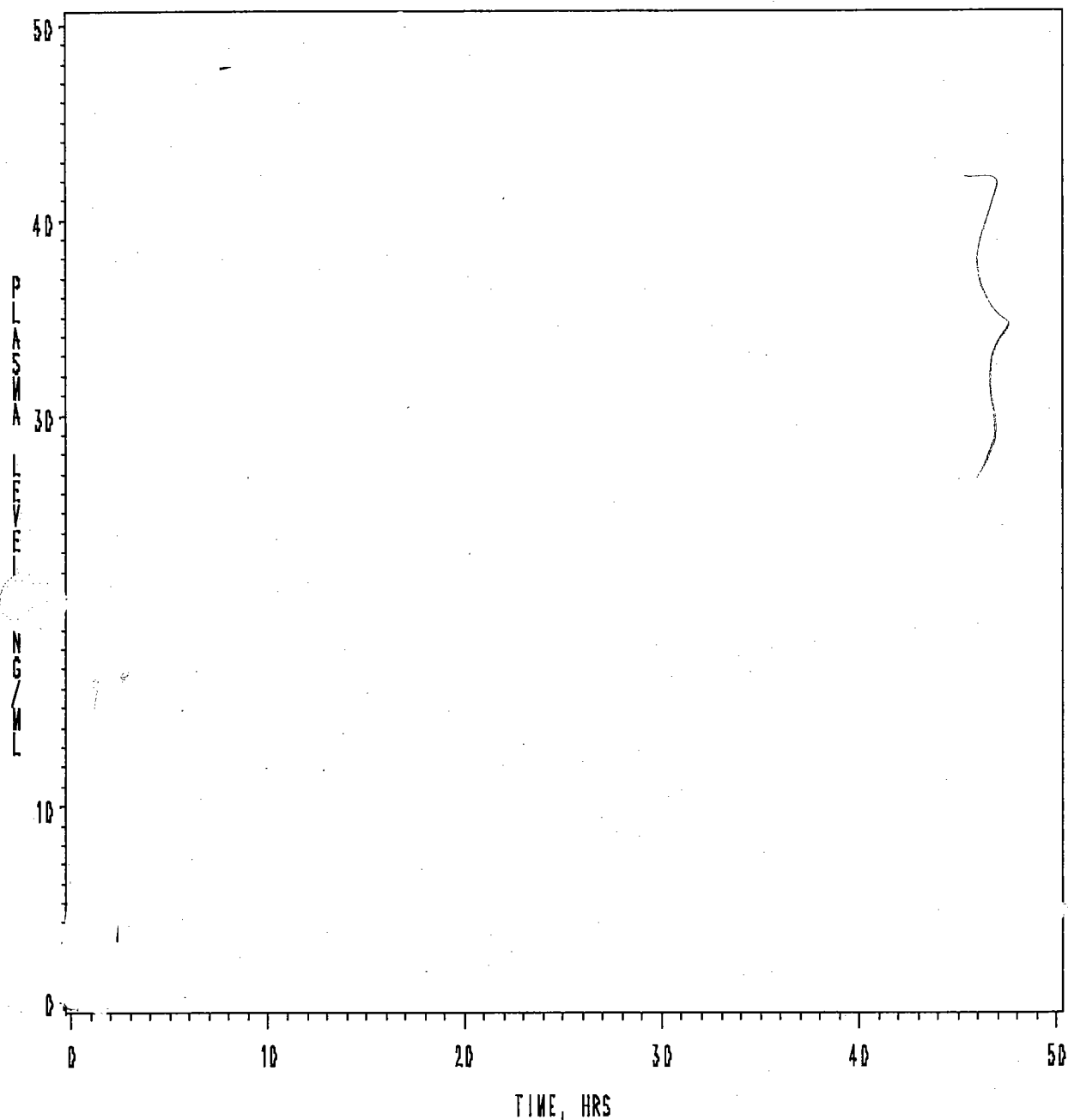
G 2. PLASMA DESACETYLDILTIAZEM LEVELS

DILTIAZEM HCL CAPSULES, 360 MG, ANDA #75-401
 UNDER FASTING CONDITIONS
 DOSE=1 X 360 MG



3. PLASMA DESMETHYLDILTIAZEM LEVELS

DILTIAZEM HCL CAPSULES, 360 MG, ANDA #75-401
 UNDER FASTING CONDITIONS
 DDSE=1 X 360 MG

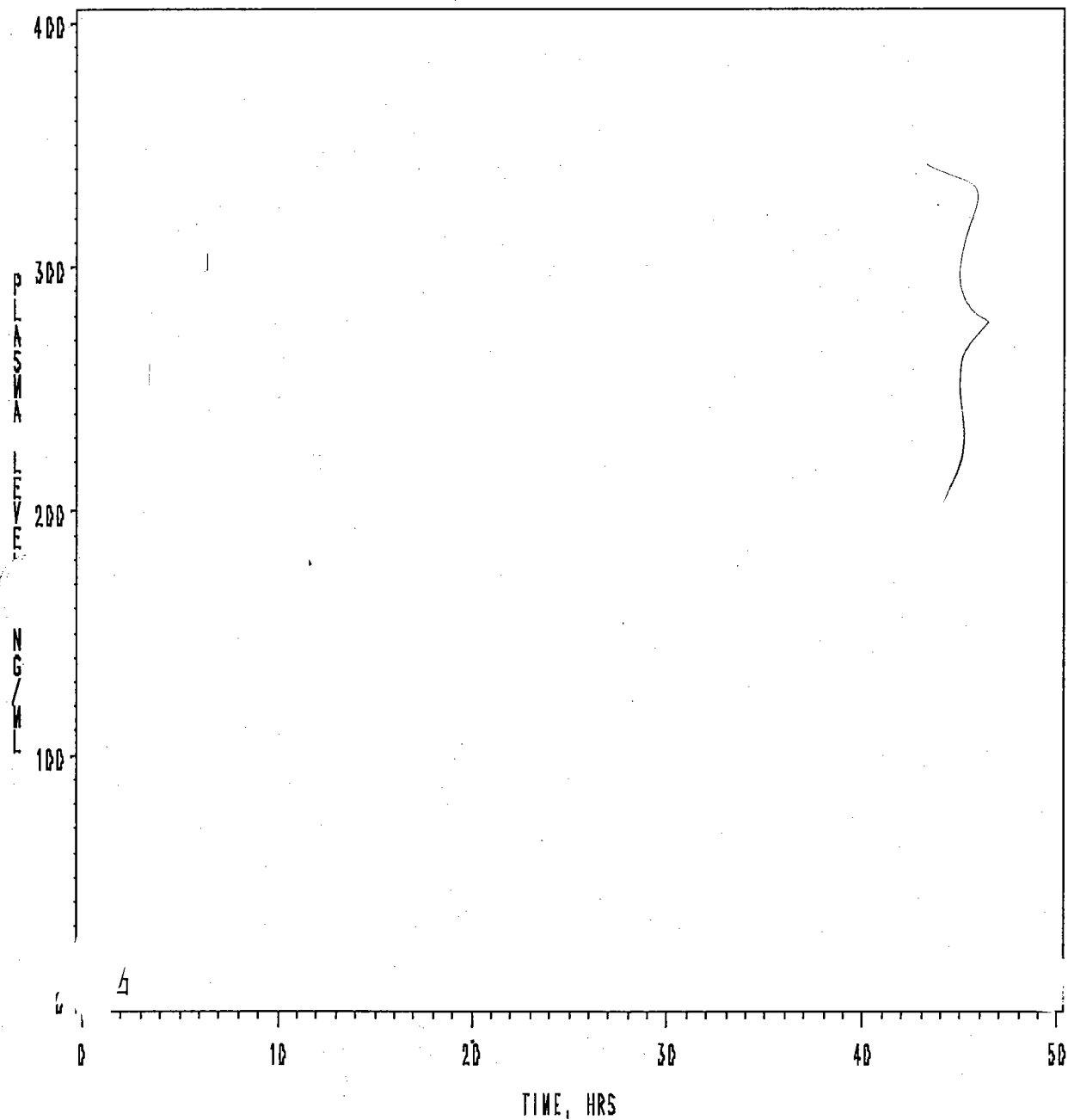


TRT ***** 1 □□□ 2

1=TEST(ANDRX) 2=REF(BIDVAIL)

FIG 4. PLASMA DILTIAZEM LEVELS

DILTIAZEM HCL ER CAPSULES, 360 MG, ANDA #75-401
UNDER FED CONDITIONS
DOSE=1 X 360 MG

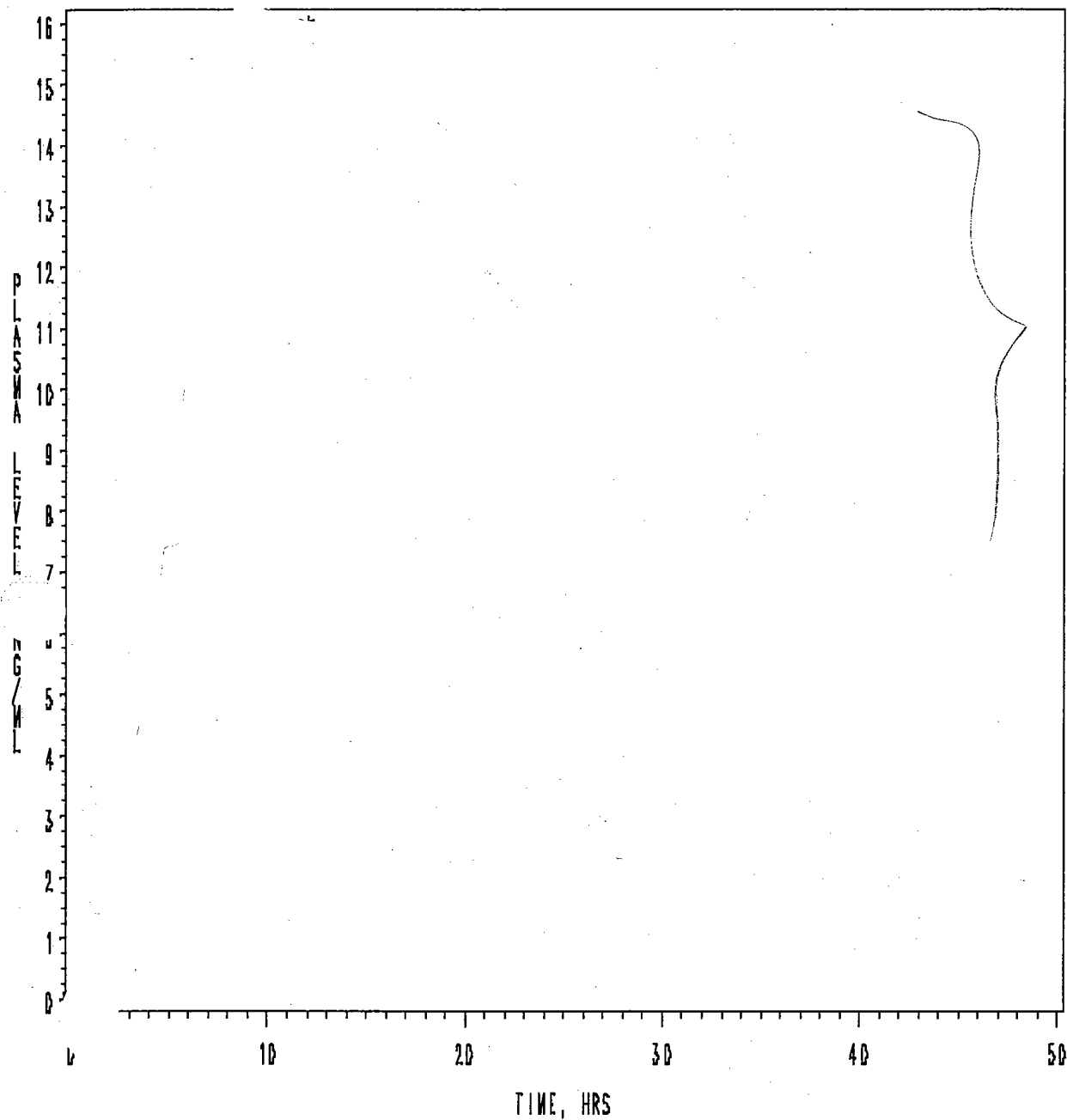


TRT ***** 1 □□□ 2

1=TEST(ANDRX) 2=REF(BIDVIAL)

5. PLASMA DESACETYLDILTIAZEM LEVELS

DILTIAZEM HCL ER CAPSULES, 360 MG, ANDA #75-401
 UNDER FED CONDITIONS
 DOSE=1 X 360 MG

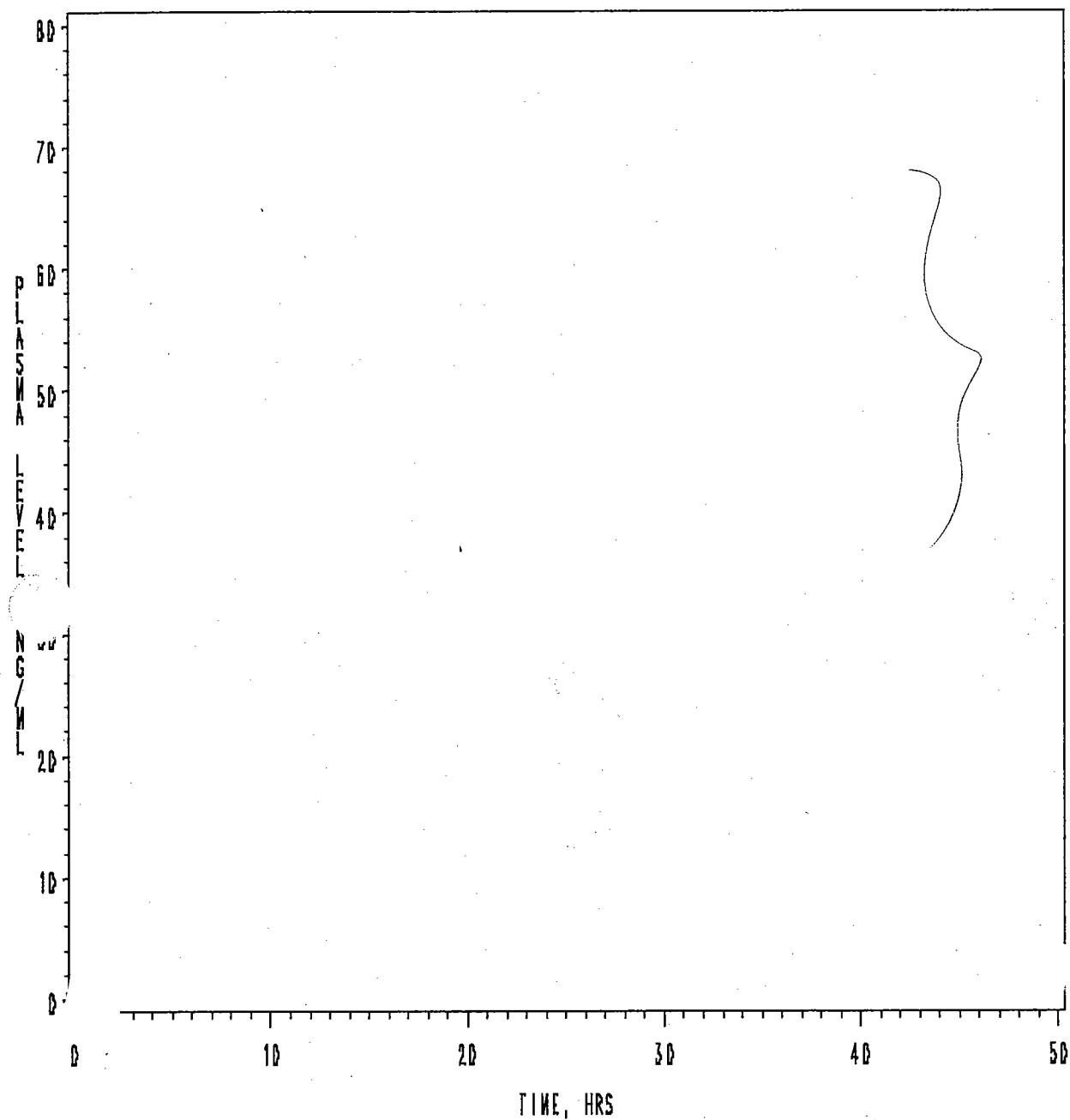


TRT *-*-* 1 □□□ 2

1=TEST(ANDRX) 2=REF(BIDVAIL)

FIG 6. PLASMA DESMETHYLDILTIAZEM LEVELS

DILTIAZEM HCL ER CAPSULES, 360 MG, ANDA #75-401
 UNDER FED CONDITIONS
 DDSE=1 X 360 MG

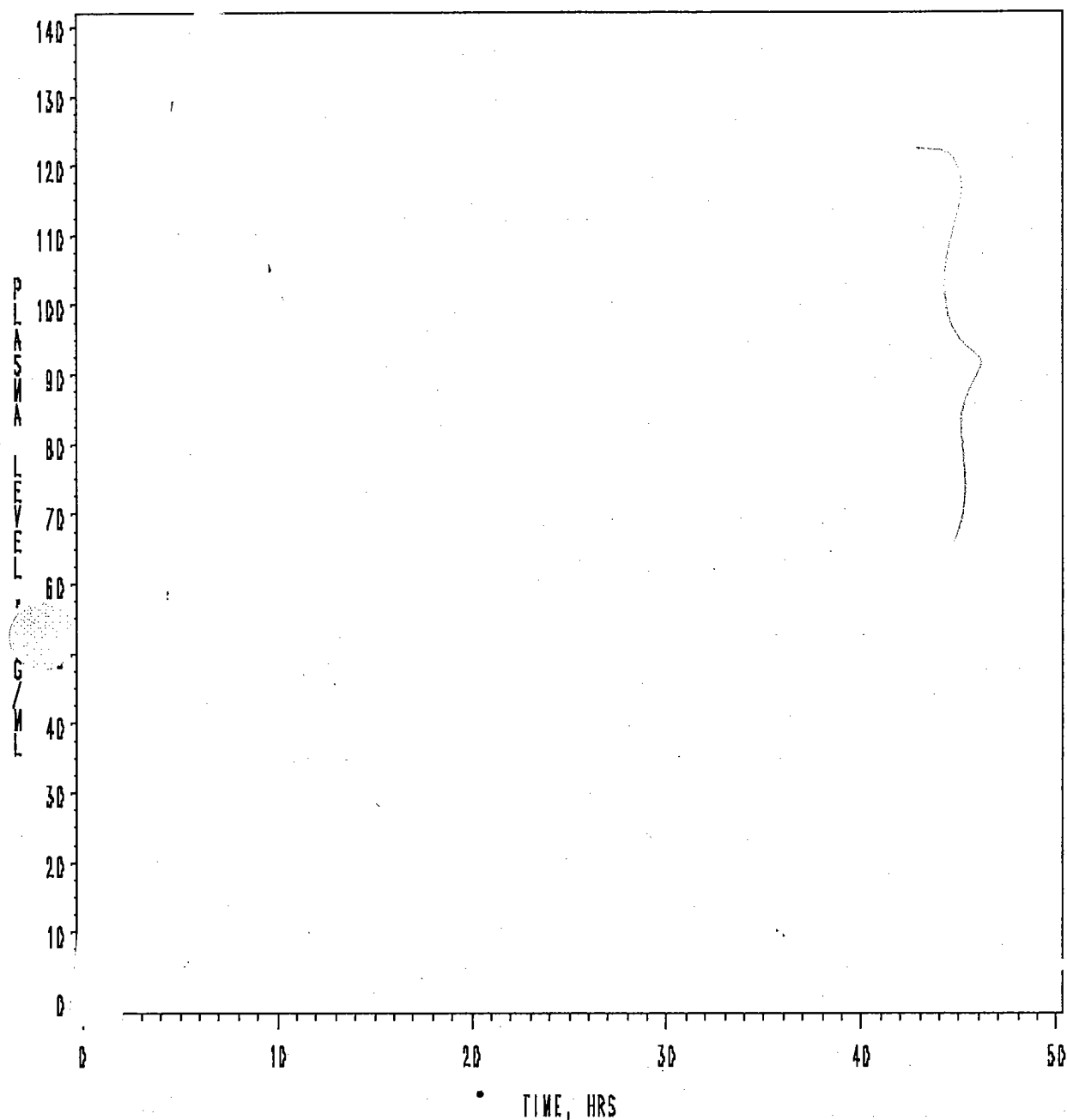


TRT **** 1 □□□ 2

1=TEST(ANDRX) 2=REF(BIDVAIL)

FIG 7. PLASMA DILTIAZEM LEVELS

DILTIAZEM HCL CAPSULES, 240 MG, ANDA #75-401
UNDER FASTING CONDITIONS
DOSE=1 X 240 MG

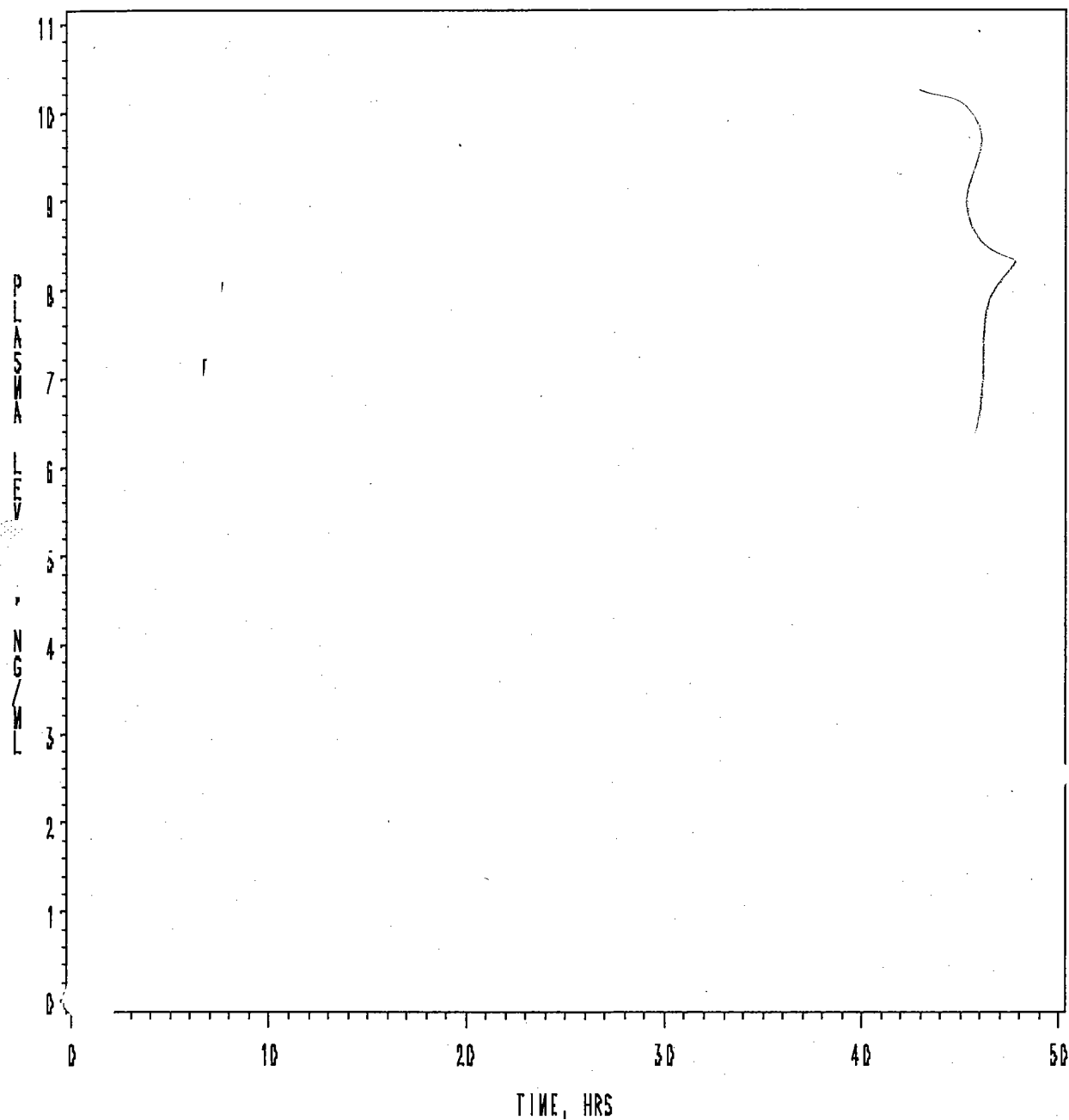


TRT **** 1 □□□ 2

1=TEST(ANDRX) 2=REF(BIDVAIL)

FIG 8. PLASMA DESACETYLDILTIAZEM LEVELS

DILTIAZEM HCL CAPSULES, 240 MG, ANDA #75-401
UNDER FASTING CONDITIONS
DOSE=1 X 240 MG

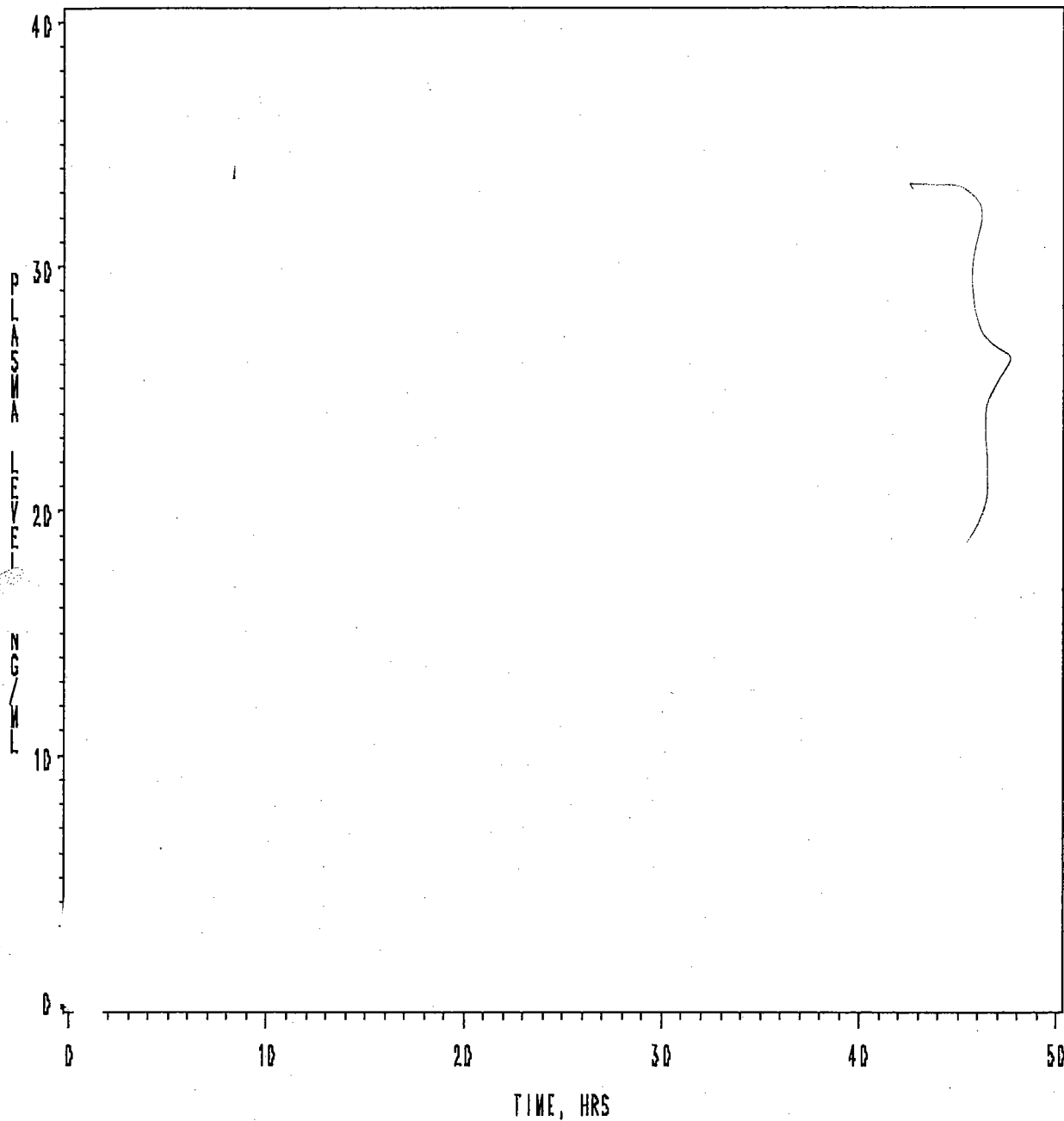


TRT **** 1 888 2

1=TEST(ANDRX) 2=REF(BIDVAIL)

3 9. PLASMA DESMETHYLDILTIAZEM LEVELS

DILTIAZEM HCL CAPSULES, 240 MG, ANDA #75-401
UNDER FASTING CONDITIONS
DDSE=1 X 240 MG

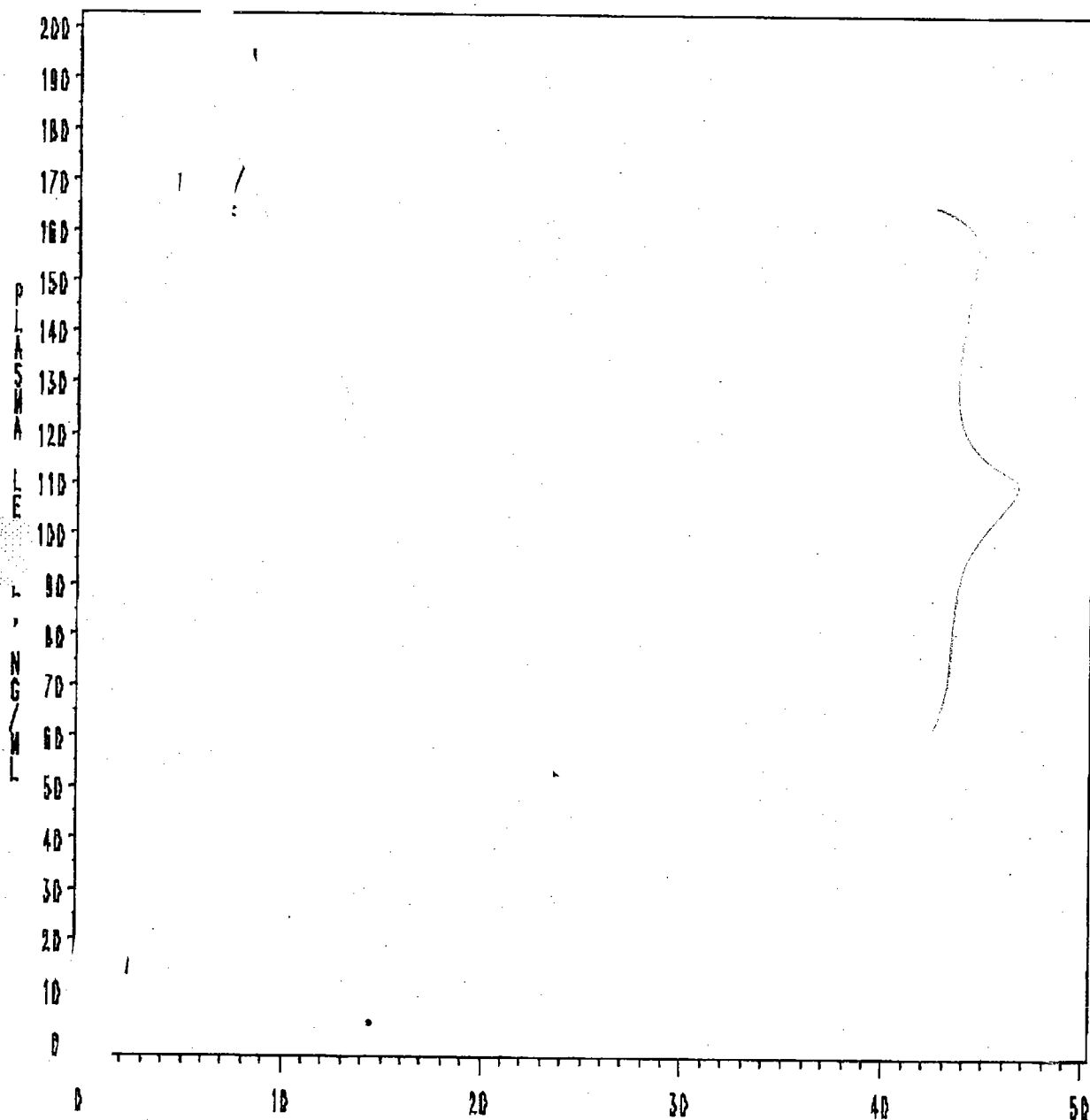


TRT ***** 1 □□□ 2

1=TEST(ANDRX) 2=REF(BIDVAIL)

FIG 10. PLASMA DILTIAZEM LEVELS

DILTIAZEM HCL CAPSULES, 360 MG, ANDA #75-401
 SPRINKLING STUDY
 DOSE=1 X 360 MG

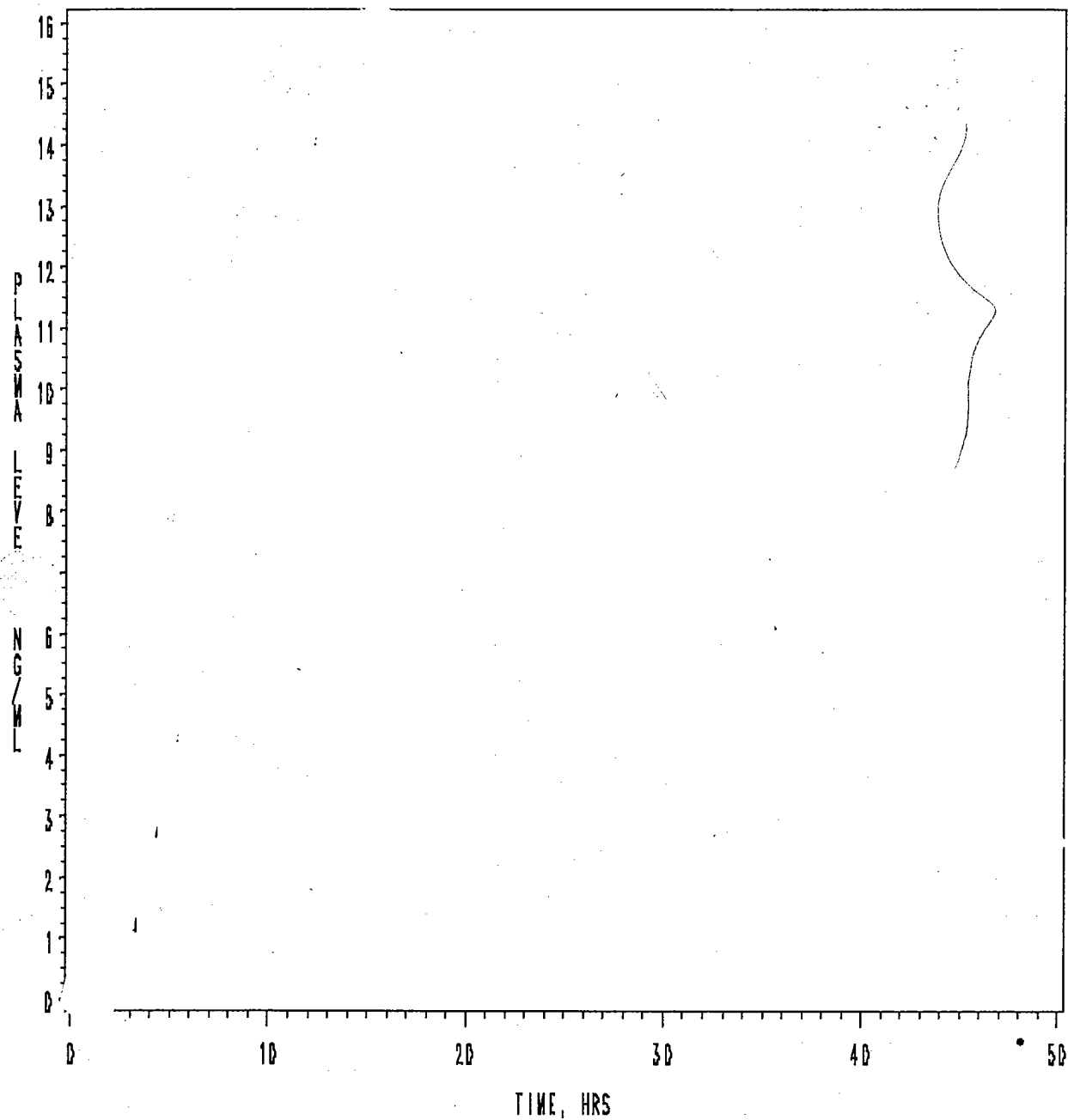


TRT *+*+* 1 888 2

1=TEST(ANDRX) 2=REF(BIDYAIL)

G 11. PLASMA DESACETYLDILTIAZEM LEVELS

DILTIAZEM HCL CAPSULES, 360 MG, ANDA #75-401
SPRINKLING STUDY
DDSE=1 X 360 MG

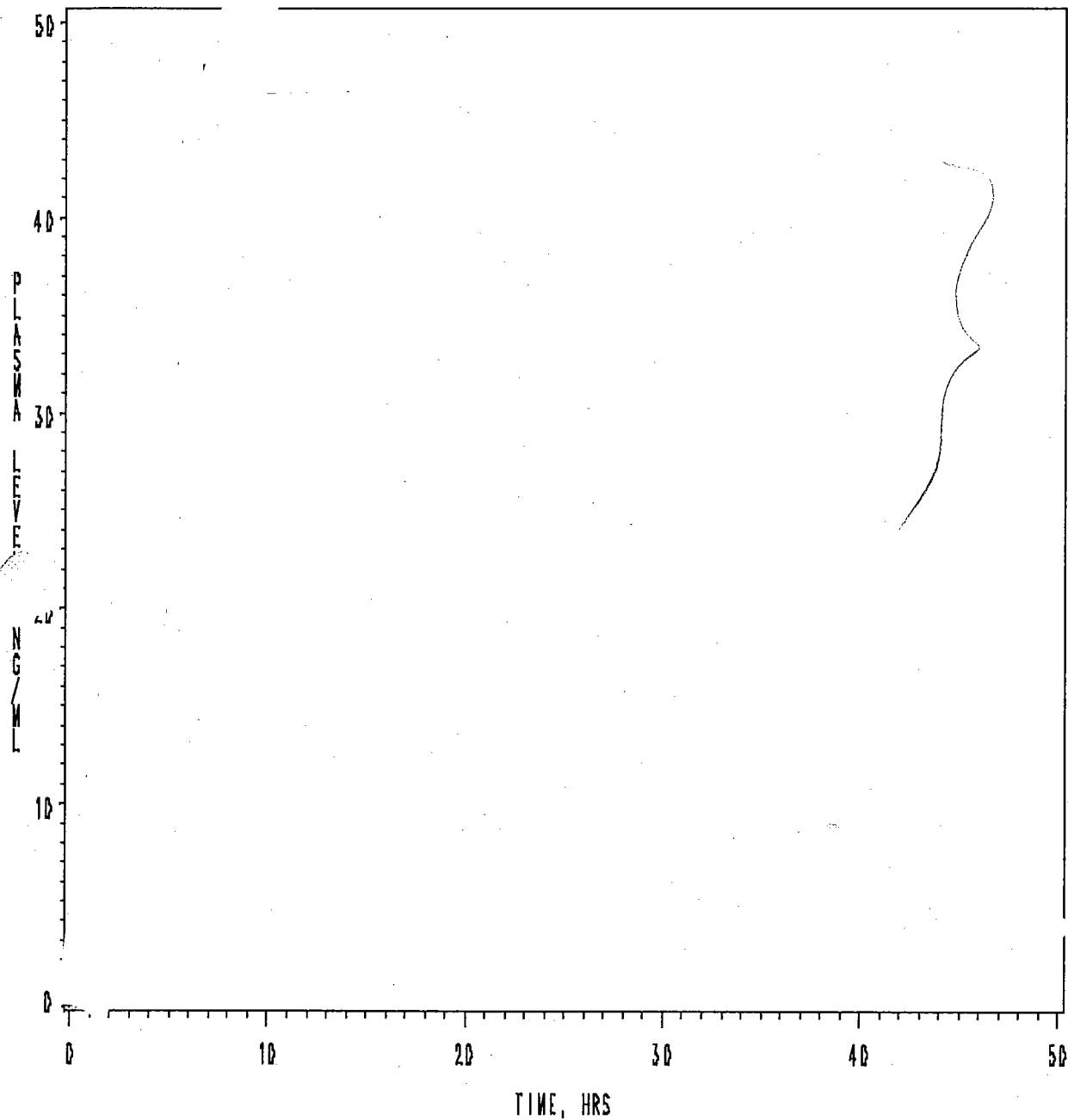


TRT *** 1 888 2

1=TEST(ANDRX) 2=REF(BIDVAIL)

12. PLASMA DESMETHYLDILTIAZEM LEVELS

DILTIAZEM HCL CAPSULES, 360 MG, ANDA #75-401
 SPRINKLING STUDY
 DOSE=1 X 360 MG

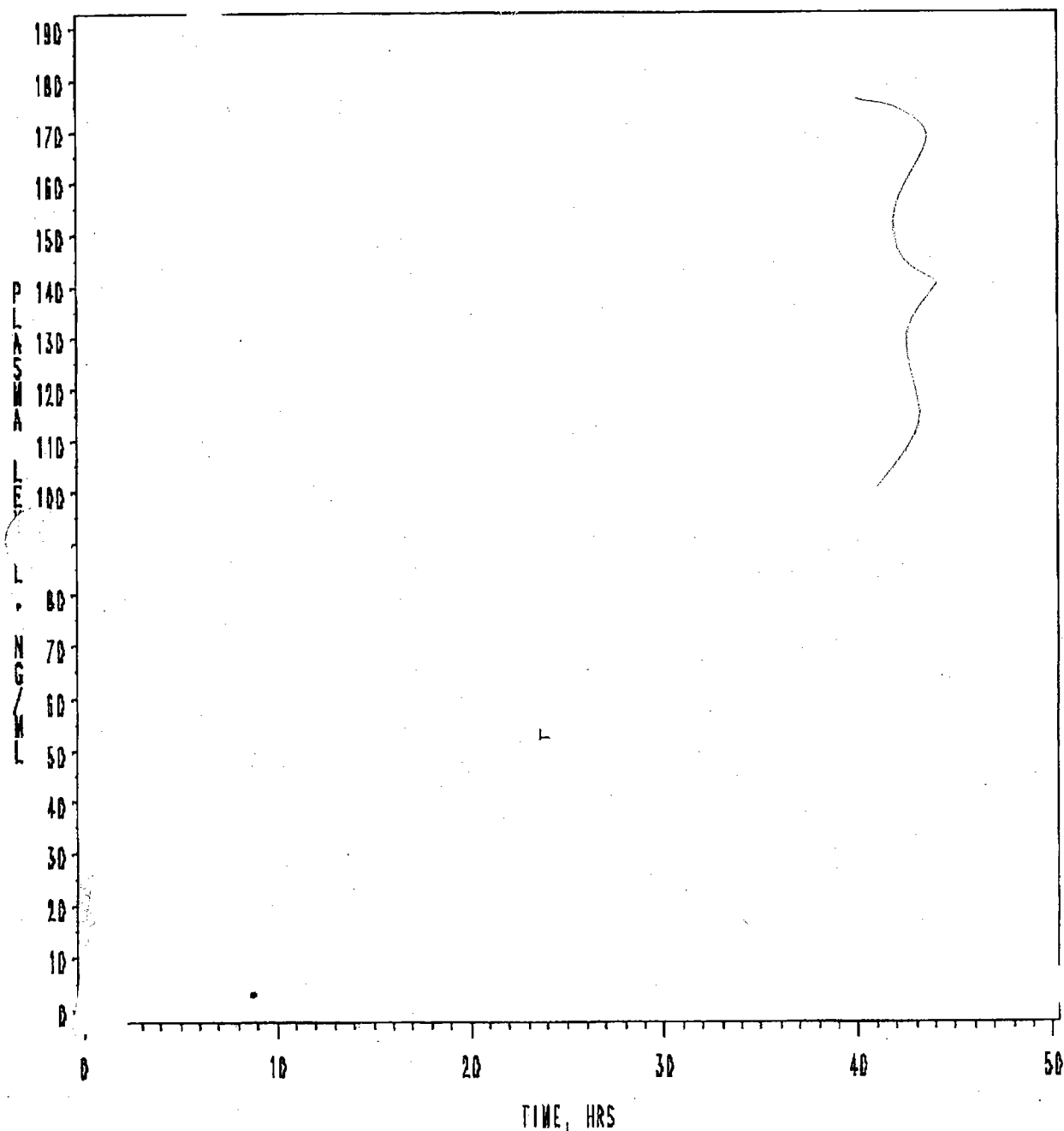


TRT *-*-* 1 □□□ 2

1=TEST(ANDRX) 2=REF(BIDVAIL)

FIG 13. PLASMA DILTIAZEM LEVELS

DILTIAZEM HCL CAPSULES, 360 MG, ANDA #75-401
SPRINKLING STUDY
DOSE=1 X 360 MG

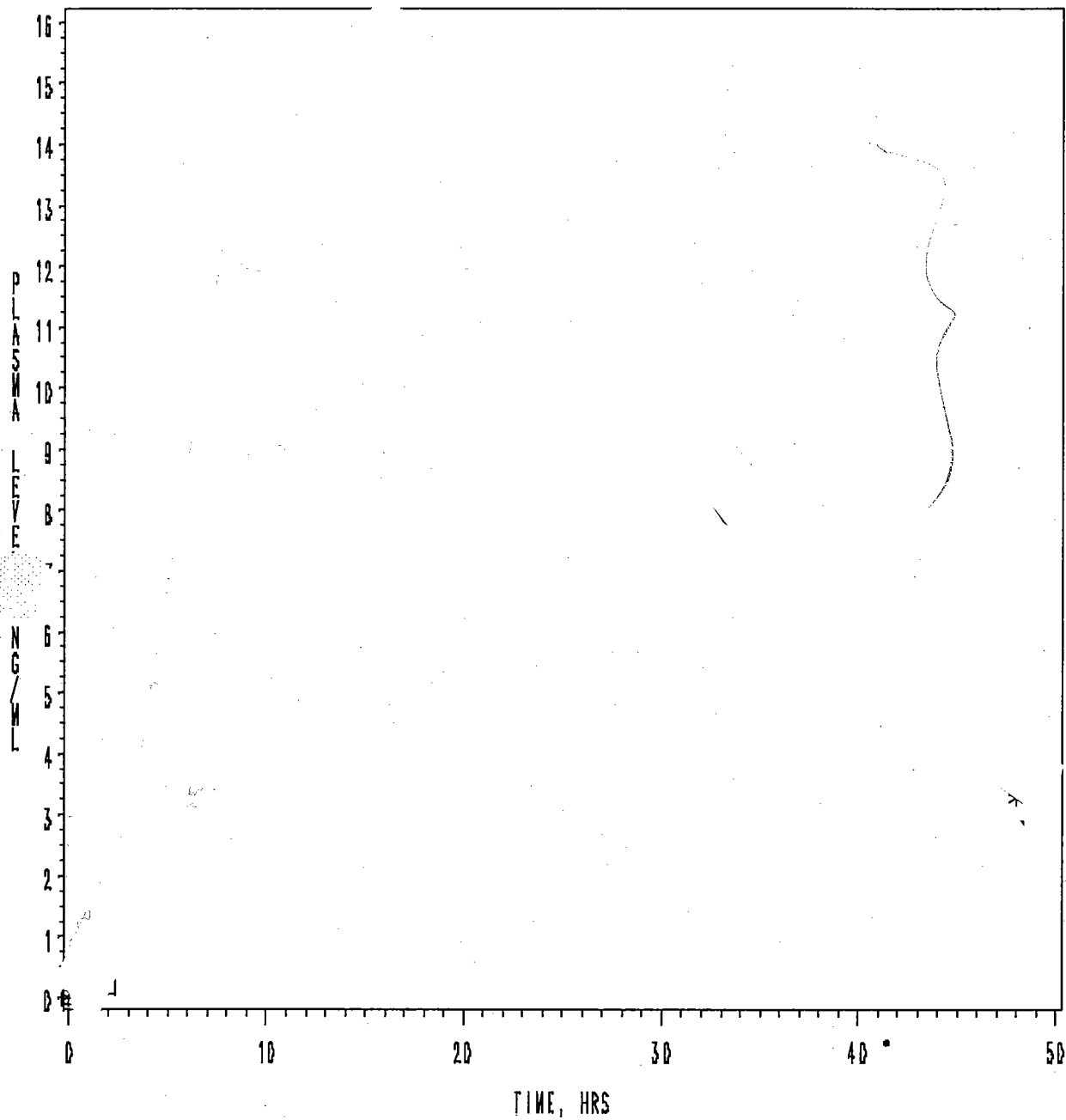


TRT **** 1 888 2

1=TEST(ANDRX) 2=REF(BIDVAIL)

3 14. PLASMA DESACETYLDILTIAZEM LEVELS

DILTIAZEM HCL CAPSULES, 360 MG, ANDA #75-401
SPRINKLING STUDY
DOSE=1 X 360 MG

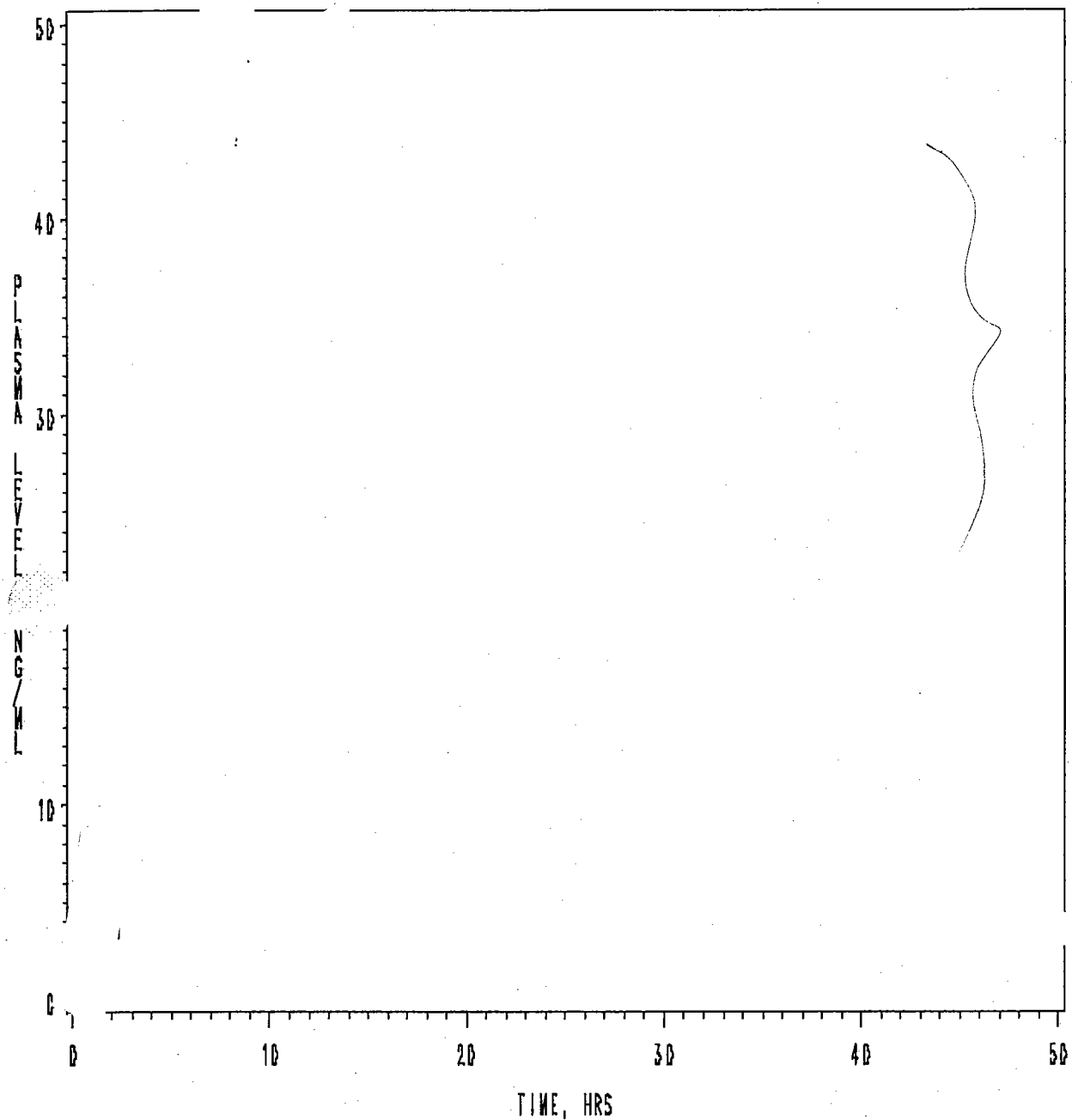


TRT **** 1 888 2

1=TEST(ANDRX) 2=REF(BIDVAIL)

15. PLASMA DESMETHYLDILTIAZEM LEVELS

DILTIAZEM HCL CAPSULES, 360 MG, ANDA #75-401
 SPRINKLING STUDY
 DOSE=1 X 360 MG



TRT **** 1 □□□ 2

1=TEST(ANDRX) 2=REF(BIDVAIL)

CC: ANDA 75-401
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)

HFD-655/Dhariwal *MD*

HFD-655/Nerurkar

HFD-617/Nwaba

HFD-650/Dale Conner *gmc 9/8/02*

7/23/02

BIOEQUIVALENCY -DEFICIENCIES

Submission Date: May 22, 2002

1. **FASTING STUDY (STF)**
Clinical: _____ Strengths: 360 MG
✓ Outcome: IC
Analytical: _____
2. **FOOD STUDY (STP)**
Clinical: _____ Strengths: 360 MG
✓ Outcome: IC
Analytical: _____
3. **FASTING STUDY (STF)**
Clinical: _____ Strengths: 240 MG
✓ Outcome: IC
Analytical: _____
4. **SPRINKLING STUDY (STF)**
Clinical: _____ Strengths: 360 MG
✓ Outcome: IC
Analytical: _____

Outcome Decisions:

IC - Incomplete

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-401

APPLICANT: Andrx

DRUG PRODUCT: Diltiazem Hydrochloride ER Capsules, USP
May 22, 2002 submission

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

Fasting study on the 360 mg capsules:

1. Sample numbers 6.07.4, 6.08.4, 10.05.1, 12.04.3, 12.05.3, 16.08.1, 16.09.1 were coded IA and were reassayed for diltiazem, desacetyldiltiazem, and desmethyldiltiazem. However, these samples do not seem to meet the definition of 'IA' given in SOP DH 8.2 (vol.10.3, page 0433). Please provide the justification for reassaying these samples and using the reassay values.
2. Please provide potency and content uniformity data of the reference product.
3. The size of the bio batch and that of the largest lot planned for full production is not given.

Fasting study on the 240 mg capsules:

1. Please clarify if the clinical study was conducted in _____ (page 4, vol. 10.13; page 1518, vol. 10.15) or in _____ (page 1523, vol. 10.15).
2. Please provide potency and content uniformity data of the test and reference products.
3. The size of the bio batch and that of the largest lot planned for full production is not given. The manufacture date of the test product should be provided.

Sprinkling study:

1. In the fed study, one subject (#22) had diltiazem C_{max} T/R ratio of 0.362 but the results were not considered enigmatic. Please explain why these results were not considered enigmatic whereas the similar results obtained in the sprinkling study (subject #21) were considered enigmatic.

2. Please clarify if the clinical study was conducted in _____ (page 3, vol. 10.19; page 1433, vol. 10.22) or in _____ (page 478, vol.10.20).

Dissolution:

Please provide volumes, compositions and molarities of the dissolution media used in the dissolution testing.

Formulation:

The quantities of active pellets' ingredients given in the master formula on page 75 vol. 9.1 differ from that given in the original application. Please provide comparative quantitative composition of all strengths of your drug product.

Sincerely yours,

Walter P. Conner

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Diltiazem Hydrochloride
Extended Release Capsules, USP
120, 180, 240, 300, 360 mg
ANDA #75-401
Reviewer: Kuldeep R. Dhariwal
V:\firmsam\Andrx\Ltrs&rev\75401summary.doc

Andrx Pharmaceuticals
4955 Orange Drive
Fort Lauderdale
Florida 33314
Submission Dates:
1998 to 2002
Control: March 5, 2002

**Summary of Andrx ANDA 75-401 Submissions, Biovail's Challenges,
Andrx's Responses and Review of Controlled Correspondence
Dated March 5, 2002 from Andrx**

The reference listed drug is Tiazac[®] by Biovail. Tiazac is currently marketed in six strengths: 120 mg, 180 mg, 240 mg, 300 mg, 360 mg and 420 mg. All strengths are marked '+' in the Orange Book.

Information from Biovail's NDA #20401 on Tiazac Capsules

Tiazac pharmacokinetics: When compared to a regimen of immediate-release tablets at steady-state, approximately 93% of drug is absorbed from the Tiazac formulation. When Tiazac was coadministered with a high fat content breakfast, the extent of diltiazem absorption was not affected; T_{max} , however, occurred slightly earlier. The apparent elimination half-life after single or multiple dosing is 4 to 9.5 hours (mean 6.5 hours).

Tiazac demonstrates non-linear pharmacokinetics. As the daily dose of Tiazac capsules is increased from 120 to 540 mg, there was a more than proportional increase in diltiazem plasma concentrations as evidenced by an increase of AUC, C_{max} and C_{min} of 6.8, 6 and 8.6 times, respectively, for a 4.5 times increase in dose.

Tiazac dose proportionality study: The study followed a randomized, 3 way, multiple dose, crossover design in 18 normal healthy male volunteers. The subjects ingested each of 120, 240 and 360 mg capsules daily for eight days during 3 phases separated by washout periods of one week. Additionally, 6 subjects who completed the above 3 phases of this study were enrolled to examine the steady-state dose tolerance and pharmacokinetics of a 540 mg dose (comprised of 180 and 360 mg capsules). The results showed a statistically significant difference among the 4 levels tested. As the dose is increased from 120 to 540 mg, slight non-linearities start to appear in AUC, C_{max} and C_{min} . All these pharmacokinetic parameters increased more than dose proportionality. Desacetyldiltiazem also showed non-linearity. However, for desmethyldiltiazem there were no statistical differences in AUC, C_{max} and C_{min} among all the 4 dose levels tested.

Pharmacokinetic parameters for diltiazem:

	120 mg	240 mg	360 mg	540 mg
AUC ₀₋₂₄	918.5	2195.79	3307.28	6238.81
C_{max}	68.43	179.93	232.37	407.52
C_{min}	13.33	34.13	57.25	115.63

Formulation of Tiazac: Tables 1 and 2. All strengths are proportionally formulated. The formulation is _____, different weights of the same _____ in different sized capsules.

Note: On March 16, 2001 (NDA 20-401, vol. A34-1), Biovail proposed changes in its manufacturing process to be filed in the Annual Report. The Biovail stated that this enhanced manufacturing process _____

On June 14, 2001, the Agency informed Biovail, "the change that Biovail appears to have made, or is in the process of making, is a major manufacturing change that is not covered by your approved drug application for Tiazac. Accordingly, Biovail is required to submit a supplemental application detailing the change and to wait for approval of that supplement before marketing the new drug product." The letter was signed by Dr. Woodcock.

Tiazac dissolution: USP test 6 method:

Medium: _____

Apparatus: _____

Specifications:	2h	NMT
	4h	_____
	8h	_____
	12h	NLT
	16h	NLT

Biovail has an established IVIV Level A correlation.

Tiazac extended-release capsules may also be administered by carefully opening the capsule and sprinkling the capsule contents on a spoonful of applesauce. Therefore, in addition to fasting and non-fasting studies, a sprinkling study is also necessary for the approval of a generic product.

History of Andrx submissions:

June 22, 1998: Andrx submitted ANDA for diltiazem hydrochloride ER capsules. The firm conducted fasting, non-fasting and multiple-dose studies on 360 mg strength. Diltiazem and the two metabolites, desmethyldiltiazem and desacetyldiltiazem were measured and subjected to 90% confidence interval approach.

July 29, 1998: Dissolution data on 120, 180, 240, and 300 mg strengths and waiver requests for these strengths.

October 16, 1998: Studies acceptable. Waivers granted. The firm was told that the dissolution testing should be conducted using USP test

6 method and the test product should meet the following interim specifications:

2h NMT _____
4h _____
8h _____
12h NLT _____
16h NLT _____

Note: The firm had proposed specifications of _____ for the 4h time interval.

October 29, 1999:

Andrx submitted an amendment to request that _____ % range at 4h as suggested in the original application be retained.

November 1, 1999:

Study amendment with more supporting data to change the suggested dissolution specifications.

November 16, 1999:

The DBE revised the 4h specifications from _____ to _____.

April 11, 2000:

The Agency requested the firm to conduct a single dose, two-way crossover sprinkling study on its 360 mg capsule because the reference listed drug labeling was amended to incorporate dosage administration by sprinkling the contents of a capsule on applesauce.

April 28, 2000:

Amendment requesting a waiver of the *in vivo* bioequivalence sprinkling study.

June 9, 2000:

The waiver was denied. The firm was requested to conduct *in vivo* bioequivalence sprinkling study.

June 26, 2000:

Firm submitted sprinkling study.

July 12, 2000:

Sprinkling study acceptable.

December 12, 2000:

Andrx requested that _____ is not a good medium for its product and therefore _____ should be replaced with _____.

The firm also requested that _____ should be changed from _____ to _____. A change in specification was not requested.

January 3, 2001:

The DBE accepted to change the dissolution medium and _____.

September 29, 2000:

ANDA was tentatively approved by the OGD.

Biovail submissions challenging Andrx:

Biovail submitted biostudies conducted under fasting conditions comparing Andrx's 120 mg capsules with Biovail's 120 mg capsules and Andrx's 240 mg capsules with Biovail's 240 mg capsules. These studies were conducted at Biovail. The 120 mg study passed but the 240 mg capsule failed bioequivalence criteria. Another study on 240 mg capsule was conducted by _____, which also did not meet the bioequivalence criteria. The clinical and analytical sites used by Andrx (studies submitted in ANDA 75401) and Biovail were inspected by the DSI. The DSI did not find any significant objectionable findings at these facilities. The DSI has also completed the inspection of _____ facility and the

findings do not change the outcome of the study. However, during the inspection, the DSI found that _____ also conducted a fasting study comparing Andrx's 360 mg capsules with Biovail's Tiazac 360 mg capsules. The results of this study showed that the two products are bioequivalent. Biovail had not revealed this study to the FDA.

Note: The DBE has not yet received the following:

- a. Bioequivalence study conducted at _____ on 360 mg capsules.
- b. Detailed DSI inspection report of _____ facility.

Biovail argues that Andrx is unable to manufacture a product that is consistently bioequivalent to Tiazac, and therefore the Andrx ANDA should not be approved. Biovail questions the manufacturing process used by the Andrx. The Division of Chemistry has reviewed CMC section and has serious concerns about the manufacturing process.

Andrx's arguments:

On October 5, 2001, Andrx submitted an amendment stating that the FDA should reject Biovail's data on both scientific and policy grounds for the following reasons:

1. The samples of all five strengths of Andrx's product were provided to Biovail in late February 2001. These samples were provided to Biovail for the sole, expressly limited purpose of evaluating whether Andrx's product infringed the U.S. patent No. 6,162,463 ("the 463 patent"). The samples were provided pursuant to a confidentiality agreement between the parties limiting Biovail's use of those samples to the infringement assessment (e.g., chemical evaluation of the product). Biovail violated that agreement and used the samples for *in vivo* testing. According to Andrx, within hours of learning of Biovail's misuse of Andrx's samples and information, a federal judge entered a protective order on an emergency basis to immediately stop Biovail from committing any further violations of the confidentiality agreement, and directed a magistrate to determine whether additional steps were needed to punish Biovail for its breach of the agreement. That magistrate found Biovail's conduct to have been unlawful and unethical, and sanctioned Biovail for its action.
2. Neither FDA nor Andrx can ensure the samples at issue were held, transported, and handled under proper conditions prior to being provided to _____ for human testing.
3. In early January 2001, Andrx manufactured a number of lots of diltiazem hydrochloride capsules as part of its on-going process development effort. These lots passed initial dissolution testing in late January 2001. Samples of each strength selected from these lots were provided to Biovail in late February. In early May 2001, Andrx determined that the 240 mg strength (lot #689B001) provided to Biovail was failing dissolution specifications with a high value seen at the 4-hour sample for the 3-month time point. All other lots, including the 120 mg capsules (lot #696B001) provided to and tested by Biovail, remained within specification after 3 months. Andrx states that since the 240 mg capsules failed dissolution testing, they were not expected to show bioequivalence to Tiazac. Therefore, FDA should not rely on the biostudy involving this batch.

4. Andrx believes that the 240 mg product failure arose from the company's efforts to optimize the manufacturing process. The ANDA 75-401 specifies a _____ for _____, of not less than _____. The _____, in the batch used for Andrx's 360 mg biostudies were _____. The batches provided to Biovail, by contrast, were _____. Both of these _____ times met the specification of ANDA 75-401. Andrx claims that its subsequent work revealed that the dissolution failure in the scale-up batches was due to the use of a _____ time, failures arise within two to three weeks following _____ and that their product is extremely sensitive to even small changes in the _____ step such as _____. Andrx intends to revise its ANDA batch record to tighten the _____ specification, as well as the _____ parameters, and report these changes in the first post-approval annual report.
5. The Andrx's diltiazem hydrochloride 240 mg capsules tested by Biovail were not representative of the Andrx's product that Andrx will sell pursuant to final approval of this ANDA.

The Division of Chemistry reviewed CMC data and concluded that the Andrx cannot produce a product of consistent quality and performance.

On October 24 and November 8, 2001, Andrx submitted amendments claiming that the firm has developed an _____ for its product. The DBE does not agree that the firm has established a _____ for its drug product.

Controlled Correspondence from Andrx: March 5, 2002

On March 5, 2002 Andrx informed the OGD that Andrx and Biovail are settling all pending litigation between them. Andrx further stated that the firm has already initiated three bioequivalence studies as follows:

1. Diltiazem hydrochloride 360 mg capsules (Andrx) vs. Tiazac 360 mg capsules (Biovail).
Single dose fasting in 40 healthy subjects
Randomized, 4 period, 2 sequence, crossover, replicate design
Measurement of diltiazem, desmethyldiltiazem and desacetyldiltiazem to 48 h
2. Diltiazem hydrochloride 360 mg capsules (Andrx) vs. Tiazac 360 mg capsules (Biovail).
Single dose fed in 24 healthy subjects
Randomized, 2 period, 2 sequence, crossover design
Measurement of diltiazem, desmethyldiltiazem and desacetyldiltiazem to 48 h
3. Diltiazem hydrochloride 240 mg capsules (Andrx) vs. Tiazac 240 mg capsules (Biovail).
Single dose fasting in 40 healthy subjects
Randomized, 4 period, 2 sequence, crossover, replicate design
Measurement of diltiazem, desmethyldiltiazem and desacetyldiltiazem to 48 h

In addition to the bioequivalence studies, Andrx plans to submit the following information:

1. Dissolution profiles for all five strengths of the test and reference products, using _____ dissolution media, as well as (_____). The F_2 factors will be calculated comparing each of the four lower strengths of the test product to the highest strength (360 mg).
2. Results of ongoing room temperature stability studies (up to 6 months) on batches produced with the scaled-up process in October 2001 will be provided.

Reviewer's comments:

The bioequivalence studies and the dissolution testing proposed by Andrx on March 5, 2002 are acceptable. The firm should, however, note that since the manufacturing process of the test product is determined to be significantly different from the one submitted earlier, a sprinkling study on the proposed highest strength is also requested for the approval of the product.

Recommendations:

The reviewer's comments may be communicated to the firm.

Mohariwal 3/8/02

Kuldeep R. Dhariwal, Ph.D.
Review Branch II, Division of Bioequivalence

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR

[Signature] Date 3/8/2002

Concur:

[Signature]

Date 3/8/02

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

for mutation

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Page(s) of trade

secret and /or

confidential

commercial

information

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75401

APPLICANT: Andrx

DRUG PRODUCT: Diltiazem Hydrochloride ER Capsules, USP
120 mg, 180 mg, 240 mg, 300 mg, 360 mg

The Division of Bioequivalence has completed its review of your submission(s) dated March 5, 2002. You stated that you have initiated three bioequivalence studies as follows:

1. Diltiazem hydrochloride 360 mg capsules (Andrx) vs. Tiazac 360 mg capsules (Biovail)
Single dose fasting in 40 healthy subjects
Randomized, 4 period, 2 sequence, crossover, replicate design
Measurement of diltiazem, desmethyldiltiazem and desacetyldiltiazem to 48 h
2. Diltiazem hydrochloride 360 mg capsules (Andrx) vs. Tiazac 360 mg capsules (Biovail)
Single dose fed in 24 healthy subjects
Randomized, 2 period, 2 sequence, crossover design
Measurement of diltiazem, desmethyldiltiazem and desacetyldiltiazem to 48 h
3. Diltiazem hydrochloride 240 mg capsules (Andrx) vs. Tiazac 240 mg capsules (Biovail)
Single dose fasting in 40 healthy subjects
Randomized, 4 period, 2 sequence, crossover, replicate design
Measurement of diltiazem, desmethyldiltiazem and desacetyldiltiazem to 48 h

In addition to the bioequivalence studies, you plan to submit the following information:

1. Dissolution profiles for all five strengths of the test and reference products, using ~~the following~~ dissolution media, as well as ~~the following~~ The F_2 factors will be calculated comparing each of the four lower strengths of the test product to the highest strength (360 mg).

2. Results of ongoing room temperature stability studies (up to 6 months) on batches produced with the scaled-up process in October 2001 will be provided.

The bioequivalence studies and the dissolution testing proposed by you on March 5, 2002 are acceptable. However, please note that since the manufacturing process of the test product is determined to be significantly different from the one submitted originally, a sprinkling study on the proposed highest strength is also requested for the approval of the product.

Sincerely yours,



Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

CC: ANDA 75-401
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)

HFD-655/Dhariwal *and 3/8/02*

HFD-655/Nerurkar

HFD-617/Nwaba

HFD-650/Dale Conner *3/11/02*

3/11/02

BIOEQUIVALENCY -DEFICIENCIES

Submission Date: March 5, 2002

1. OTHER (OTH)
March 5, 2002

Strengths: All

✓ Outcome: IC

Outcome Decisions: IC
IC - Incomplete

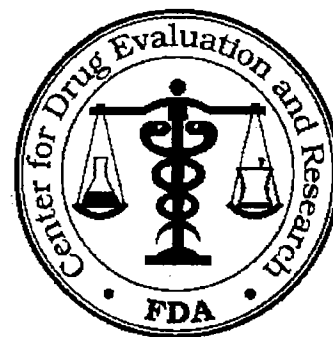
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BIOEQUIVALENCY AMENDMENT

ANDA 75-401

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

MAR 12 2002



APPLICANT: Andrx Pharmaceuticals, Inc

TEL: 954-585-1412

ATTN: Diane Servello

FAX: 954-587-1054

FROM: Nina Nwaba

PROJECT MANAGER: 301-827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on October 5, 2002, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Diltiazem HCL Extended-Release Capsules, 120mg, 180mg, 240mg, 300mg, and 360mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 2 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

**OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE**

ANDA # : 75-401

SPONSOR : Andrx Pharmaceuticals

DRUG AND DOSAGE FORM : Diltiazem Hydrochloride ER Capsules, USP

STRENGTH(S) : 120 mg, 180 mg, 240 mg, 300 mg, 360 mg

TYPES OF STUDIES : N/A

CLINICAL STUDY SITE(S) : N/A

ANALYTICAL SITE(S) : N/A

Amendment

STUDY SUMMARY : N/A

DISSOLUTION : The dissolution testing should be conducted in _____
The test product should meet the following specifications:
2h= NMT _____ 4h= _____ 8h= _____, 12h= NLT _____, 16 h= NLT _____

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic Yes	Inspection requested:	
New facility _____	Inspection completed: (date)	
For cause _____		
Other _____		

PRIMARY REVIEWER : Kuldeep R. Dhariwal BRANCH : II

INITIAL : MD DATE : 12/21/00

TEAM LEADER : S. Nerurkar BRANCH : II

INITIAL : GS DATE : 12-28-00

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : DC DATE : 1/3/01

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-401

APPLICANT: Andrx Pharmaceuticals

DRUG PRODUCT: Diltiazem Hydrochloride ER Capsules, USP
120 mg, 180 mg, 240 mg, 300 mg, 360 mg
Amendment dated 12/12/00

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

The dissolution testing should be conducted in _____
_____ at 37°C using _____
_____ The test product should meet the
following specifications:

2h	NMT
4h	_____
8h	_____
12h	NLT
16h	NLT

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,



Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Specifications: The test product should meet the following interim specifications:

2h	NMT
4h	
8h	
12h	NLT
16h	NLT

The firm in this amendment states the following:

1. During the scale-up of this product for commercial introduction, we discovered that the initial dissolution profile of the ER _____ when tested using _____ as the dissolution medium, is approximately _____ slower at the 8 hour dissolution time point than ER _____ that have been equilibrated with ambient moisture conditions. This phenomenon only occurs when the product is tested using _____ as the dissolution medium, as opposed to the _____ medium originally used for dissolution testing of our ANDA batches.

2. The changes to the dissolution method being requested at this time are the replacement of _____ with the _____ dissolution medium and change of the _____ from _____

Comments:

The submitted data show that the dissolution profile of the test product is better in _____ compared to _____. Therefore, the firm may use _____ as dissolution medium.

Recommendations:

The dissolution testing should be conducted in _____ using _____. The test product should meet the following interim specifications:

2h	NMT
4h	
8h	
12h	NLT
16h	NLT

Moharawal 12/21/00
Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S.NERURKAR
FT INITIALED S.NERURKAR Gurjpal Singh Date 12-28-00

Concur: Dale P. Conner Date 1/3/01
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

APPEARS THIS WAY
ON ORIGINAL

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information

(8)

**OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE**

ANDA # : 75401

SPONSOR : Andrx Pharmaceuticals

DRUG AND DOSAGE FORM : Diltiazem Hydrochloride ER Capsule

STRENGTH(S) : 120, 180, 240, 300, and 360 mg

TYPES OF STUDIES : Sprinkling bioequivalence study

CLINICAL STUDY SITE(S) : _____

ANALYTICAL SITE(S) : _____

STUDY SUMMARY : The sprinkling bio-study is acceptable.

DISSOLUTION : Acceptable.

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic Yes	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
Other _____		

PRIMARY REVIEWER : Kuldeep Dhariwal

BRANCH : II

INITIAL : MD

DATE : 7/11/00

TEAM LEADER : S. Nerurkar

BRANCH : II

INITIAL : [Signature]

DATE : 7/12/2000

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : DR

DATE : 7/12/00

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-401

APPLICANT: Andrx Pharmaceuticals

DRUG PRODUCT: Diltiazem Hydrochloride ER Capsules
120 mg, 180 mg, 240 mg, 300 mg, 360 mg
Amendment dated 6/26/00

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

The dissolution testing should be conducted in _____

The test product should meet the following specifications:

2h	NMT
4h	
8h	
12h	NLT
16h	NLT

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,



Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 75401
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-655/ Dhariwal

V:\FIRMSAM\ANDRX\LTRS&REV\75401SDW.600

Printed in final on 07/11/00

Endorsements: (Final with Dates)

HFD-655/ Dhariwal *MS* 7/11/00

HFD-655/ Nerurkar

HFD-650/ D. Conner *DK* 7/12/00

7/12/00

BIOEQUIVALENCY - ACCEPTABLE

Submission date: 6/26/00

1. FASTING STUDY (STF)

Strengths: 360 mg

SPRINKLING STUDY

Clinical: _____

Analytical: _____

✓ Outcome: AC

Outcome Decisions: AC - Acceptable

WinBio Comments: The sprinkling study is acceptable.

APPEARS THIS WAY
ON ORIGINAL

Andrx Pharmaceuticals
4001 S.W. 47th Avenue
Ft. Lauderdale
Florida 33314
Submission Date:
June 26, 2000

June 22, 1998: Fasting, non-fasting, and multi-dose studies and dissolution data on 360 mg strength.

July 29, 1998: Dissolution data on 120, 180, 240, and 300 mg strengths and waiver requests.

October 16, 1998: Studies acceptable. Waivers granted.

October 29, 1999: Study amendment to change the suggested dissolution specifications.

November 1, 1999: Study amendment with more supporting data to change the suggested dissolution specifications.

November 16, 1999: Dissolution specifications were revised.

April 11, 2000: The Agency requested the firm to conduct a single dose, two-way crossover sprinkling study on its 360 mg capsule because the reference listed drug labeling was amended to incorporate dosage administration by sprinkling the contents of a capsule on applesauce.

April 28, 2000: Amendment requesting a waiver of the *in vivo* bioequivalence sprinkling study.

June 9, 2000: The waiver was denied. The firm was requested to conduct *in vivo* bioequivalence sprinkling study.

June 26, 2000: This submission containing sprinkling study data.

A. Study Information:

Protocol # _____ R00-272
 IRB Approval: Yes
 Consent Form Signed: Yes
 Clinical Site: _____

Medical Investigator: _____
Principal Investigator: _____
Sub-Investigator: _____
Analytical Facility: _____
Analytical Manager: _____
Statistical Analysis: _____
Study Dates: Period I May 13-15, 2000
Period II May 20-22, 2000
Analysis Dates: May 24 to June 14, 2000
Storage Period: 32 days
Study Design: Randomized, two-way crossover design
with a wash-out period of 7 days
Randomization Scheme: AB: 3,5,6,7,9,13,16,17,18,19,23,
24,25,28,29,
BA: 1,2,4,8,10,11,12,14,15,20,
21,22,26,27,30
Treatments:

A: Diltiazem Hydrochloride ER Capsules, 1x360 mg; Andrx
Pharmaceuticals; Lot #700R001A; Lot Size: _____ capsules;
Manufacture Date: 11/26/97; Assay: 101.6%

B: Tiazac® ER Capsules, 1x360 mg; Biovail; Lot #990905;
Expiry Date: 02/02; Assay: 101.8%

Subjects: 30 healthy male subjects were enrolled in
the study according to inclusion/exclusion
criteria specified in the protocol
Housing: At least 10 hour before dosing until at
least 24 hours after dosing
Dosing: Immediately prior to dose administration,
the contents of one capsule were sprinkled
on a tablespoon of applesauce, and swallowed
without chewing followed by 240 mL of water
under fasting conditions. Water was not
allowed within 1 hour of dosing. Subjects
fasted for 4.25 hours following dose
administration.
Sample Collection: Blood samples (10 mL) were collected into
heparinized Vacutainers at predose (0 h) and
at following times post-dose: 1, 2, 3, 4, 5,
6, 7, 8, 10, 12, 16, 20, 24, 36, and 48
hours.

B. Study Results:

1. Clinical:

Drop-outs:

Subject #7 elected to withdraw prior to period II dose administration.

Adverse Events:

Thirty-seven adverse events were reported. The events were comparable on test and reference products. The most often reported adverse event was headache. Some subjects experienced hypokinesia, nausea, urethritis, and sinus pressure. Subject #6 vomited approximately 12.5 hours after period I dose administration (test drug).

Protocol Deviations: 1. There were a few sampling deviations. Pharmacokinetic parameters were calculated using the actual sampling times.
2. Some subjects took ibuprofen during the study for headache. Subject #17 took doxycycline on May 16,17,18,19,21,22, and 23 (Period I: May 13-15, Period II: May 20-22).

2. Analytical: NOT TO BE RELEASED UNDER FOI



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secret and /or

confidential

commercial

information

3. Pharmacokinetics/Statistics:

DILTIAZEM:

Mean Plasma Concentrations:	Table 1 and Figure 1
Pharmacokinetic Parameters:	Table 1
90% Confidence Intervals:	LAUC _{0-t} 93.98%-105.07%
	LAUC _{0-inf} 94.29%-105.17%
	LC _{max} 92.82%-107.69%
Test/Reference Ratios:	AUC _{0-t} 0.65-1.44 (mean 1.01)
	AUC _{0-inf} 0.65-1.43 (mean 1.01)
	C _{max} 0.61-1.81 (mean 1.03)
AUC _{0-t} /AUC _{0-inf} Ratios:	Test 0.88-1.00 (mean 0.98)
	Reference 0.93-1.00 (mean 0.98)
Root MSE:	LAUC _{0-t} 0.12456
	LAUC _{0-inf} 0.12203
	LC _{max} 0.16602

DESACETYLDILTIAZEM:

Mean Plasma Concentrations: Table 2 and Figure 2
Pharmacokinetic Parameters: Table 2
90% Confidence Intervals: LAUC_{0-t} 98.48%-108.59%
LAUC_{0-inf} 94.45%-105.59%
LC_{max} 96.58%-108.06%
Test/Reference Ratios: AUC_{0-t} 0.78-1.38 (mean 1.05)
AUC_{0-inf} 0.67-1.35 (mean 1.01)
C_{max} 0.79-1.50 (mean 1.04)
AUC_{0-t}/AUC_{0-inf} Ratios: Test 0.38-0.96 (mean 0.81)
Reference 0.41-0.96 (mean 0.79)

The ratios for following subjects were very poor:

Treatment	Subject	Ratio
Test	3	0.38
Test	6	0.69
Test	8	0.59
Test	15	0.61
Test	29	0.64
Reference	3	0.41
Reference	5	0.65
Reference	6	0.52
Reference	11	0.47
Reference	14	0.56
Reference	15	0.60

Root MSE: LAUC_{0-t} 0.10928
LAUC_{0-inf} 0.11796
LC_{max} 0.12555

DESMETHYLDILTIAZEM:

Mean Plasma Concentrations: Table 3 and Figure 3
Pharmacokinetic Parameters: Table 3
90% Confidence Intervals: LAUC_{0-t} 96.55%-103.37%
LAUC_{0-inf} 96.80%-103.47%
LC_{max} 95.40%-106.11%
Test/Reference Ratios: AUC_{0-t} 0.84-1.30 (mean 1.00)
AUC_{0-inf} 0.81-1.27 (mean 1.01)
C_{max} 0.69-1.37 (mean 1.02)
AUC_{0-t}/AUC_{0-inf} Ratios: Test 0.76-0.98 (mean 0.94)
Reference 0.78-0.98 (mean 0.94)
Root MSE: LAUC_{0-t} 0.07618
LAUC_{0-inf} 0.07447
LC_{max} 0.11891

Comments:

1. The reviewer recalculated the pharmacokinetic parameters and 90% confidence intervals. The reported values are in good agreement with those obtained by the reviewer.
2. Desacetyldiltiazem: The elimination constant and therefore $AUC_{0-\infty}$ could not be calculated for subject #24 on test product and for subject #12 and 24 on reference product. The reviewer agrees with this observation.
3. No subjects with 0 h drug level, no subjects with first scheduled post-dose time point as T_{max} , and no subjects with first measurable drug concentration as C_{max} .
4. The 90% confidence intervals for log transformed AUC_{0-t} , $AUC_{0-\infty}$, C_{max} for diltiazem, desmethyldiltiazem, and desacetyldiltiazem are within acceptable limits. There was no statistically significant period, sequence, or treatment effect for any of these parameters.
5. Subject #6 vomited approximately 12.5 hours after period I (test drug) dose administration. The 90% confidence intervals for diltiazem, desmethyldiltiazem, and desacetyldiltiazem remained within acceptable limits after dropping this subject.
6. The test lot used in this sprinkling study was manufactured in November 1997. The fasting, non-fasting, and multi-dose studies submitted earlier (file name: 75401SDW.698) were also conducted using the capsules from this lot. The test capsules were 2 years and 6 months old at the time of sprinkling study (5/00). The dissolution testing specifications of these capsules (released on 5/1/00) were within acceptable limits. The assay results (101.6%) released on 2/15/00 were within specifications.
7. The reference capsules used in the fasting, non-fasting, and multi-dose studies were from lot #960108. Since this lot had an expiry date of June 1998, the reference capsules from a different lot (#990905) were used for the sprinkling study. The firm submitted the dissolution data on test (lot #700R001A) and reference (lot #990905) products in the previous amendment (file name: 75401SDW.400). The testing results are acceptable.
8. The sprinkling study is acceptable.

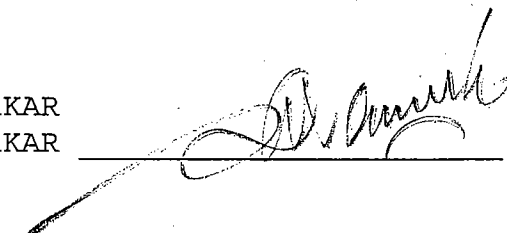
Recommendations:

The sprinkling bioequivalence study conducted by Andrx on its Diltiazem Hydrochloride, 360 mg ER capsule, lot #700R001A, comparing it to the reference product Tiazac® 360 mg ER capsule, lot #990905 manufactured by Biovail has been found acceptable by the Division of Bioequivalence. The study demonstrates that Andrx's Diltiazem Hydrochloride ER 360 mg capsule is bioequivalent to Biovail's Tiazac® 360 mg ER capsule when administered sprinkled on applesauce.

Mohariwal

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S.NERURKAR
FT INITIALED S.NERURKAR


Date 7/12/2000

Concur:


Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Date 7/12/00

Table 1

MEAN PLASMA DILTIAZEM LEVELS (ng/mL) FOR TEST (1) AND REFERENCE (2) PRODUCTS, n=29

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	6.27	5.94	0.31	1.21	19.93
2	25.84	13.36	10.96	6.50	2.36
3	46.49	14.67	56.15	31.92	0.83
4	77.55	27.06	110.42	62.31	0.70
5	141.65	61.97	164.60	71.31	0.86
6	171.32	92.02	183.88	72.50	0.93
7	183.83	84.86	195.89	81.48	0.94
8	199.79	86.26	203.34	87.79	0.98
10	188.33	77.75	187.83	70.60	1.00
12	180.21	75.85	171.40	56.11	1.05
16	131.92	50.32	123.69	37.53	1.07
20	92.65	36.87	84.39	24.38	1.10
24	73.70	28.13	70.20	22.82	1.05
36	20.90	12.09	20.12	11.32	1.04
48	5.72	5.08	5.87	5.00	0.98

UNIT: PLASMA LEVEL=NG/ML TIME=HRS
ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	3698.14	1383.64	3656.31	1081.24	1.01
AUCT	3616.55	1350.47	3580.03	1055.50	1.01
CMAX	218.90	93.20	219.41	89.93	1.00
KE	0.11	0.02	0.11	0.02	1.01
LAUCI	3495.35	0.33	3515.03	0.28	0.99
LAUCT	3416.74	0.33	3442.89	0.28	0.99
LCMAX	203.67	0.37	203.79	0.38	1.00
THALF	6.52	1.23	6.67	1.57	0.98
TMAX	8.90	2.87	7.31	2.04	1.22

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	3698.38	3651.80	1.01	94.60	107.95
AUCT	3616.27	3575.36	1.01	94.39	107.90
CMAX	218.67	219.19	1.00	90.11	109.42
LAUCI	3495.50	3510.16	1.00	94.29	105.17
LAUCT	3416.25	3437.89	0.99	93.98	105.07
LCMAX	203.56	203.61	1.00	92.82	107.69

Table 2

MEAN PLASMA DESACETYLDILTIAZEM LEVELS (ng/mL) FOR TEST (1) AND REFERENCE (2) PRODUCTS, n=29

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	0.08	0.41	0.00	0.00	.
2	0.00	0.00	0.00	0.00	.
3	0.64	1.07	0.71	1.24	0.91
4	2.59	1.90	3.73	3.31	0.69
5	6.24	3.99	7.48	4.94	0.83
6	9.18	5.93	10.10	5.71	0.91
7	11.62	7.31	12.76	6.94	0.91
8	14.59	8.70	15.20	7.97	0.96
10	18.04	10.96	18.17	10.08	0.99
12	20.77	14.24	19.76	12.55	1.05
16	21.94	16.06	20.74	15.31	1.06
20	21.32	16.11	19.63	15.59	1.09
24	20.76	18.43	19.14	17.83	1.08
36	12.24	16.00	11.55	17.45	1.06
48	4.89	9.33	5.58	10.87	0.88

UNIT: PLASMA LEVEL=NG/ML TIME=HRS
ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	742.18	768.97	781.63**	890.43	0.95
AUCT	646.14	606.28	624.59	617.81	1.03
CMAX	24.11	17.95	23.23	17.58	1.04
KE	0.07	0.02	0.06**	0.02	1.09
LAUCI	539.62	0.74	562.24	0.73	0.96
LAUCT	452.71	0.84	437.46	0.83	1.03
LCMAX	19.06	0.68	18.65	0.65	1.02
THALF	11.88	5.00	13.26	5.68	0.90
TMAX	16.55	6.34	15.17	5.92	1.09

* n=28, **n=27

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	737.84	755.72	0.98	89.17	106.10
AUCT	646.33	624.32	1.04	96.61	110.44
CMAX	24.09	23.19	1.04	95.76	112.01
LAUCI	537.96	538.69	1.00	94.45	105.59
LAUCT	452.34	437.41	1.03	98.48	108.59
LCMAX	19.04	18.64	1.02	96.58	108.06

Table 3

MEAN PLASMA DESMETHYLDILTIAZEM LEVELS (ng/mL) FOR TEST (1) AND REFERENCE (2) PRODUCTS, n=29

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	0.77	1.48	0.00	0.00	.
2	5.50	2.73	2.07	1.72	2.66
3	10.86	3.21	10.83	3.83	1.00
4	17.64	5.33	20.38	7.54	0.87
5	28.02	8.91	30.50	9.49	0.92
6	34.19	11.61	36.33	8.87	0.94
7	39.12	11.23	40.99	10.21	0.95
8	42.74	11.58	44.59	11.90	0.96
10	45.37	11.05	46.06	10.54	0.98
12	47.49	12.78	46.86	10.94	1.01
16	42.74	10.91	41.59	8.95	1.03
20	34.15	9.40	32.55	6.70	1.05
24	28.52	8.04	27.20	5.39	1.05
36	12.77	5.49	12.23	5.11	1.04
48	4.78	3.22	4.81	3.16	0.99

UNIT: PLASMA LEVEL=NG/ML TIME=HRS
ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	1222.52	341.53	1213.14	282.12	1.01
AUCT	1139.24	300.74	1128.38	228.46	1.01
CMAX	49.20	12.55	48.58	10.88	1.01
KE	0.08	0.02	0.08	0.02	1.02
LAUCI	1182.26	0.26	1182.47	0.23	1.00
LAUCT	1103.97	0.25	1105.97	0.20	1.00
LCMAX	47.77	0.24	47.47	0.22	1.01
THALF	9.42	2.26	9.82	3.09	0.96
TMAX	11.38	2.32	11.59	2.47	0.98

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
LSMEANS AND 90% CONFIDENCE INTERVALS

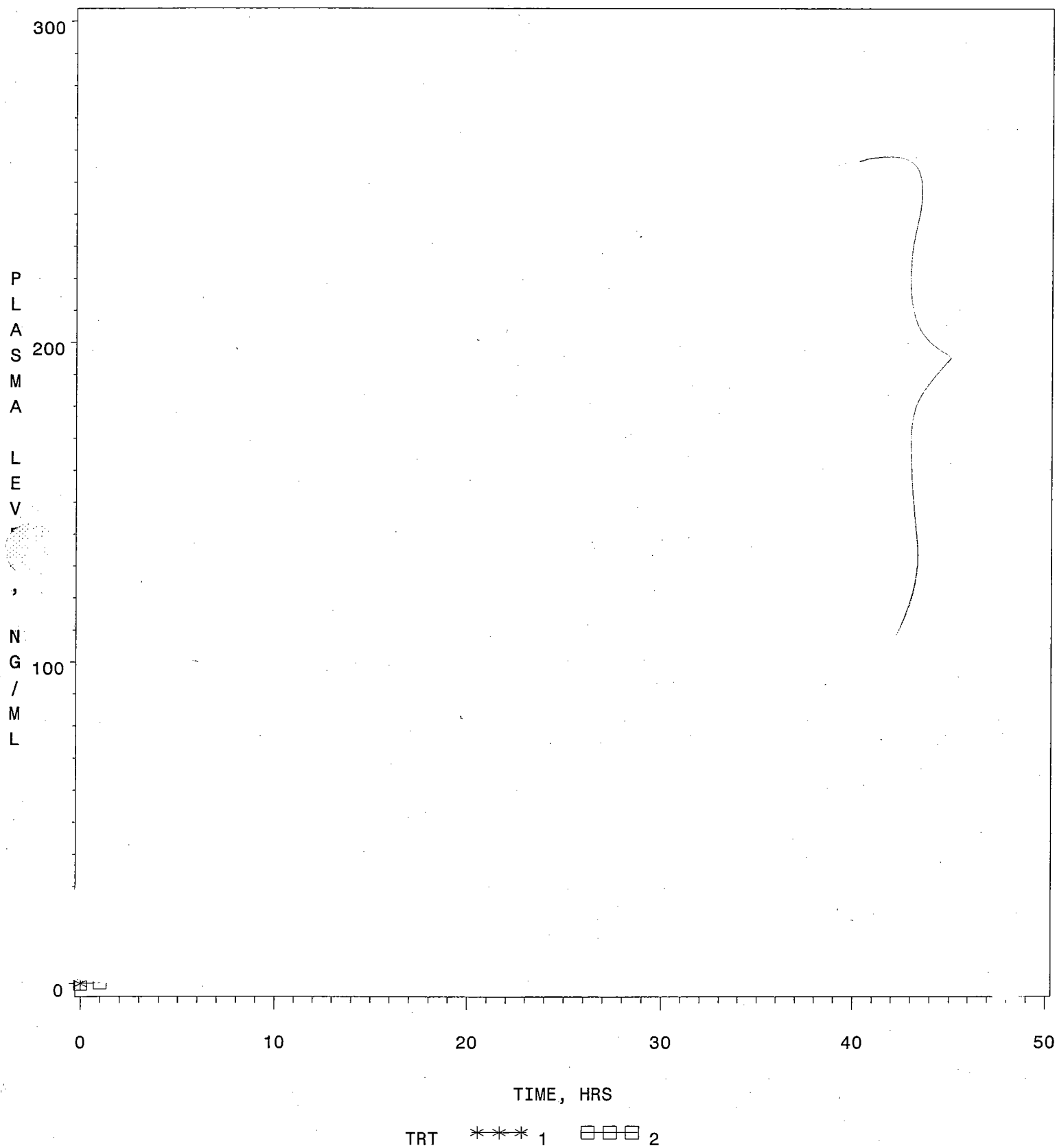
	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	1222.57	1212.28	1.01	97.14	104.56
AUCT	1139.05	1127.33	1.01	97.21	104.87
CMAX	49.17	48.56	1.01	95.39	107.12
LAUCI	1182.49	1181.57	1.00	96.80	103.47
LAUCT	1103.87	1104.96	1.00	96.55	103.37
LCMAX	47.76	47.47	1.01	95.40	106.11

FIG 1. PLASMA DILTIAZEM LEVELS

DILTIAZEM HYDROCHLORIDE ER CAPSULES, 360 MG, ANDA #75-401

UNDER FASTING CONDITIONS

DOSE=1 X 360 MG



1=TEST (ANDRX) 2=REF (BIOVAIL)

FIG 2. PLASMA DESACETYLDILTIAZEM LEVELS

DILTIAZEM HYDROCHLORIDE ER CAPSULES, 360 MG, ANDA #75-401

UNDER FASTING CONDITIONS

DOSE=1 X 360 MG

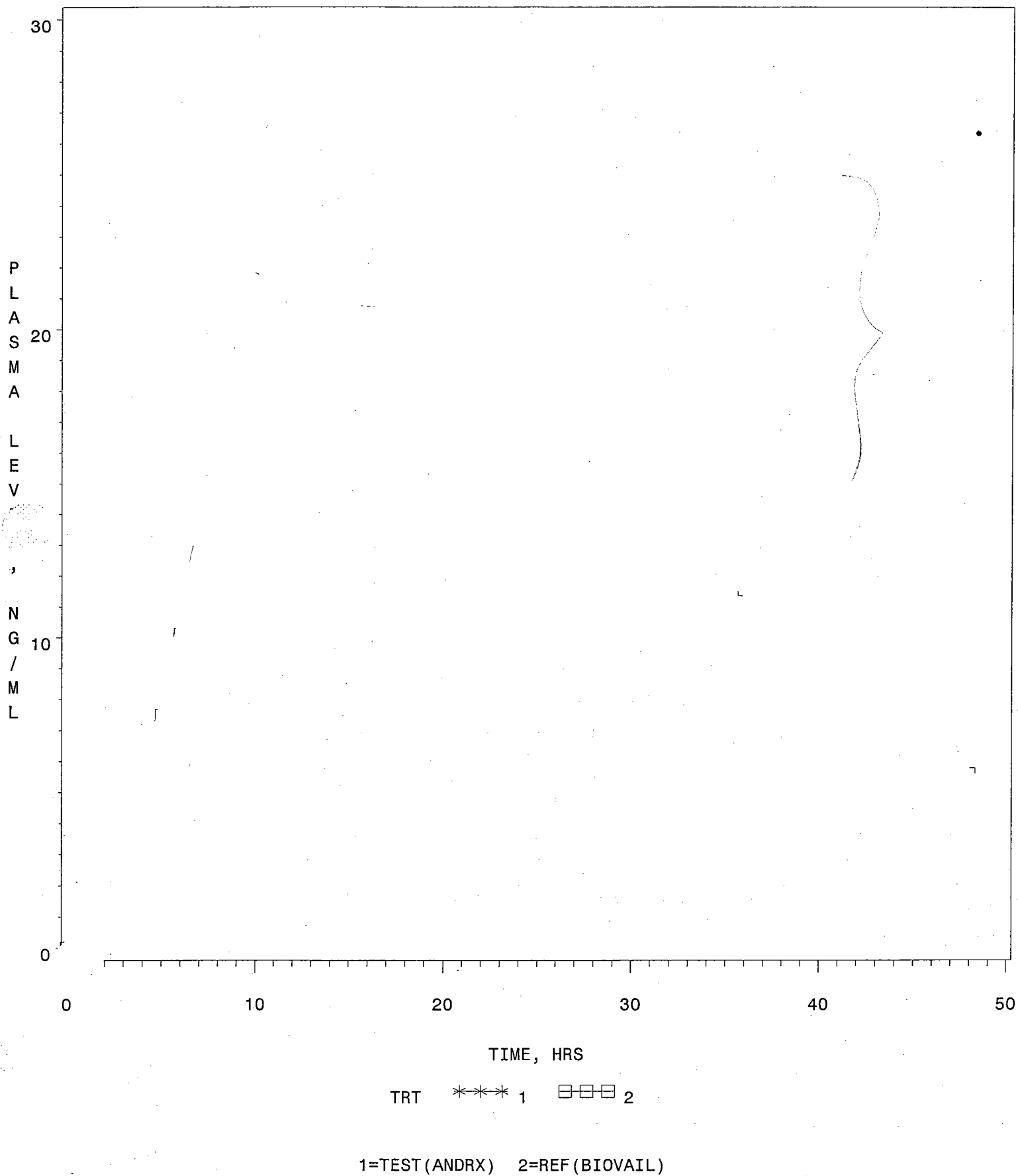
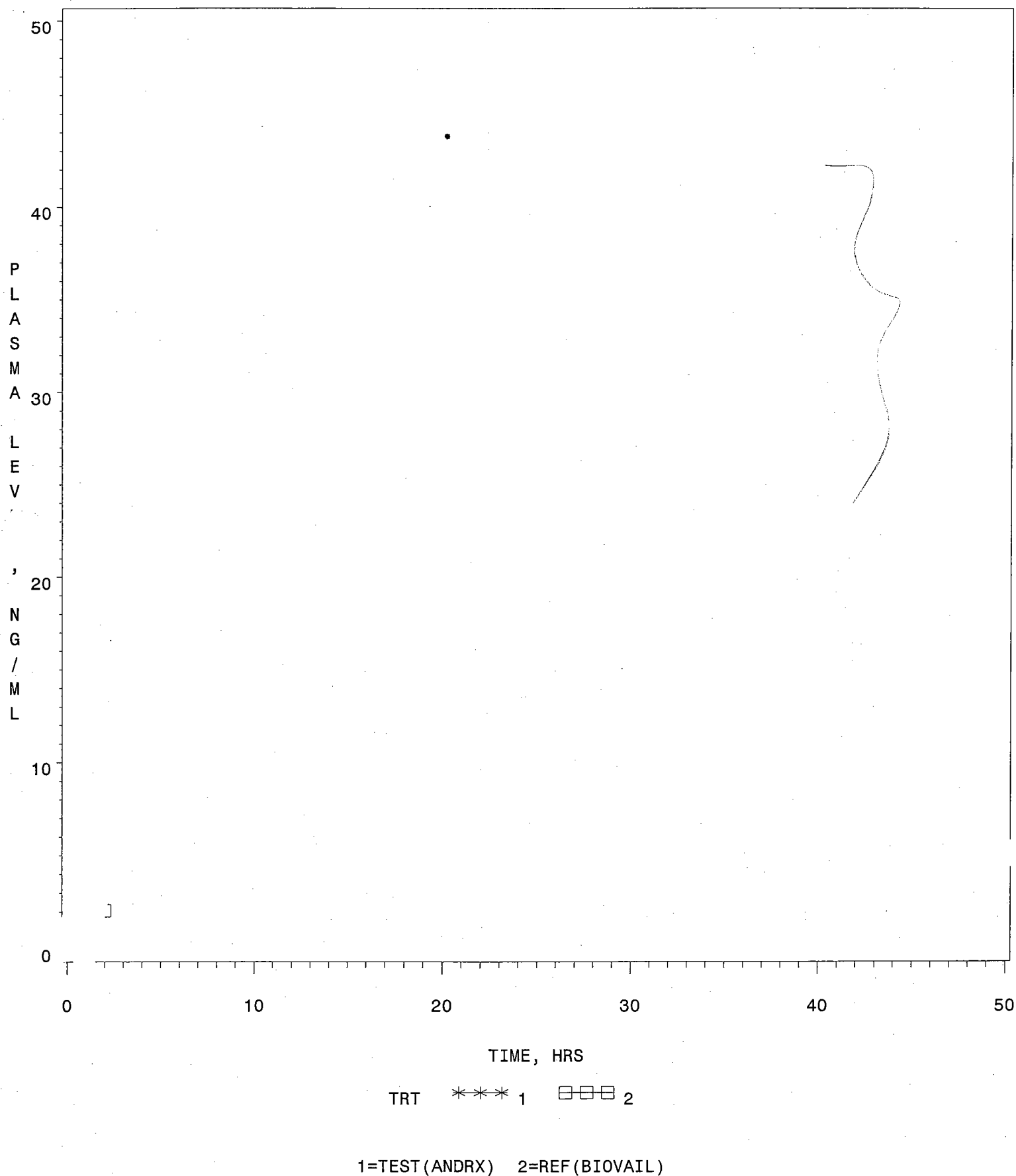


FIG 3. PLASMA DESMETHYLDILTIAZEM LEVELS

DILTIAZEM HYDROCHLORIDE ER CAPSULES, 360 MG, ANDA #75-401

UNDER FASTING CONDITIONS

DOSE=1 X 360 MG



JUN 19 2000

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75401

APPLICANT: Andrx Pharmaceuticals

DRUG PRODUCT: Diltiazem Hydrochloride ER Capsules
120 mg, 180 mg, 240 mg, 300 mg, 360 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet.

You state that _____ is used in the test and reference products. Your data show that the dissolution profiles of intact capsules and capsule contents sprinkled on applesauce are similar when the tests are conducted using _____ and _____ as dissolution medium. You did not compare the dissolution in _____, which is the recommended medium for the test product. However, it is the current practice of the Division of Bioequivalence to request an additional sprinkling bioequivalence study when the dosage and administration section of the labeling describes administration of the product sprinkled on food. Therefore your waiver request for sprinkling bioequivalence study on diltiazem hydrochloride ER 360 mg capsule is denied.

Sincerely yours,



Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Diltiazem Hydrochloride
Extended Release Capsules
120, 180, 240, 300, 360 mg
ANDA #75-401
Reviewer: Kuldeep R. Dhariwal
File name: 75401SDW.400

Andrx Pharmaceuticals
4001 S.W. 47th Avenue
Ft. Lauderdale
Florida 33314
Submission Date:
April 28, 2000

Review of an Amendment

Submission History:

June 22, 1998: Fasting, non-fasting, and multi-dose studies and dissolution data on 360 mg strength.

July 29, 1998: Dissolution data on 120, 180, 240, and 300 mg strengths and waiver requests.

October 16, 1998: Studies acceptable. Waivers granted.

October 29, 1999: Study amendment to change the suggested dissolution specifications.

November 1, 1999: Study amendment with more supporting data to change the suggested dissolution specifications.

November 16, 1999: Dissolution specifications were revised.

April 11, 2000: The Agency requested the firm to conduct a single dose, two-way crossover sprinkling study on its 360 mg capsule because the reference listed drug labeling was amended to incorporate dosage administration by sprinkling the contents of a capsule on applesauce.

April 28, 2000: This amendment requesting a waiver of the *in vivo* bioequivalence sprinkling study.

Firm's response:

1. Andrx generated *in vitro* dissolution data under the following conditions:

Dissolution conditions	Test Product		Reference Product	
	Intact capsule shells	No shell/ Applesauce ¹	Intact capsule shells	No shell/ Applesauce ¹
[]	X	X	X	X
	X	X	X	X
	X		X	

¹ The _____ were removed from the capsule shell and sprinkled on 9 g of applesauce just prior to introduction into the dissolution media.

Dissolution method: The _____ were removed from the shell and sprinkled on the applesauce (spoonful is defined as 9 g) just prior to introduction into the dissolution media. The weighing boat was introduced into the media to assure complete introduction of the sample. In addition, a 900 mL media blank containing an accurately weighed 9 g applesauce was held at 37°C and sampled during the course of the dissolution profile.

The similarity factor, f_2 was calculated for the following comparisons:

- Test product: intact capsules vs. _____ on applesauce in _____ buffer, $f_2 =$ _____
- Test product: intact capsules vs. _____ on applesauce in _____, $f_2 =$ _____
- Reference product: intact capsules vs. _____ on applesauce in _____ buffer, $f_2 =$ _____
- Reference product: intact capsules vs. _____ on applesauce in _____, $f_2 =$ _____
- Test product vs. reference product: intact capsules in _____, $f_2 =$ _____

The data demonstrate that the dissolution profiles for this product, in various media, remain unchanged whether the testing is conducted on intact capsules or _____ sprinkled on applesauce.

Reviewer's comments: The reviewer agrees with the observation that, under the described testing conditions, the dissolution profiles remain unchanged whether the testing is conducted on intact capsules or on capsule contents sprinkled on applesauce. The firm however did not compare the dissolution in _____ which is the recommended medium for the test product.

2. The food effect study results, submitted with original ANDA, showed that there is no statistical difference in food effect between the test and reference products. It should be noted that the high-fat breakfast used in the food study provides a much greater "worst case scenario" than the applesauce treatment.

Reviewer's comments: The differences in test and reference products in food effect study were within acceptable limits.

3. The release-controlling _____ used in the test product is exactly the same as that used in the reference product.
4. The dissolution profiles are similar with or without applesauce; demonstrating that applesauce does not have an effect on the release-controlling polymer used in the formulation.
5. There are no safety and efficacy concerns of medical significance when the test and reference products are administered as a 'sprinkle'.

Reviewer's comments: The _____ is used in test and reference products. The dissolution profiles of intact capsules and capsule contents sprinkled on applesauce are similar for test and reference products. However, it is the current practice of the Division of Bioequivalence to request an additional sprinkling bioequivalence study when the dosage and administration section of the labeling describes administration of the product sprinkled on food.

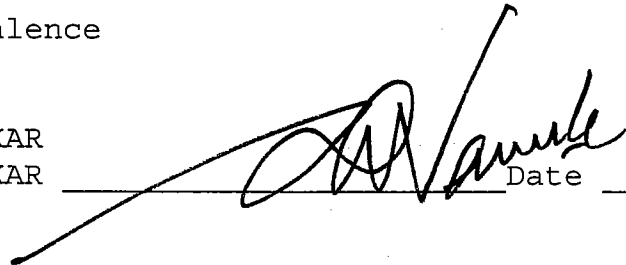
Recommendations:

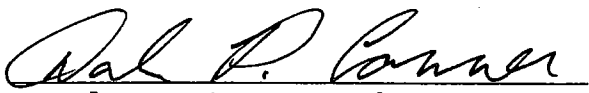
1. The firm should conduct a single dose, two-way crossover sprinkling study on its 360 mg ER capsule.
2. In this study its 360 mg ER capsule should be compared to the 360 mg ER Tiazac capsule by sprinkling both on applesauce.
3. The equivalent bioavailability of the two treatments will be determined by the 90% confidence interval criterion.
4. With the acceptable sprinkling study on its 360 mg ER capsule, the firm does not need to conduct any sprinkling study on its ER capsules of the lower strengths.
5. The firm may submit a protocol for this study or may select the conventional two-way crossover design with particular attention to the dosage and administration section of the amended labeling.

Moharwal.

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S.NERURKAR
FT INITIALED S.NERURKAR

 Date 5/22/00

Concur:  Date 6/2/00
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

V:\FIRMSAM\ANDRX\LTRS&REV\75401sdw.400

APPEARS THIS WAY
ON ORIGINAL

Table 1. In Vitro Dissolution Testing						
Drug (Generic Name): Diltiazem Hydrochloride ER Capsules Dose Strength: 120, 180, 240, 300, 360 mg ANDA No.: 75-401 Firm: Andrx Submission Date: April 28, 2000 File Name: 75401SDW.400						
I. Conditions for Dissolution Testing:						
USP XXIII Basket: Paddle: x RPM: _____ No. Units Tested: 12 Medium: _____ Volume: _____ Specifications: Reference Drug: Tiazac (Biovail) Assay Methodology: _____						
II. Results of In Vitro Dissolution Testing:						
Sampling Times (hours)	Test Product, _____ sprinkled on applesauce. Lot #700R001A Strength(mg) 360			Test Product, intact capsule Lot #700R001A Strength(mg) 360		
	Mean %	Range	%CV	Mean %	Range	%CV
1	8		10	8		11.4
2	13		9.0	14		8.3
4	28		6.1	34		5.5
6	54		4.2	60		5.4
8	70		6.0	73		5.5
10	79		5.8	80		5.1
12	84		5.5	85		4.8
14	86		5.5	88		4.4
16	88		5.4	90		4.3
Sampling Times (hours)	Reference Product, sprinkled on applesauce. Lot #990905 Strength(mg) 360			Reference Product, intact capsule Lot #990905 Strength(mg) 360		
	Mean %	Range	%CV	Mean %	Range	%CV
1	2		15.1	2		21.2
2	8		6.4	8		5.5
4	29		2.5	30		2.9
6	45		3.2	47		2.3
8	56		4.4	57		2.8
10	64		4.5	65		3.1
12	69		4.4	70		3.4
14	73		4.1	74		3.3
16	76		4.0	77		3.1

Table 2. In Vitro Dissolution Testing						
Drug (Generic Name): Diltiazem Hydrochloride ER Capsules						
Dose Strength: 120, 180, 240, 300, 360 mg						
ANDA No.: 75-401						
Firm: Andrx						
Submission Date: April 28, 2000						
File Name: 75401SDW.400						
I. Conditions for Dissolution Testing:						
USP XXIII Basket: Paddle: x RPM: _____						
No. Units Tested: 12						
Medium: _____ Volume: _____						
Specifications:						
Reference Drug: Tiazac (Biovail)						
Assay Methodology: _____						
II. Results of In Vitro Dissolution Testing:						
Sampling Times (hours)	Test Product, _____ sprinkled on applesauce. Lot #700R001A Strength(mg) 360			Test Product, intact capsule Lot #990905 Strength(mg) 360		
	Mean %	Range	%CV	Mean %	Range	%CV
1	6	_____	11.5	7	_____	13.7
2	10	_____	9.4	11	_____	10.1
4	30	_____	7.3	30	_____	3.0
6	47	_____	4.5	49	_____	1.6
8	63	_____	2.7	62	_____	1.6
10	72	_____	2.6	71	_____	1.5
12	78	_____	3.9	77	_____	1.7
14	83	_____	3.0	82	_____	1.6
16	87	_____	2.4	86	_____	1.5
Sampling Times (Minutes)	Reference Product, sprinkled on applesauce. Lot #990905 Strength(mg) 360			Reference Product, intact capsule Lot #990905 Strength(mg) 360		
	Mean %	Range	%CV	Mean %	Range	%CV
1	3	_____	22.7	4	_____	16.6
2	14	_____	14.4	15	_____	6.7
4	39	_____	4.1	45	_____	2.7
6	59	_____	3.8	64	_____	1.9
8	70	_____	1.9	75	_____	1.6
10	81	_____	2.1	82	_____	1.3
12	85	_____	1.5	87	_____	1.2
14	89	_____	2.3	90	_____	1.1
16	91	_____	2.5	92	_____	1.0

Table 3. In Vitro Dissolution Testing

Drug (Generic Name): Diltiazem Hydrochloride ER Capsules

Dose Strength: 120, 180, 240, 300, 360 mg

ANDA No. : 75-401

Firm: Andrx

Submission Date: April 28, 2000

File Name: 75401SDW.400

I. Conditions for Dissolution Testing:

USP XXIII Basket: Paddle: x RPM:

No. Units Tested: 12

Medium: ~~1000~~ Volume: ~~1000~~

Specifications:

Reference Drug: Tiazac (Biovail)

Assay Methodology: ~~unpublished~~

II. Results of In Vitro Dissolution Testing:

Sampling Times (hours)	Test Product, intact capsule Lot #700R001A Strength(mg) 360			Reference Product, intact capsule Lot #990905 Strength(mg) 360		
	Mean %	Range	%CV	Mean %	Range	%CV
0	0			0		
2	13		8.0	11		8.7
4	28		3.5	36		4.1
8	70		1.8	67		2.2
12	88		1.7	81		1.9
16	95		1.8	89		1.4

[illegible]

APPEARS THIS WAY
ON ORIGINAL

Diltiazem Hydrochloride
Extended Release Capsules
120, 180, 240, 300, 360 mg
ANDA #75-401
Reviewer: S. G. Nerurkar
File name: 75401A.A00

Andrx Pharmaceuticals
4001 S.W. 47th Avenue
Ft. Lauderdale
Florida 33314
Submission Date:
April 6, 2000

Amendment to the Earlier Review

Submission History:

June 22, 1998: Fasting, non-fasting, and multi-dose studies on 360 mg strength and dissolution data submitted to the Agency.

July 29, 1998: Dissolution data on 120, 180, 240, and 300 mg strengths and waiver requests.

October 16, 1998: Studies acceptable. Waivers granted.

October 29, 1999: Study amendment to change the suggested dissolution specifications.

November 1, 1999: Study amendment with more supporting data to change the suggested dissolution specifications.

April 6, 2000: This not a submission from the Firm. This review became necessary when the innovator amended its labeling.

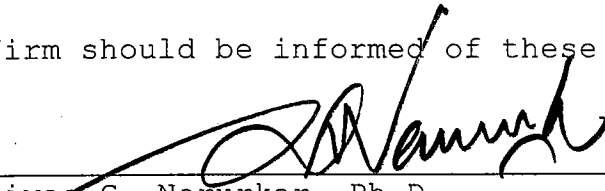
The innovator amended its labeling to incorporate dosage administration by sprinkling the contents of a capsule on applesauce. As per the attached E-mail from Dr. Marroum of OCPB, the innovator conducted a sprinkling study on the 420-mg ER capsule of Tiazac. In that two-way crossover study, the intact capsule was compared with the capsule opened and sprinkled on applesauce. The two treatments were shown to be bioequivalent by 90% confidence interval criterion. Because of this study (and the change in the labeling), the Division of Bioequivalence is requesting Andrx to conduct a sprinkling bioequivalence study on its 360mg ER capsule.

Recommendations:

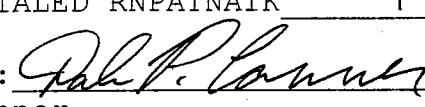
1. The firm should conduct a single dose, two-way crossover sprinkling study on its 360mg ER capsule.
2. In this study its 360mg ER capsule should be compared to the 360mg ER Tiazac capsule by sprinkling both on applesauce.

3. The equivalent bioavailability of the two treatments will be determined by the 90% confidence interval criterion.
4. With the acceptable sprinkling study on its 360mg ER capsule, the firm does not need to conduct any sprinkling study on its ER capsules of the lower strengths.
5. The firm may submit a protocol for this study or may select the conventional two-way crossover design with particular attention to the dosage and administration section of the amended labeling.

The firm should be informed of these recommendations.

 4/10/2000
Shriniwas G. Nerurkar, Ph.D.
Team Leader Branch 2.

RD INITIALED RNPATNAIK
FD INITIALED RNPATNAIK

 4/10/2000
Concur : Dale Conner
Dale Conner
Director, Division Of Bioequivalence

CC: ANDA 75 401
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-655/ Nerurkar

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Printed in final on
Endorsements: (Final with Dates)
HFD-655/ Nerurkar
HFD-650/ D. Conner  4/11/00

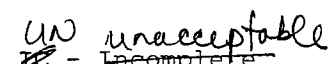
BIOEQUIVALENCY - incomplete

Submission date: initiated by
DBE on 4-6-2000 (U2 document)

1. STUDY AMENDMENT (STA)
10/29/99

Strengths: all
Outcome: ~~IC~~ UN 

A sprinkling study is requested.

Outcome Decisions: ~~IC~~ - ~~Incomplete~~  UN unacceptable

WinBio Comments: A sprinkling study is requested.

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-401

APPLICANT: Andrx Pharmaceuticals

DRUG PRODUCT: Diltiazem HCl Extended Release Capsules, 360mg, 300mg, 240mg, 180mg, and 120mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. The reference listed drug labeling has been amended to incorporate dosage administration by sprinkling the contents of a capsule on applesauce. The Division of Bioequivalence current practice is to request an additional sprinkling bioequivalence study when the dosage and administration section of the labeling describes administration of the product sprinkled on food.
2. A single dose, two-way crossover sprinkling study on the 360mg ER capsule should be conducted comparing your 360mg ER capsule to the 360mg ER Tiazac capsule by sprinkling both on applesauce.
3. The bioequivalence of the two treatments will be determined using the 90% confidence interval criterion.
4. Sprinkling studies on your ER capsules of the lower strengths are not necessary if the sprinkling study on your 360mg ER capsule is acceptable.
5. You may submit a protocol for this study or may select the conventional two-way crossover design with particular attention to the dosage and administration section of the amended labeling.

Sincerely yours,



Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75401

APPLICANT: Andrx Pharmaceuticals

DRUG PRODUCT: Diltiazem Hydrochloride ER Capsules
120 mg, 180 mg, 240 mg, 300 mg, 360 mg
Amendments dated 10/29/99 and 11/1/99

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in _____ at _____
The test product should meet the following interim specifications:

2h	NMT	_____
4h	_____	_____
8h	_____	_____
12h	NLT	_____
16h	NLT	_____

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,



 Dale P. Conner, Pharm. D.
Director

Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-655/ Dhariwal

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Printed in final on 11/3/99

Endorsements: (Final with Dates)

HFD-655/ Dhariwal *MS* 11/3/99

HFD-655/ Nerurkar

HFD-650/ D. Conner *for Ave* 11/16/99

11/15/99

BIOEQUIVALENCY - ACCEPTABLE

Submission date: 10/29/99
11/1/99

1. STUDY AMENDMENT (STA)
10/29/99

Strengths: all
✓ Outcome: AC

Study amendment to change the suggested dissolution specifications.

2. STUDY AMENDMENT (STA)
11/1/99

Strengths: all
✓ Outcome: AC

Study amendment with more supporting data, not submitted earlier.

Outcome Decisions: AC - Acceptable

WinBio Comments: Dissolution specifications revised.

APPEARS THIS WAY
ON ORIGINAL

Diltiazem Hydrochloride
Extended Release Capsules
120, 180, 240, 300, 360 mg
ANDA #75-401
Reviewer: Kuldeep R. Dhariwal
File name: 75401SDW.N99

Andrx Pharmaceuticals
4001 S.W. 47th Avenue
Ft. Lauderdale
Florida 33314
Submission Date:
October 29, 1999
November 1, 1999

Review of Two Amendments

Submission History:

June 22, 1998: Fasting, non-fasting, and multi-dose studies on 360 mg strength and dissolution data submitted to the Agency.
July 29, 1998: Dissolution data on 120, 180, 240, and 300 mg strengths and waiver requests.
October 16, 1998: Studies acceptable. Waivers granted.
October 29, 1999: Study amendment to change the suggested dissolution specifications.
November 1, 1999: Study amendment with more supporting data to change the suggested dissolution specifications.

The firm was given the following dissolution method and specifications:

Method: _____

Specifications: The test product should meet the following interim specifications:

2h	NMT
4h	_____
8h	_____
12h	NLT
16h	NLT

The firm in these amendments states the following:

1. The initial release test data from our ANDA test batches showed 4-hour dissolution values ranging from _____ (mean 30%). A review of the 4-hour dissolution values from stability testing conducted to-date shows values of _____ (mean 29%). Based on this data, Andrx believes our originally

proposed limit of _____ for the 4 hour time interval is appropriate and justified.

2. The Tiazac® product uses a formulation and extended-release manufacturing technology that is different from the Andrx product ' _____. The use of the different formulations and technologies leads to differences in the dissolution profiles of the two products, even though the products meet the requirements for bioequivalence.
3. Dissolution results below _____ have already been observed at the 4-hour interval in stability studies conducted on the ANDA biobatches (Graphs attached). As shown, all dissolution values at the 4-hour interval from stability studies on biobatches are clustered at the lower end of the _____ range.
4. As shown in the multiple dose bioequivalence study, Andrx's product has slightly higher (about 2%) values than the reference product in both AUC and Cmax. Increasing the dissolution specification at 4 hours from our proposed value of _____ to a even higher value of _____ as requested in your October 25, 1999 fascimile, may in fact increase the Cmax value of the test product and may result in a bioinequivalent product. We request that our 4 hour dissolution specification be based on our submitted *in vivo* data, as well as *in vitro* data generated on our biobatches rather than attempting to force our product to meet the USP specifications which were developed for the reference product only.

Comments:

1. The reviewer discussed the dissolution data and specification with DBE dissolution focal point, Dr. N. Tran and arrived at the conclusion that firm does have the problem of meeting the specification at 4 hour. However, firm's proposed specification of _____ at 4 hour is too liberal. The stability graphs submitted by firm show that none of the tablets dissolve less than _____. Therefore the firm would be given an interim specification of : _____ at 4 hour.

**APPEARS THIS WAY
ON ORIGINAL**

1. The dissolution testing should be conducted in 0.1N HCl

2h	NMT
4h	
8h	
12h	NLT
16h	NLT

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RD INITIALED S.NERURKAR
FT INITIALED S.NERURKAR

Date 11/15/99

Concur :

No Caluária

Date 11/16/99

for Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

**APPEARS THIS WAY
ON ORIGINAL**

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2.1 *Ver*
BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75401

APPLICANT: Andrx Pharmaceuticals

DRUG PRODUCT: Diltiazem Hydrochloride ER Capsules
120 mg, 180 mg, 240 mg, 300 mg, 360 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23, Supplement 8, Test 6.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,



Dale P. Conner, Pharm. D.

Director

Division of Bioequivalence

Office of Generic Drugs

Center for Drug Evaluation and Research

CC: ANDA 75401
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)

HFD-655/Dhariwal *MS 10/5/98*

HFD-655/Nerurkar

HFD-617/Sanchez

HFD-650/Dale Conner *MC 10/16/98*

AD 10/2/98

Printed in Final on 10/8/98

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BIOEQUIVALENCY - DEFICIENCIES

Submission Date: June 22, 1998

July 29, 1998

1.	FASTING STUDY (STF) Clinical: _____ Analytical: _____	Strengths: 360 mg Outcome: AC
2.	FOOD STUDY (STP) Clinical: _____ Analytical: _____	Strengths: 360 mg Outcome: AC
3.	MULTIPLE DOSE STUDY (STM) Clinical: _____ Analytical: _____	Strengths: 360 mg Outcome: AC
4.	DISSOLUTION WAIVER (DIW)	Strengths: 300 mg Outcome: AC
5.	DISSOLUTION WAIVER (DIW)	Strengths: 120 mg Outcome: AC
6.	DISSOLUTION WAIVER (DIW)	Strengths: 180 mg Outcome: AC
7.	DISSOLUTION WAIVER (DIW)	Strengths: 240 mg Outcome: AC

Outcome Decisions:

AC: Acceptable

WinBio Comments

Diltiazem Hydrochloride

Extended Release Capsules

120, 180, 240, 300, 360 mg

ANDA # 75-401

Reviewer: Kuldeep R. Dhariwal

File name: 75401SDW.698

Andrx Pharmaceuticals

4001 S.W. 47th Avenue

Ft. Lauderdale

Florida 33314

Submission Date:

June 22, 1998

July 29, 1998

**Review of Fasting, Non-Fasting, and Multi-Dose Studies,
Dissolution Data and Waiver Requests**

The firm submitted fasting, non-fasting, and multi-dose studies and dissolution data comparing its diltiazem hydrochloride ER capsule, 360 mg with Biovail's Tiazac® ER 360 mg capsule on June 22, 1998. The firm later submitted an amendment on July 29, 1998 requesting for a waiver of *in vivo* bioequivalence study requirements for its 120, 180, 240, and 300 mg capsules. To support the request, the firm submitted comparative dissolution profiles on 120, 180, 240, and 300 mg strengths of its product and reference listed drug Tiazac®, 120, 180, 240, and 300 mg capsules. This is a first generic for Tiazac® ER capsules. The usual starting doses are 120 to 240 mg once daily.

Introduction:

Tiazac® is a calcium ion cellular influx inhibitor indicated for the treatment of hypertension. It is well absorbed from gastrointestinal tract but undergoes substantial hepatic first-pass effect. The two primary metabolites are desacetyldiltiazem and desmethyldiltiazem. When Tiazac® was coadministered with a high fat content breakfast, the extent of diltiazem absorption was not affected; T_{max} , however, occurred slightly earlier. The apparent elimination half-life after single or multiple dosing is 4 to 9.5 hours. Tiazac® demonstrates non-linear pharmacokinetics.

Diltiazem hydrochloride extended release capsules are also marketed under brand name Cardizem CD (120 mg, 180 mg, 240 mg, 300 mg), Cardizem SR (60 mg, 90 mg, 120 mg), Dilacor XR (120 mg, 180 mg, 240 mg).

Bioequivalence Study Under Fasting Conditions:

A. Objective:

To assess the bioequivalence of a generic diltiazem hydrochloride extended release 360 mg capsule formulation, compared with Bivail's Tiazac® 360 mg capsule, following a single 360 mg dose.

B. Study Information:

Protocol #	P97-502
IRB Approval:	Yes
Consent Form Signed:	Yes
Clinical Site:	
Medical Investigator:	
Sub-Investigator:	
Sub-Investigator:	
Analytical Facility:	
Analytical Manager:	
Statistical Analysis:	
Study Dates:	Period I February 14-16, 1998 Period II February 21-23, 1998
Analysis Dates:	February 25 to March 21, 1998
Study Design:	Randomized, two-way crossover design with a wash-out period of 7 days
Randomization Scheme:	AB: 1,5,6,8,9,10,12,13,14,16,19,21,22,27,29, BA: 2,3,4,7,11,15,17,18,20,23,24,25,26,28,30

Treatments:

A: Diltiazem Hydrochloride Capsules, 1x360 mg; Andrx Pharmaceuticals; Lot #700R001A; Lot Size: _____ capsules; Manufacture Date: 11/26/97; Uniformity of Dosage Units: 100%

B: Tiazac® Capsules, 1x360 mg; Biovail; Lot #960108; Expiry Date: June 98; Uniformity of Dosage Units: 100.5%

Formulation of Test Product: Table 1

Subjects: 30 healthy male subjects were enrolled in the study according to inclusion/exclusion criteria specified in the protocol

Housing: At least 10 hour before dosing until at least 24 hours after dosing

Dosing: After 10 hour fast, with 240 mL of water. Water was not allowed from 1 hour prior to dosing until 2 hours after dosing. No food for 4 hours post-dose.

Sample Collection: Blood samples (10 mL) were collected into heparinized Vacutainers at predose (0 h) and at following times post-dose: 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 20, 24, 36, and 48 hours.

B. Study Results:

1. Clinical:

Drop-outs: None

Adverse Events: Thirty-three adverse events were reported. The events were comparable on test and reference products. The most often reported adverse events were headaches. Some subjects experienced first degree AV block, pharyngitis, and purpura.

Protocol Deviations: 1. There were a few sampling deviations. Pharmacokinetic parameters were calculated using the actual sampling times.

2. Analytical: NOT TO BE RELEASED UNDER FOI

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3. Pharmacokinetics/Statistics:

DILTIAZEM:

Mean Plasma Concentrations:	Table 2 and Figure 1	
Pharmacokinetic Parameters:	Table 2	
90% Confidence Intervals:	LAUC _{0-t}	89.75%-99.55%
	LAUC _{0-inf}	90.29%-99.62%
	LC _{max}	85.17%-101.60%
Test/Reference Ratios:	AUC _{0-t}	0.64-1.39 (mean 0.96)
	AUC _{0-inf}	0.65-1.33 (mean 0.96)
	C _{max}	0.59-1.78 (mean 0.97)
AUC _{0-t} /AUC _{0-inf} Ratios:	Test	0.77-1.00 (mean 0.97)
	Reference	0.90-1.00 (mean 0.97)

DESMETHYLDILTIAZEM:

Mean Plasma Concentrations:	Table 3 and Figure 2	
Pharmacokinetic Parameters:	Table 3	
90% Confidence Intervals:	LAUC _{0-t}	92.24%-98.97%
	LAUC _{0-inf}	94.88%-100.77%
	LC _{max}	89.05%-100.82%
Test/Reference Ratios:	AUC _{0-t}	0.78-1.23 (mean 0.96)
	AUC _{0-inf}	0.80-1.16 (mean 0.98)
	C _{max}	0.64-1.51 (mean 0.97)
AUC _{0-t} /AUC _{0-inf} Ratios:	Test	0.85-0.97 (mean 0.92)
	1 subject's ratios were 0.58	
	Reference	0.85-0.98 (mean 0.94)

DESACETYLDILTIAZEM:

Mean Plasma Concentrations:	Table 4 and Figure 3	
Pharmacokinetic Parameters:	Table 4	
90% Confidence Intervals:	LAUC _{0-t}	93.35%-102.19%
	LAUC _{0-inf}	95.31%-106.03%
	LC _{max}	93.43%-105.93%
Test/Reference Ratios:	AUC _{0-t}	0.75-1.26 (mean 0.99)
	AUC _{0-inf}	0.75-1.30 (mean 1.01)
	C _{max}	0.71-1.66 (mean 1.01)

AUC_{0-t}/AUC_{0-inf} Ratios:

Test	0.60-0.94 (mean 0.84)
Reference	0.62-0.96 (mean 0.88)

For some subjects ratios were very poor:

Treatment	Subject	Ratio
Test	8	0.60
Test	18	0.74
Test	24	0.76
Test	28	0.68
Reference	27	0.73
Reference	28	0.62

Comments:

1. The pharmacokinetic parameters and 90% confidence intervals were recalculated by the reviewer. The reported values are in good agreement with those obtained by the reviewer.

2. Desacetyldiltiazem: The elimination constant and therefore AUC_{0-inf} could not be calculated for subject #12, 16, 17, 19, 21, 22, 23, and 29 on test product and for subject #6, 12, 17, 19, 21, 22, 23, 26, and 30 on reference product.

3. No subjects with 0 h drug level, no subjects with first scheduled post-dose time point as T_{max}, and no subjects with first measurable drug concentration as C_{max}.

4. The 90% confidence intervals for log transformed AUC_{0-t}, AUC_{0-inf}, C_{max} for diltiazem, desmethyldiltiazem, and desacetyldiltiazem are within acceptable limits. There were no statistically significant period, sequence, or treatment effect for any of these parameters except for the following:

Desmethyldiltiazem: significant treatment effect for AUC_{0-t}

Desacetyldiltiazem: significant sequence effect for AUC_{0-t} and C_{max}.

Significant sequence effect is acceptable because it is a single-dose study, drug is not an endogenous entity, it includes only healthy subjects, and the study is based upon an acceptable study protocol, contains an acceptable validated assay method and acceptable confidence intervals are achieved.

5. The fasting study is acceptable.

Bioavailability Study Under Non-Fasting Conditions:

A. Study Information:

Protocol # P97-503
IRB Approval: Yes
Consent Form Signed: Yes
Clinical Site: _____
Medical Investigator: _____
Sub-Investigator: _____
Sub-Investigator: _____
Analytical Facility: _____
Analytical Manager: _____
Statistical Analysis: _____
Study Dates: Period I March 21-23, 1998
Period II March 28-30, 1998
Period III April 4-6, 1998
Analysis Dates: April 8 to May 3, 1998
Study Design: Randomized, three-period, three-treatment, six sequence crossover study with a wash-out period of 7 days.
Randomization Scheme: ABC: 6,12,21,23
CAB: 18,19,20,24
BCA: 1,7,15,22
CBA: 2,4,9,13
BAC: 3,8,16,17
ACB: 5,10,11,14

Treatments:

A: Diltiazem Hydrochloride ER Capsules, 1x360 mg; Andrx Pharmaceuticals, Inc.; Lot #700R001A; administered after an overnight fast

B: Diltiazem Hydrochloride ER Capsules, 1x360 mg; Andrx Pharmaceuticals, Inc.; Lot #700R001A; administered after a standard breakfast

C: Tiazac® Capsules, 1x360 mg; Biovail; Lot #960108; Expiry Date: June 1998; administered after a standard breakfast

Lot numbers of drug products administered in this study are the same as those for the fasting study.

Subjects: 24 male subjects were enrolled.
Housing: At least 10 hours before dosing until at least 24 hours after dosing
Dosing: Treatments B and C: Subjects were given OGD approved standardized breakfast 30 minutes before dosing after a fast lasting at least 10 hours. All subjects finished their entire breakfast within 30 minutes. The subjects were then immediately dosed with 240 mL of water.
Treatment A: Subjects were given assigned formulation with 240 mL of water after a 10 hour fast
Sample Collection: Blood samples (10 mL) were collected into heparinized Vacutainers at 0 (predose), 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 20, 24, 36, and 48 hours.

B. Study Results:

1. Clinical:

Drop-outs: Subject #17 withdrew prior to period II dosing for personal reasons.
Adverse Events: Sixty-nine adverse events were reported. The events were comparable on test and reference products. Most often reported adverse event was headache. Six subjects experienced first degree AV Block. Other reported adverse events were malaise, nausea, fatigue etc.
Protocol Deviations: 1. There were a few sampling deviations. Pharmacokinetic parameters were calculated using the actual sampling times.
2. Some subjects took ibuprofen for headaches. Subject #23 took sulfamethoxazole for testicular infection during the study.

2. Analytical: NOT TO BE RELEASED UNDER FOI

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samples for 20 weeks. Samples in the present study were stored for less than 43 days.

3. Pharmacokinetics/Statistics:

DILTIAZEM:

Mean Plasma Concentrations: Table 5, Figure 4

Pharmacokinetic Parameters: Table 6

Comparison of test and reference products after a meal: The ratios of arithmetic means, LS means, and geometric means for AUC_{0-t} , AUC_{0-inf} , and C_{max} are within acceptable limits (Table 6).

The AUC_{0-t}/AUC_{0-inf} ratios ranged from 0.71-0.99 (mean 0.97) for test fasting, from 0.97-1.00 (mean 0.99) for test non-fasting, and from 0.97-1.00 (mean 0.99) for reference non-fasting.

DESMETHYLDILTIAZEM:

Mean Plasma Concentrations: Table 7, Figure 5

Pharmacokinetic Parameters: Table 8

Comparison of test and reference products after a meal: The ratios of arithmetic means, LS means, and geometric means for AUC_{0-t} , AUC_{0-inf} , and C_{max} are within acceptable limits (Table 8).

The AUC_{0-t}/AUC_{0-inf} ratios ranged from 0.91-0.97 (mean 0.92, one subject had 0.43) for test fasting, from 0.91-0.98 (mean 0.96) for test non-fasting, and from 0.92-0.97 (mean 0.95) for reference non-fasting.

DESACETYLDILTIAZEM:

Mean Plasma Concentrations: Table 9, Figure 6

Pharmacokinetic Parameters: Table 10

Comparison of test and reference products after a meal: The ratios of arithmetic means, LS means, and geometric means for AUC_{0-t} , AUC_{0-inf} , and C_{max} are within acceptable limits (Table 10).

The AUC_{0-t}/AUC_{0-inf} ratios ranged from 0.81-0.95 (mean 0.87, ratio for subject #2, 0.64, subject #14, 0.65, and for subject #21, 0.72) for test fasting, from 0.83-0.96 (mean 0.87, ratio for subject #2, 0.62, subject #16, 0.63) for test non-fasting, and from 0.79-0.94 (mean 0.88, ratio for subject #2, 0.58) for reference non-fasting.

Comments:

1. The pharmacokinetic parameters and ratios of means were recalculated by the reviewer. The reported values are in good agreement with those obtained by the reviewer.
2. Desacetyldiltiazem: The elimination constant and therefore AUC_{0-inf} could not be calculated for subject #3 and 15 on test fasting conditions.
3. No subjects with 0 h drug level, no subjects with first scheduled post-dose time point as T_{max} , and no subjects with first measurable drug concentration as C_{max} .
4. The non-fasting study is acceptable.

**Bioavailability of Diltiazem HCl ER Capsules, 360 mg:
Multidose Study**

A. Study Information:

Protocol #	~97-504
IRB Approval:	Yes
Consent Form Signed:	Yes
Clinical Site:	_____
Medical Investigator:	_____
Sub-Investigator:	_____
Sub-Investigator:	_____
Analytical Facility:	_____
Analytical Manager:	_____
Statistical Analysis:	_____
Study Dates:	Period I March 28-April 4, 1998 Period II April 18-April 25, 1998
Analysis Dates:	May 4-21, 1998
Study Design:	Randomized, multi-dose, two-period,

two-treatment crossover study with a wash-out period of 15 days between dose 7 of period I and dose 1 of period II.

Randomization Scheme: AB: 2,4,5,6,9,11,12,13,14,17,22,25,27,28
BA: 1,3,7,8,10,15,16,18,19,20,21,23,
24,26

Treatments:

A: Diltiazem Hydrochloride ER Capsules; Andrx Pharmaceuticals, Inc.; Lot #700R001A

B: Tiazac® Capsules; Biovail; Lot #960108; Expiry Date: June 1998

Lot numbers of drug products administered in this study are the same as those for the fasting and non-fasting study.

Subjects: 28 male subjects were enrolled.

Housing: At least 10 hours before dosing until at least 168 hours after dose 1 each period

Dosing: The drug products were administered with 240 mL of water. The dose (1x360 mg) was administered at 0,24,48,72,96,120, and 144 hours (every 24 hours, 7 doses).

Sample Collection: Blood samples (10 mL) were collected into heparinized Vacutainers within one hour prior to dose 1 (0 hour), immediately prior to dose 2, dose 3, dose 4, dose 5, dose 6, dose 7 and after dose 7 at 1,2,3,4,5,6,7,8,10,12,14,16, 20, 24 hours.

B. Study Results:

1. Clinical:

Drop-outs: Subject #15 withdrew prior to period II dosing and subject #27 withdrew during period II.

Adverse Events: One hundred fifty-five adverse events were reported. The events were comparable on test and reference products. Most often reported adverse events were headaches and dyspepsia.

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3. Pharmacokinetics/Statistics:

DILTIAZEM:

Mean Plasma Concentrations:	Table 11, Figure 7	
Pharmacokinetic Parameters:	Table 11	
90% Confidence Intervals:	LAUC ₁₄₄₋₁₆₈	96.14%-107.38%
	LC _{max}	92.89%-112.34%
	LC _{min}	92.19%-107.96%
Percent Fluctuation:	Test 144, Reference 140	

DESMETHYLDILTIAZEM:

Mean Plasma Concentrations:	Table 12, Figure 8	
Pharmacokinetic Parameters:	Table 12	
90% Confidence Intervals:	LAUC ₁₄₄₋₁₆₈	98.26%-104.73%
	LC _{max}	98.59%-107.56%
	LC _{min}	95.77%-106.44%
Percent Fluctuation:	Test 86, Reference 84	

DESACETYLDILTIAZEM:

Mean Plasma Concentrations:	Table 13, Figure 9	
Pharmacokinetic Parameters:	Table 13	
90% Confidence Intervals:	LAUC ₁₄₄₋₁₆₈	100.03%-108.65%
	LC _{max}	102.69%-111.77%
	LC _{min}	95.98%-109.15%
Percent Fluctuation:	Test 63, Reference 58	

Comments:

1. The firm used plasma concentration at 144 h as C_{min} . The reviewer used the lowest concentration during 144-168 hour as C_{min} . The 90% CI as well as ratios of means between test and reference products are within acceptable limits.
2. The half-life of diltiazem is about 8 hours. Therefore steady state concentrations should theoretically reach in about 40 hours (5 half-lives). In this study, steady-state period was 144-168 hours.
3. The reviewer also checked the attainment of steady-state in individual subjects by PROC REG programme using plasma concentrations at 72, 96, 120, and 144 hours. All those subjects whose slopes showed significantly different from zero (p values <0.05) were dropped from statistical analyses. The analyses were repeated for diltiazem, desmethyldiltiazem, and desacetyldiltiazem. The 90% CI for $LAUC_{144-168}$, LC_{max} , and LC_{min} remained within acceptable limits for parent compound as well as metabolites.
4. Significant sequence effect for desacetyldiltiazem $LAUC_{144-168}$ and LC_{max} was observed. Significant treatment effect was observed for desacetyldiltiazem LC_{max} .
5. The multi-dose study is acceptable.

In Vitro Dissolution Testing:

The firm has submitted results of dissolution testing using

_____ at _____ The firm also performed
dissolution testing in _____

NOT TO BE RELEASED UNDER FOI: The innovator (Biovail) uses
_____ at _____ as medium.
Following are the specifications:

2h

4h

8h	
12h	NLT
16h	NLT

This is Test 6 method described for diltiazem hydrochloride ER capsules in USP 23 supplement 8.

The firm has used this method and the results are given in Table 14. The firm would be given the above specifications for manufacturing controls and stability programs.

Waiver Request:

The firm is requesting for waiver of *in vivo* bioequivalence study requirements for 120 mg, 180 mg, 240 mg, and 300 mg capsules. The compositions of all strengths are proportional to that of the highest strength (360 mg) and the capsules contain identical pellets (Table 1). The dissolution profiles of all strengths are similar to that of the 360 mg strength. The waiver can be granted.

NOT TO BE RELEASED UNDER FOI:

As per the current Division practice, biostudies are required on



Recommendations:

1. The *in vivo* bioequivalence study conducted under fasting conditions by Andrx on its Diltiazem Hydrochloride, 360 mg ER capsules, lot #700R001A, comparing it to the reference product Tiazac® 360 mg ER capsules, lot #960108 manufactured by Biovail has been found acceptable by the Division of Bioequivalence. The study demonstrates that Andrx Pharmaceutical's Diltiazem

Hydrochloride ER 360 mg capsule is bioequivalent to the reference product, Tiazac® ER 360 mg capsule manufactured by Biovail.

2. The *in vivo* bioequivalence study conducted under non-fasting conditions by Andrx on its Diltiazem Hydrochloride, 360 mg ER capsules, lot #700R001A, comparing it to the reference product Tiazac® 360 mg ER capsules, lot #960108 manufactured by Biovail has been found acceptable by the Division of Bioequivalence. The study demonstrates that under non-fasting conditions, the bioavailability of Andrx Pharmaceutical's Diltiazem Hydrochloride ER 360 mg capsule is similar to that of the reference product, Tiazac® ER 360 mg capsule manufactured by Biovail.

3. The multi-dose bioequivalence study conducted by Andrx Pharmaceuticals on its Diltiazem Hydrochloride ER, 360 mg capsule, lot #700R001A comparing it to the reference product Tiazac® 360 mg ER capsules, lot #960108 manufactured by Biovail has been found acceptable by the Division of Bioequivalence. The study demonstrates that Andrx Pharmaceutical's Diltiazem Hydrochloride ER 360 mg capsule is bioequivalent to the reference product, Tiazac® ER 360 mg capsule manufactured by Biovail.

4. The dissolution testing conducted by the firm on its Diltiazem Hydrochloride ER 360 mg capsules is acceptable. The firm has conducted acceptable *in vivo* bioequivalence studies comparing 360 mg capsule of the test product with 360 mg capsules of the reference product Tiazac® manufactured by Biovail. The formulation of the 120, 180, 240, and 300 mg strength of the test product is proportionally similar to the 360 mg strength of the test product which underwent bioequivalency testing. The waiver of *in vivo* bioequivalence study requirements for the 120, 180, 240, and 300 mg strength is granted. The 120, 180, 240, and 300 mg ER capsules of the test product are therefore deemed bioequivalent to the 120, 180, 240, and 300 mg capsules respectively of Tiazac® manufactured by Biovail.

5. The dissolution testing should be incorporated into firm's manufacturing controls and stability programs. The dissolution testing should be conducted in _____

_____ The test product should meet the following interim specifications:

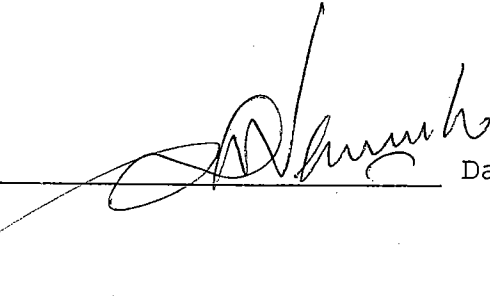
2h not more than —
4h between —
8h between —
12h not less than —
16h not less than —

6. From bioequivalence point of view, the firm has met the requirements of *in vivo* bioequivalency and *in vitro* dissolution testing and the application is acceptable.

Meharwal

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S.NERURKAR
FT INITIALED S.NERURKAR

 Date 10/9/1998

Concur: Dale P. Conner Date 10/16/98
Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence

Draft: 092498; Final: 100898

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Table 2
MEAN PLASMA DILTIAZEM LEVELS FOR TEST (1) AND REFERENCE (2) PRODUCTS
IN FASTING STUDY, N=30

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	4.88	4.31	5.75	6.45	0.85
2	32.00	16.65	34.68	25.76	0.92
3	54.48	28.18	77.57	43.36	0.70
4	84.82	48.05	111.96	53.39	0.76
5	146.54	73.91	160.88	65.73	0.91
6	155.50	67.97	174.85	89.12	0.89
7	159.32	68.18	168.50	85.44	0.95
8	163.76	67.91	176.17	93.12	0.93
10	147.96	57.67	167.54	97.13	0.88
12	140.67	50.99	158.90	87.27	0.89
16	115.01	46.75	124.66	69.28	0.92
20	79.17	32.19	85.37	42.60	0.93
24	64.55	26.06	67.61	34.57	0.95
36	23.30	13.33	21.98	13.34	1.06
48	6.32	5.12	5.66	5.05	1.12

ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	3306.53	1252.97	3568.70	1726.77	0.93
AUCT	3195.40	1213.59	3471.87	1717.74	0.92
CMAX	184.09	70.70	202.67	96.61	0.91
KE	0.10	0.03	0.10	0.03	0.97
LAUCI	3089.18	0.38	3257.29	0.42	0.95
LAUCT	2984.39	0.38	3157.31	0.43	0.95
LCMAX	171.81	0.38	184.70	0.43	0.93
THALF	7.69	2.75	7.30	2.08	1.05
TMAX	7.97	2.61	7.93	2.99	1.00

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	3306.53	3568.70	0.93	85.83	99.48
AUCT	3195.40	3471.87	0.92	84.93	99.14
CMAX	184.09	202.67	0.91	80.75	100.91
LAUCI	3089.18	3257.29	0.95	90.29	99.62
LAUCT	2984.39	3157.31	0.95	89.75	99.55
LCMAX	171.81	184.70	0.93	85.17	101.60

TABLE 3
MEAN PLASMA DESMETHYLDILTIAZEM LEVELS FOR TEST (1) AND REFERENCE (2)
PRODUCTS IN FASTING STUDY, N=30

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	0.40	0.93	0.26	0.80	1.58
2	6.31	2.23	6.61	2.81	0.95
3	11.18	2.59	14.73	3.81	0.76
4	17.28	4.62	21.83	5.39	0.79
5	27.64	8.62	30.77	6.74	0.90
6	32.66	9.20	34.94	8.38	0.93
7	35.68	9.97	37.47	9.86	0.95
8	37.94	10.25	40.37	11.76	0.94
10	39.08	10.46	41.71	13.03	0.94
12	39.94	8.75	42.69	13.19	0.94
16	36.80	9.07	38.05	11.99	0.97
20	28.40	7.08	29.95	9.12	0.95
24	24.07	6.06	24.95	7.76	0.96
36	11.81	4.12	11.46	4.32	1.03
48	4.19	2.32	4.14	2.16	1.01

UNIT: PLASMA LEVEL=NG/ML TIME=HRS
ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	1089.30	252.35	1119.43	296.72	0.97
AUCT	996.03	229.08	1049.27	286.21	0.95
CMAX	42.61	9.71	45.48	13.17	0.94
KE	0.07	0.01	0.07	0.02	0.94
LAUCI	1060.22	0.24	1084.26	0.25	0.98
LAUCT	969.37	0.24	1014.54	0.26	0.96
LCMAX	41.53	0.23	43.83	0.27	0.95
THALF	10.62	3.00	9.91	2.27	1.07
TMAX	11.10	2.89	10.40	2.98	1.07

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	1089.30	1119.43	0.97	93.86	100.76
AUCT	996.03	1049.27	0.95	91.08	98.77
CMAX	42.60	45.48	0.94	87.01	100.33
LAUCI	1060.22	1084.26	0.98	94.88	100.77
LAUCT	969.37	1014.54	0.96	92.24	98.97
LCMAX	41.53	43.83	0.95	89.05	100.82

TABLE 4
MEAN PLASMA DESACETYLDILTIAZEM LEVELS FOR TEST (1) AND REFERENCE (2)
PRODUCTS IN FASTING STUDY, N=30

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	0.00	0.00	0.00	0.00	.
2	0.16	0.63	0.19	0.74	0.86
3	1.55	1.62	2.45	1.80	0.63
4	3.57	2.42	4.97	2.24	0.72
5	6.91	3.91	7.91	3.91	0.87
6	8.95	4.52	10.14	4.61	0.88
7	11.01	5.45	11.43	5.19	0.96
8	13.08	7.68	13.15	5.56	0.99
10	14.72	7.76	14.81	6.42	0.99
12	15.77	9.09	15.93	8.11	0.99
16	16.99	11.33	16.77	10.44	1.01
20	15.37	10.61	15.51	10.47	0.99
24	14.94	12.33	14.65	10.71	1.02
36	9.02	12.66	7.88	9.94	1.15
48	3.61	7.39	3.17	6.68	1.14

UNIT: PLASMA LEVEL=NG/ML TIME=HRS
ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	505.59	346.32	486.86	304.03	1.04
AUCT	492.67	441.88	482.60	371.97	1.02
CMAX	18.38	12.75	18.08	11.03	1.02
KE	0.06	0.02	0.07	0.02	0.88
LAUCI	439.19	0.51	433.23	0.46	1.01
LAUCT	384.41	0.66	393.59	0.61	0.98
LCMAX	15.64	0.54	15.72	0.51	0.99
THALF	11.93	3.67	10.33	2.82	1.15
TMAX	15.43	5.43	13.40	4.11	1.15

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	509.76	497.75	1.02	96.95	107.88
AUCT	492.67	482.60	1.02	95.99	108.18
CMAX	18.38	18.08	1.02	94.62	108.64
LAUCI	444.68	442.36	1.01	95.31	106.03
LAUCT	384.41	393.59	0.98	93.35	102.19
LCMAX	15.64	15.72	0.99	93.43	105.93

* N=22
* N=21

TABLE 5
MEAN PLASMA DILTIAZEM LEVELS FOR TEST AND REFERENCE PRODUCTS IN NON-FASTING STUDY, N=23

TIME HR	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
0	0.00	0.00	0.00	0.00	0.00	0.00	.
1	9.04	8.95	3.56	10.04	0.43	1.21	2.54
2	43.59	23.31	20.73	22.93	14.94	17.75	2.10
3	70.47	28.40	57.33	33.22	69.17	39.85	1.23
4	121.29	54.91	107.32	61.40	134.80	66.12	1.13
5	218.60	93.80	236.00	91.68	248.87	69.78	0.93
6	227.83	79.35	262.13	91.35	252.30	72.84	0.87
7	222.65	78.68	266.96	87.75	240.65	73.78	0.83
8	223.91	80.39	258.61	84.98	229.96	66.65	0.87
10	191.44	64.15	231.61	88.61	200.43	54.44	0.83
12	173.00	64.63	198.78	71.59	177.40	51.33	0.87
16	133.53	69.08	145.54	58.56	132.26	47.08	0.92
20	94.57	53.15	100.50	44.90	92.51	38.38	0.94
24	70.74	32.44	74.47	33.82	69.90	30.00	0.95
36	23.53	14.73	19.58	11.63	19.01	11.76	1.20
48	6.68	5.06	4.60	4.09	5.21	4.27	1.45

(CONTINUED)

UNIT: PLASMA LEVEL=NG/ML TIME=HRS
MEAN PLASMA DILTIAZEM LEVELS FOR TEST AND REFERENCE PRODUCTS

TIME HR	RMEAN13	RMEAN23
0	.	.
1	21.21	8.36
2	2.92	1.39
3	1.02	0.83
4	0.90	0.80
5	0.88	0.95
6	0.90	1.04
7	0.93	1.11
8	0.97	1.12
10	0.96	1.16
12	0.98	1.12
16	1.01	1.10
20	1.02	1.09
24	1.01	1.07
36	1.24	1.03
48	1.28	0.88

1= TEST FASTING
2= TEST NON-FASTING
3= REF. NON-FASTING

TABLE 6

DILTIAZEM ARITHMETIC MEANS AND RATIOS IN NON-FASTING STUDY, N=23

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
PARAMETER							
AUCI	4045.39	1590.29	4285.22	1633.52	4013.48	1352.01	0.94
AUCT	3902.87	1537.47	4224.13	1611.69	3954.70	1320.49	0.92
CMAX	262.22	88.73	284.91	97.14	263.00	73.35	0.92
KE	0.10	0.02	0.12	0.02	0.11	0.02	0.86
LAUCI	3788.65	0.36	4019.36	0.36	3808.90	0.33	0.94
LAUCT	3659.65	0.36	3961.56	0.36	3755.30	0.33	0.92
LCMAX	247.86	0.35	269.23	0.35	252.94	0.29	0.92
THALF	7.28	1.79	6.07	0.95	6.37	1.06	1.20
TMAX	6.74	2.05	6.70	1.55	5.83	0.89	1.01

(CONTINUED)

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
 LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
 ARITHMETIC MEANS AND RATIOS

	RMEAN13	RMEAN23
PARAMETER		
AUCI	1.01	1.07
AUCT	0.99	1.07
CMAX	1.00	1.08
KE	0.90	1.05
LAUCI	0.99	1.06
LAUCT	0.97	1.05
LCMAX	0.98	1.06
THALF	1.14	0.95
TMAX	1.16	1.15

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
 LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
 LSMEANS AND RATIOS

	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
PARAMETER						
AUCI	4058.39	4296.88	4038.74	0.94	1.00	1.06
AUCT	3909.40	4231.86	3975.81	0.92	0.98	1.06
CMAX	264.87	287.51	266.25	0.92	0.99	1.08
LAUCI	3805.76	4035.15	3838.22	0.94	0.99	1.05
LAUCT	3670.63	3973.33	3780.82	0.92	0.97	1.05
LCMAX	250.12	271.60	256.05	0.92	0.98	1.06

1= TEST FASTING
 2= TEST NON-FASTING
 3= REF NON-FASTING

TABLE 7

MEAN PLASMA DESMETHYLDILTIAZEM LEVELS FOR TEST AND REFERENCE PRODUCTS IN NON-FASTING STUDY, N=23

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
TIME HR							
0	0.00	0.00	0.00	0.00	0.00	0.00	.
1	0.77	1.63	0.32	1.11	0.00	0.00	2.41
2	8.09	3.68	3.02	3.65	2.00	2.99	2.68
3	13.97	3.26	10.93	4.98	12.62	6.29	1.28
4	23.14	5.91	21.45	7.74	26.67	9.13	1.08
5	38.98	11.18	44.40	12.08	49.02	8.98	0.88
6	44.97	11.05	56.22	14.12	57.48	12.36	0.80
7	48.22	11.85	61.86	15.17	60.16	13.36	0.78
8	50.01	12.00	63.41	14.97	62.15	14.95	0.79
10	50.78	12.79	60.71	14.41	58.14	13.13	0.84
12	49.49	12.37	57.73	13.14	54.70	12.28	0.86
16	41.44	11.09	46.77	11.74	44.63	10.31	0.89
20	32.87	9.81	35.83	9.58	34.70	8.28	0.92
24	26.83	8.00	28.70	8.34	27.17	7.17	0.94
36	13.00	6.55	12.20	5.46	11.43	4.64	1.07
48	4.67	2.91	3.99	2.52	4.25	2.34	1.17

(CONTINUED)

UNIT: PLASMA LEVEL=NG/ML TIME=HRS

MEAN PLASMA DESMETHYLDILTIAZEM LEVELS FOR TEST AND REFERENCE PRODUCTS

	RMEAN13	RMEAN23
TIME HR		
0	.	.
1	.	.
2	4.05	1.51
3	1.11	0.87
4	0.87	0.80
5	0.80	0.91
6	0.78	0.98
7	0.80	1.03
8	0.80	1.02
10	0.87	1.04
12	0.90	1.06
16	0.93	1.05
20	0.95	1.03
24	0.99	1.06
36	1.14	1.07
48	1.10	0.94

1= TEST FASTING
2= TEST NON-FASTING
3= REF NON-FASTING

TABLE 8

DESMETHYLDILTIAZEM ARITHMETIC MEANS AND RATIOS IN NON-FASTING STUDY, N=23

PARAMETER	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
AUCI	1294.78	377.36	1373.13	375.19	1342.48	335.41	0.94
AUCT	1175.00	341.74	1310.57	347.10	1276.26	308.11	0.90
CMAX	54.09	12.18	65.27	16.03	63.49	15.02	0.83
KE	0.07	0.02	0.08	0.01	0.08	0.01	0.87
LAUCI	1246.50	0.28	1325.33	0.27	1303.40	0.25	0.94
LAUCT	1131.32	0.28	1266.90	0.27	1240.67	0.25	0.89
LCMAX	52.88	0.22	63.50	0.24	61.88	0.23	0.83
THALF	10.53	3.25	8.79	1.35	9.34	1.39	1.20
TMAX	9.22	2.02	8.39	1.78	8.17	1.53	1.10

(CONTINUED)

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
 LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
 ARITHMETIC MEANS AND RATIOS

PARAMETER	RMEAN13	RMEAN23
AUCI	0.96	1.02
AUCT	0.92	1.03
CMAX	0.85	1.03
KE	0.92	1.07
LAUCI	0.96	1.02
LAUCT	0.91	1.02
LCMAX	0.85	1.03
THALF	1.13	0.94
TMAX	1.13	1.03

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
 LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
 LSMEANS AND RATIOS

PARAMETER	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
AUCI	1292.78	1369.90	1340.34	0.94	0.96	1.02
AUCT	1169.35	1305.13	1271.95	0.90	0.92	1.03
CMAX	53.93	65.08	63.37	0.83	0.85	1.03
LAUCI	1245.34	1322.95	1302.45	0.94	0.96	1.02
LAUCT	1126.42	1261.78	1237.15	0.89	0.91	1.02
LCMAX	52.77	63.34	61.82	0.83	0.85	1.02

1= TEST FASTING
 2= TEST NON-FASTING
 3= REF NON-FASTING

TABLE 9

MEAN PLASMA DESACETYLDILTIAZEM LEVELS FOR TEST AND REFERENCE PRODUCTS IN NON-FASTING STUDY, N=23

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
TIME HR							
0	0.00	0.00	0.00	0.00	0.00	0.00	.
1	0.00	0.00	0.00	0.00	0.00	0.00	.
2	0.38	1.03	0.19	0.90	0.00	0.00	2.01
3	1.66	1.85	0.69	1.64	1.24	1.85	2.40
4	4.56	2.12	3.66	2.05	4.67	2.77	1.24
5	8.98	4.62	8.71	3.24	9.74	3.38	1.03
6	12.07	6.35	12.51	5.05	13.13	5.23	0.97
7	14.95	8.88	15.74	7.35	15.32	6.90	0.95
8	16.64	10.43	17.98	9.24	17.41	8.19	0.93
10	18.71	12.41	20.81	13.05	18.69	9.73	0.90
12	19.57	14.87	21.38	15.33	19.43	12.10	0.92
16	19.07	17.89	20.32	15.99	18.28	14.61	0.94
20	18.20	19.06	18.33	15.69	17.23	14.05	0.99
24	17.08	23.72	16.26	17.46	15.29	15.93	1.05
36	5.29	4.87	6.84	10.99	6.68	10.10	0.77
48	1.48	2.59	2.05	5.78	1.66	4.34	0.72

(CONTINUED)

UNIT: PLASMA LEVEL=NG/ML TIME=HRS
 MEAN PLASMA DESACETYLDILTIAZEM LEVELS FOR TEST AND REFERENCE PRODUCTS

	RMEAN13	RMEAN23
TIME HR		
0	.	.
1	.	.
2	.	.
3	1.34	0.56
4	0.98	0.79
5	0.92	0.89
6	0.92	0.95
7	0.98	1.03
8	0.96	1.03
10	1.00	1.11
12	1.01	1.10
16	1.04	1.11
20	1.06	1.06
24	1.12	1.06
36	0.79	1.02
48	0.89	1.24

1= TEST FASTING
 2= TEST NON-FASTING
 3= REF NON-FASTING

TABLE 10

DESACETYLDILTIAZEM ARITHMETIC MEANS AND RATIOS IN NON-FASTING STUDY, N=23

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
PARAMETER							
AUCI	490.05	281.26	608.13	631.79	580.57	590.73	0.81
AUCT	470.74	345.08	534.48	535.79	513.78	517.57	0.88
CMAX	22.30	22.98	22.54	16.67	21.13	15.22	0.99
KE	0.07	0.02	0.08	0.02	0.08	0.02	0.92
LAUCI	442.19	0.42	485.65	0.57	465.46	0.57	0.91
LAUCT	397.36	0.54	422.52	0.61	408.24	0.60	0.94
LCMAX	18.00	0.56	19.53	0.48	18.55	0.45	0.92
THALF	9.99	2.28	9.15	2.00	9.27	2.19	1.09
TMAX	11.83	4.10	11.52	3.86	11.13	3.85	1.03

(CONTINUED)

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
 LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
 ARITHMETIC MEANS AND RATIOS

	RMEAN13	RMEAN23
PARAMETER		
AUCI	0.84	1.05
AUCT	0.92	1.04
CMAX	1.06	1.07
KE	0.93	1.01
LAUCI	0.95	1.04
LAUCT	0.97	1.03
LCMAX	0.97	1.05
THALF	1.08	0.99
TMAX	1.06	1.04

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
 LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
 LSMEANS AND RATIOS

	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
PARAMETER						
AUCI	630.76	637.41	610.75	0.99	1.03	1.04
AUCT	490.35	554.95	535.52	0.88	0.92	1.04
CMAX	23.28	23.42	22.06	0.99	1.05	1.06
LAUCI	485.63	494.91	475.33	0.98	1.02	1.04
LAUCT	404.76	429.16	416.18	0.94	0.97	1.03
LCMAX	18.39	19.90	18.96	0.92	0.97	1.05

1= TEST FASTING
 2= TEST NON-FASTING
 3= REF NON-FASTING

TABLE 11

MEAN PLASMA DILTIAZEM LEVELS FOR TEST (1) AND REFERENCE (2)
PRODUCTS IN MULTI-DOSE STUDY, N=26

TIME HR	MEAN1	SD1	MEAN2	SD2	RMEAN12
0	0		0		
24	67.48	26.96	70.25	26.95	0.96
48	72.00	28.32	75.81	31.31	0.95
72	72.06	27.47	72.01	32.97	1.00
96	73.34	31.38	72.69	28.23	1.00
120	76.68	33.55	78.81	33.48	0.97
144	78.22	31.98	83.51	36.73	0.94
145	90.22	37.08	92.31	43.59	0.98
146	139.08	54.19	141.63	60.10	0.98
147	171.26	59.31	219.04	82.03	0.78
148	222.22	82.45	264.91	113.64	0.84
149	293.00	112.65	310.00	125.48	0.95
150	314.58	115.58	297.19	103.41	1.06
151	300.12	95.45	285.85	93.93	1.05
152	300.77	115.61	270.15	87.82	1.11
154	255.62	94.75	239.31	89.84	1.07
156	227.77	80.03	220.52	84.31	1.03
158	197.62	71.29	192.22	75.70	1.03
160	169.48	65.92	167.91	70.92	1.01
164	112.33	45.89	111.84	54.34	1.00
168	74.77	31.36	75.87	38.01	0.99

UNIT: PLASMA LEVEL=NG/ML TIME=HRS
ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCT	4490.05	1537.32	4464.84	1664.62	1.01
CAVG	187.09	64.06	186.03	69.36	1.01
CMAX	338.81	130.10	329.46	123.84	1.03
CMIN	71.21	31.12	73.15	35.92	0.97
FLUC1	1.44	0.37	1.40	0.25	1.02
LAUCT	4225.79	0.37	4159.04	0.39	1.02
LCAVG	176.07	0.37	173.29	0.39	1.02
LCMAX	314.26	0.41	307.64	0.38	1.02
LCMIN	64.82	0.45	64.98	0.50	1.00
LFLUC1	1.40	0.24	1.38	0.18	1.01
TMAX	6.92		6.12		1.13

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	LOWCI12	UPPCI12
PARAMETER				
AUCT	4490.05	4464.84	95.35	105.78
CAVG	187.09	186.03	95.35	105.78
CMAX	338.81	329.46	92.96	112.71
CMIN	71.21	73.15	90.54	104.16
FLUC1	1.44	1.40	93.91	111.02
LAUCT	4225.79	4159.04	96.14	107.38
LCAVG	176.07	173.29	96.14	107.38
LCMAX	314.26	307.64	92.89	112.34
LCMIN	64.82	64.98	92.19	107.96
LFLUC1	1.40	1.38	93.46	109.34

TABLE 12

MEAN PLASMA DESMETHYLDILTIAZEM LEVELS FOR TEST (1) AND REFERENCE (2)
PRODUCTS IN MULTI-DOSE STUDY, N=26

TIME HR	MEAN1	SD1	MEAN2	SD2	RMEAN12
0	0		0		
24	26.50	9.01	26.54	6.95	1.00
48	30.79	9.96	31.25	9.21	0.98
72	31.35	9.65	30.94	11.28	1.01
96	32.51	11.08	31.62	9.10	1.03
120	33.49	12.22	33.08	10.57	1.01
144	35.05	12.54	36.11	12.39	0.97
145	35.12	11.81	35.96	13.18	0.98
146	41.18	13.18	41.50	13.20	0.99
147	46.36	14.52	51.28	15.30	0.90
148	53.78	17.32	57.88	17.03	0.93
149	62.63	20.09	67.61	21.89	0.93
150	71.44	23.03	72.33	23.94	0.99
151	76.53	23.60	75.57	23.22	1.01
152	79.50	26.76	76.43	25.27	1.04
154	76.77	26.08	72.28	23.38	1.06
156	73.67	24.80	70.52	23.08	1.04
158	67.24	21.41	64.25	19.57	1.05
160	60.60	20.22	59.11	19.93	1.03
164	45.33	16.13	44.95	18.10	1.01
168	33.92	11.66	33.58	13.18	1.01

UNIT: PLASMA LEVEL=NG/ML TIME=HRS
ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCT	1390.15	443.01	1373.18	444.49	1.01
CAVG	57.92	18.46	57.22	18.52	1.01
CMAV	82.14	27.32	79.42	24.85	1.03
CMIN	32.63	12.01	32.43	12.12	1.01
FLUC1	0.86	0.18	0.84	0.17	1.03
LAUCT	1332.83	0.29	1313.84	0.30	1.01
LCAVG	55.53	0.29	54.74	0.30	1.01
LCMAV	78.51	0.30	76.23	0.28	1.03
LCMIN	30.75	0.35	30.46	0.36	1.01
LFLUC1	0.84	0.22	0.82	0.21	1.03
TMAX	9.15		8.31		1.10

UNIT: AUC=NG HR/ML CMAV=NG/ML TMAX=HR
LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	LOWCI12	UPPCI12
PARAMETER				
AUCT	1390.15	1373.18	98.21	104.26
CAVG	57.92	57.22	98.21	104.26
CMAV	82.14	79.42	98.95	107.91
CMIN	32.63	32.43	96.34	104.91
FLUC1	0.86	0.84	97.19	108.61
LAUCT	1332.83	1313.84	98.26	104.73
LCAVG	55.53	54.74	98.26	104.73
LCMAV	78.51	76.23	98.59	107.56
LCMIN	30.75	30.46	95.77	106.44
LFLUC1	0.84	0.82	96.85	109.09

TABLE 13
MEAN PLASMA DESACETYLDILTIAZEM LEVELS FOR TEST (1) AND REFERENCE (2)
PRODUCTS IN MULTI-DOSE STUDY, N=26

TIME HR	MEAN1	SD1	MEAN2	SD2	RMEAN12
0	0		0		
24	19.20	14.18	19.71	15.86	0.97
48	28.34	26.72	27.38	24.10	1.03
72	31.19	31.73	30.66	31.82	1.02
96	32.14	33.67	30.94	30.81	1.04
120	30.94	31.16	30.07	29.01	1.02
144	31.62	30.97	31.15	29.19	1.02
145	31.38	32.47	30.44	30.06	1.03
146	31.23	31.42	31.23	31.29	1.00
147	32.73	32.21	33.45	31.56	0.98
148	34.39	32.61	35.75	32.63	0.96
149	37.23	33.79	38.10	33.71	0.98
150	42.38	35.62	41.56	35.58	1.02
151	44.35	36.35	42.95	36.70	1.03
152	46.23	38.09	43.95	37.12	1.05
154	46.88	39.01	43.42	36.16	1.08
156	45.23	39.82	42.10	36.33	1.07
158	44.00	38.59	41.10	36.24	1.07
160	41.99	38.87	39.43	35.07	1.06
164	34.85	32.65	34.88	32.86	1.00
168	31.00	33.12	30.09	31.33	1.03

UNIT: PLASMA LEVEL=NG/ML TIME=HRS
ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCT	938.42	851.19	906.19	814.80	1.04
CAVG	39.10	35.47	37.76	33.95	1.04
CMAV	48.55	39.53	45.71	37.50	1.06
CMIN	28.70	29.93	28.52	29.34	1.01
FLUC1	0.63	0.22	0.58	0.23	1.09
LAUCT	698.76	0.73	670.28	0.75	1.04
LCAVG	29.11	0.73	27.93	0.75	1.04
LCMAV	37.98	0.67	35.45	0.69	1.07
LCMIN	19.61	0.82	19.16	0.87	1.02
LFLUC1	0.59	0.38	0.54	0.40	1.10
TMAX	9.96		9.00		1.10

UNIT: AUC=NG HR/ML CMAV=NG/ML TMAX=HR
LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	LOWCI12	UPPCI12
PARAMETER				
AUCT	938.42	906.19	100.67	106.44
CAVG	39.10	37.76	100.67	106.44
CMAV	48.55	45.71	102.87	109.55
CMIN	28.70	28.52	97.16	104.16
FLUC1	0.63	0.58	100.40	116.67
LAUCT	698.76	670.28	100.03	108.65
LCAVG	29.11	27.93	100.03	108.65
LCMAV	37.98	35.45	102.69	111.77
LCMIN	19.61	19.16	95.98	109.15
LFLUC1	0.59	0.54	100.98	118.74

Table 14 . In Vitro Dissolution Testing

Drug (Generic Name): Diltiazem Hydrochloride ER Capsules

Dose Strength: 120, 180, 240, 300, and 360 mg

ANDA No.: 75-401

Firm: Andrx Pharmaceuticals

Submission Date: June 22, 1998; July 29, 1998

File Name: 75401SDW.698

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle: X RPM: —

No. Units Tested: 12

Medium: Water Volume: —

Specifications: see text

Reference Drug: Tiazac® (Biovail)

Assay Methodology: —

II. Results of In Vitro Dissolution Testing:

Sampling Times (Hours)	Test Product Lot # 696R001 Strength(mg) 120			Reference Product Lot # 960115 Strength(mg) 120		
	Mean %	Range	%CV	Mean %	Range	%CV
2	15		15.8	14		8.4
4	29		9.9	35		8.0
8	71		4.3	64		6.2
12	89		3.7	77		5.0
16	96		3.5	85		4.4

Sampling Times (Hours)	Test Product Lot # 697R001 Strength(mg) 180			Reference Product Lot # 961112 Strength(mg) 180		
	Mean %	Range	%CV	Mean %	Range	%CV
2	14		10.6	12		12.9
4	30		7.3	35		5.9
8	72		2.5	65		3.5
12	90		1.8	79		2.8
16	97		1.7	86		2.5

Continued....

Table 14 . In Vitro Dissolution Testing

Drug (Generic Name): Diltiazem Hydrochloride ER capsules
 Dose Strength: 120, 180, 240, 300, and 360 mg
 ANDA No.: 75401
 Firm: Andrx Pharmaceuticals
 Submission Date: June 22, 1998; July 29, 1998
 File Name: 75401SDW.698

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle: X RPM: _____
 No. Units Tested: 12
 Medium: Water Volume: _____
 Specifications: see text
 Reference Drug: Tiazac® (Biovail)
 Assay Methodology: _____

II. Results of In Vitro Dissolution Testing:

Sampling Times (Hours)	Test Product Lot # 698R001 Strength(mg) 240			Reference Product Lot # 970615 Strength(mg) 240		
	Mean %	Range	%CV	Mean %	Range	%CV
2	14	_____	11.4	22	_____	5.9
4	29	_____	6.6	51	_____	3.0
8	71	_____	3.1	79	_____	1.6
12	89	_____	2.7	90	_____	1.6
16	97	_____	2.6	95	_____	1.3

Sampling Times (Hours)	Test Product Lot # 699R001 Strength(mg) 300			Reference Product Lot # 970923 Strength(mg) 300		
	Mean %	Range	%CV	Mean %	Range	%CV
2	14	_____	15.8	15	_____	4.5
4	29	_____	7.7	46	_____	2.2
8	72	_____	2.3	78	_____	1.5
12	89	_____	2.0	90	_____	1.5
16	97	_____	2.0	96	_____	1.5

Continued.... Table 14 . In Vitro Dissolution Testing						
Drug (Generic Name): Diltiazem Hydrochloride ER capsules Dose Strength: 120, 180, 240, 300, and 360 mg ANDA No.: 75401 Firm: Andrx Pharmaceuticals Submission Date: June 22,1998; July 29, 1998 File Name: 75401SDW.698						
I. Conditions for Dissolution Testing:						
USP XXII Basket: Paddle: X RPM: ~~100~~ No. Units Tested: 12 Medium: ~~Water~~ Volume: ~~500 mL~~ Specifications: see text Reference Drug: Tiazac® (Biovail) Assay Methodology: ~~UV Spectrophotometry~~						
II. Results of In Vitro Dissolution Testing:						
Sampling Times (Hours)	Test Product Lot # 700R001 Strength(mg) 360			Reference Product Lot # 960108 Strength(mg) 360		
	Mean %	Range	%CV	Mean %	Range	%CV
2	14		6.8	16		5.4
4	29		5.6	38		4.1
8	72		4.6	66		3.0
12	90		3.3	79		2.8
16	97		2.7	86		2.7

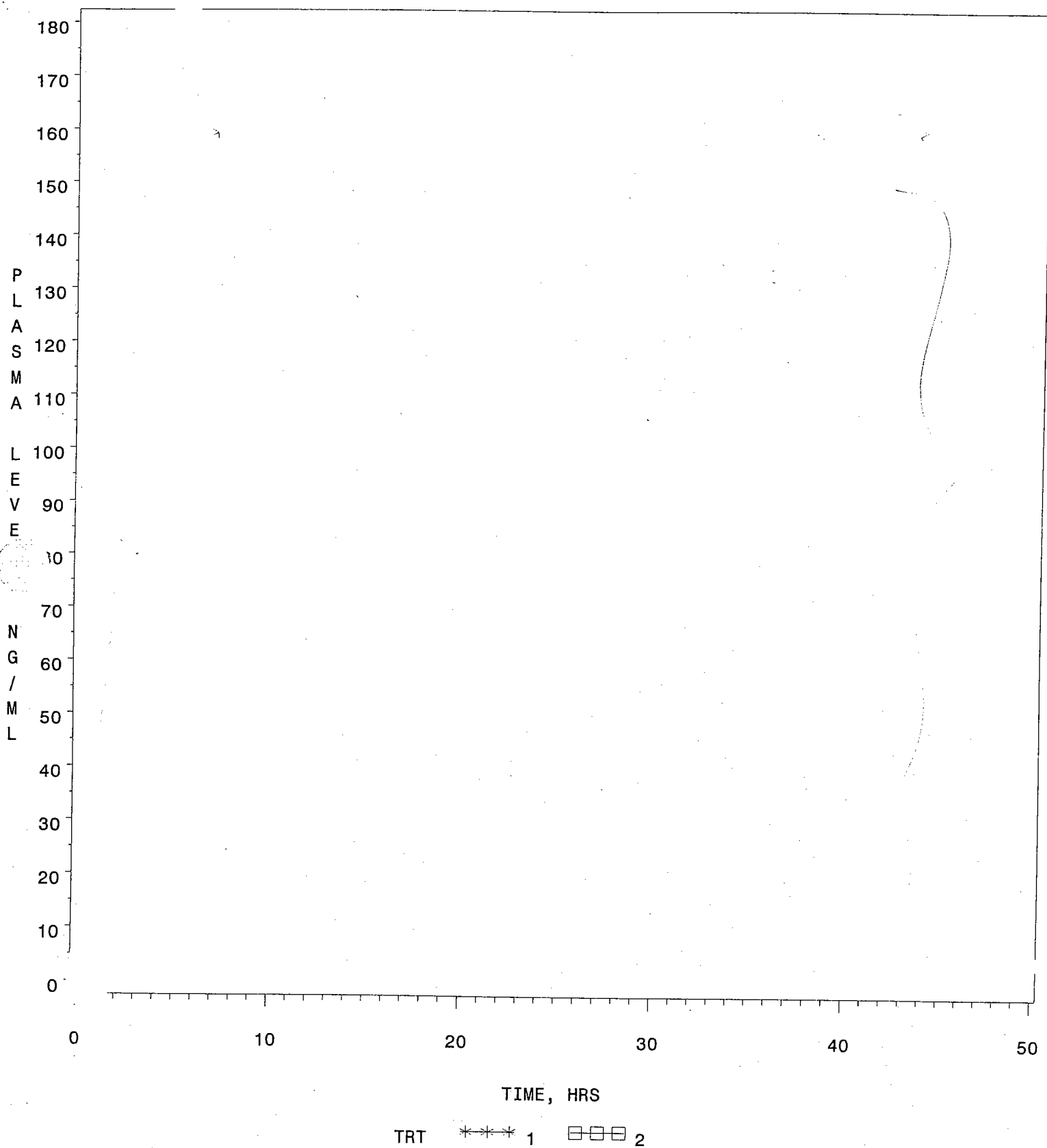
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FIG 1. PLASMA DILTIAZEM LEVELS

DILTIAZEM HYDROCHLORIDE ER CAPSULES, 360 MG, ANDA #75-401

UNDER FASTING CONDITIONS

DOSE=1 X 360 MG



1=TEST (ANDRX) 2=REF (BIOVAIL)

FIG 2. PLASMA DESMETHYLDILTIAZEM LEVELS

DILTIAZEM HYDROCHLORIDE ER CAPSULES, 360 MG, ANDA #75-401

UNDER FASTING CONDITIONS

DOSE=1 X 360 MG

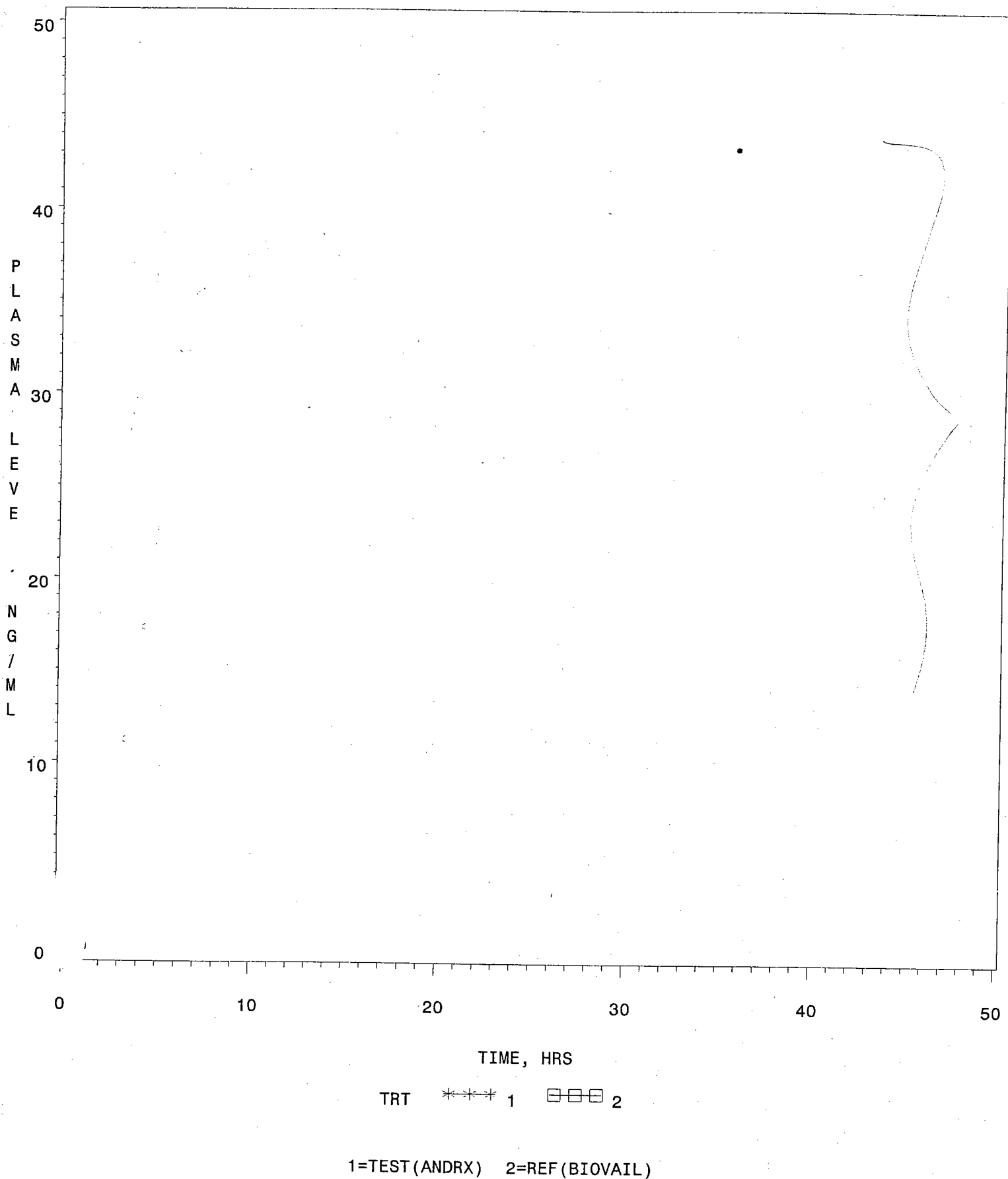


FIG 3. PLASMA DESACETYLDILTIAZEM LEVELS

DILTIAZEM HYDROCHLORIDE ER CAPSULES, 360 MG, ANDA #75-401

UNDER FASTING CONDITIONS

DOSE=1 X 360 MG

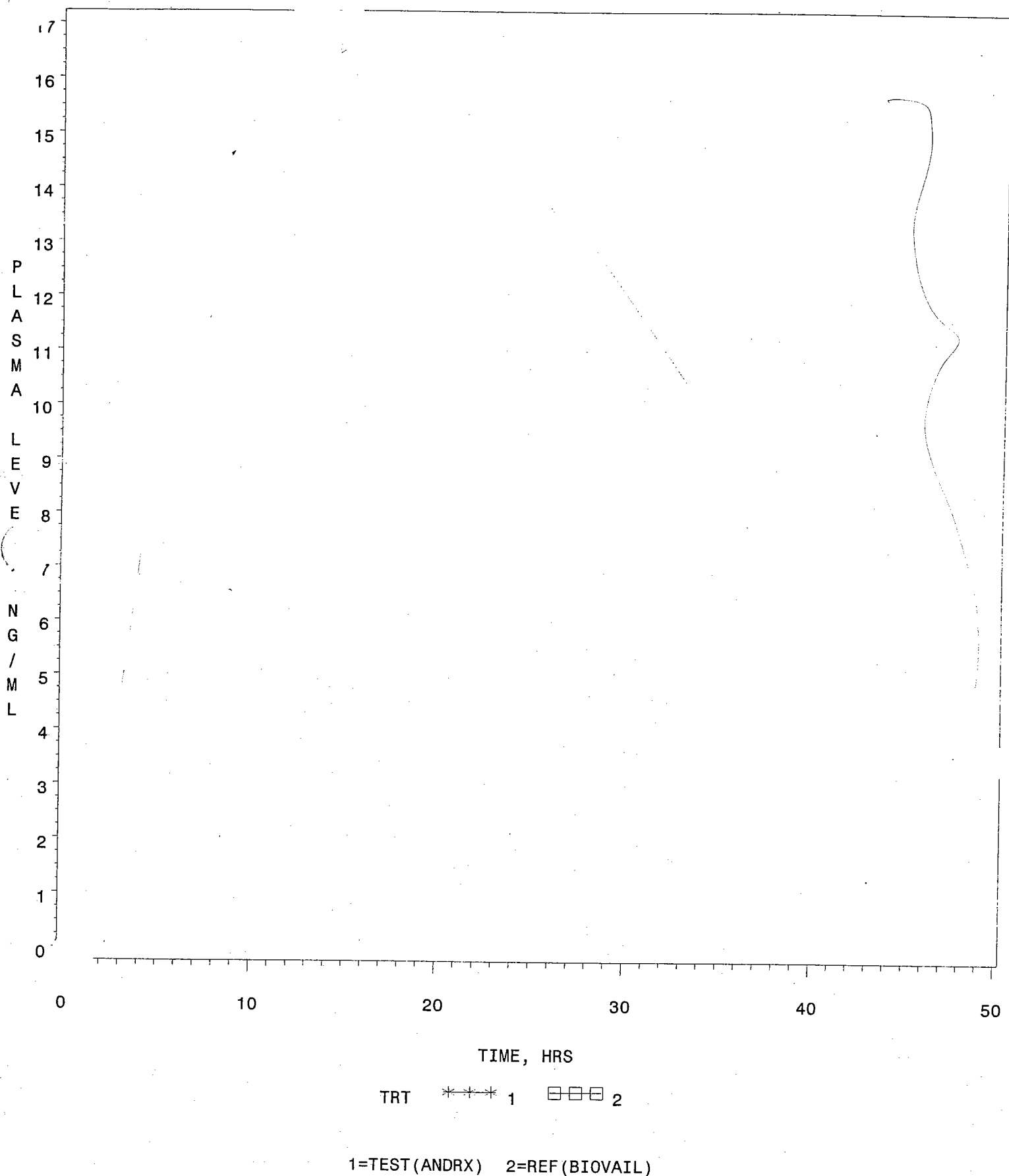


FIG 4. PLASMA DILTIAZEM LEVELS

DILTIAZEM HYDROCHLORIDE ER CAPSULES, 360 MG, ANDA #75-401

UNDER FASTING/NONFASTING CONDITIONS

DOSE=1 X 360 MG

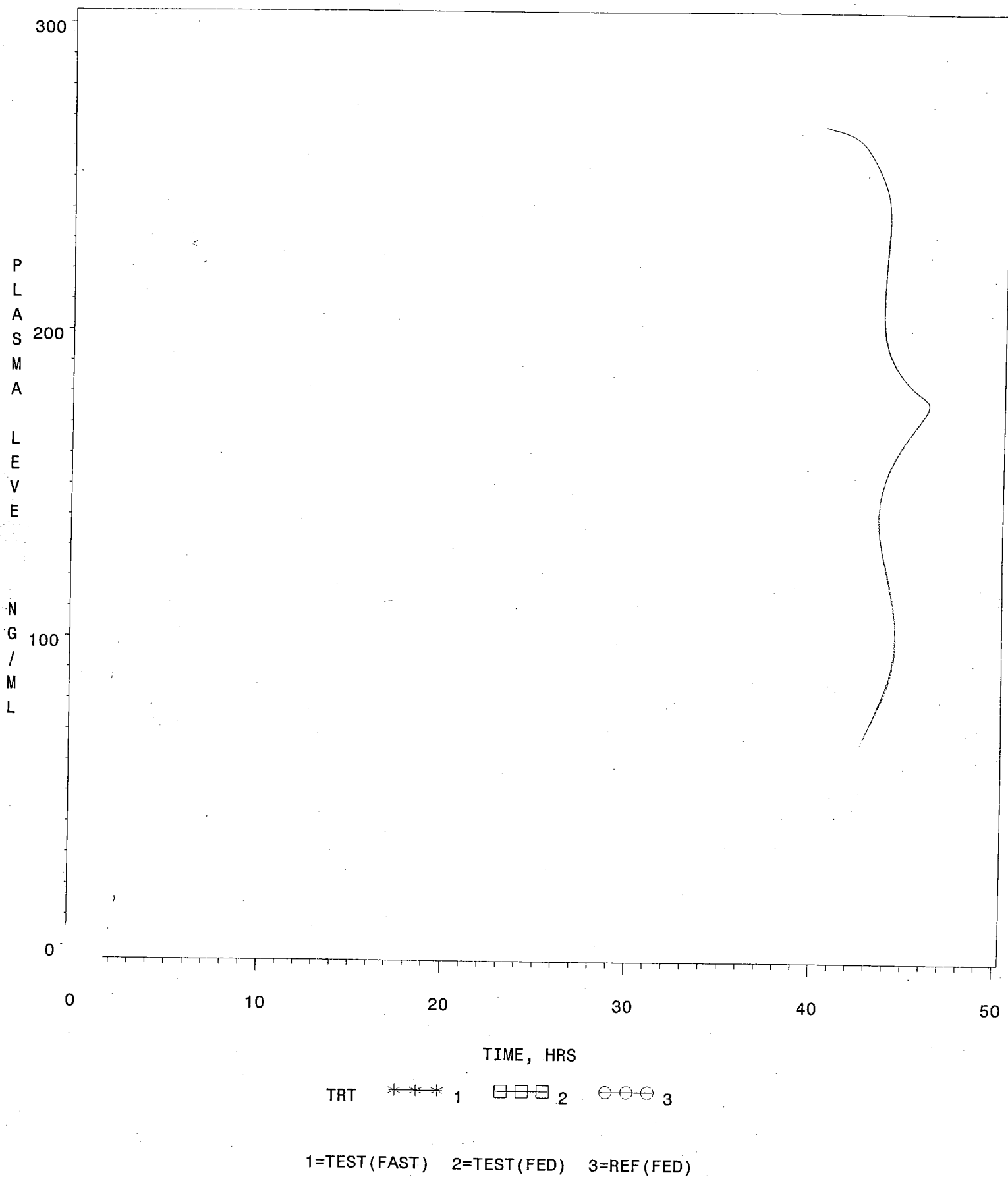


FIG 5. PLASMA DESMETHYLDILTIAZEM LEVELS

DILTIAZEM HYDROCHLORIDE ER CAPSULES, 360 MG, ANDA #75-401

UNDER FASTING/NONFASTING CONDITIONS

DOSE=1 X 360 MG

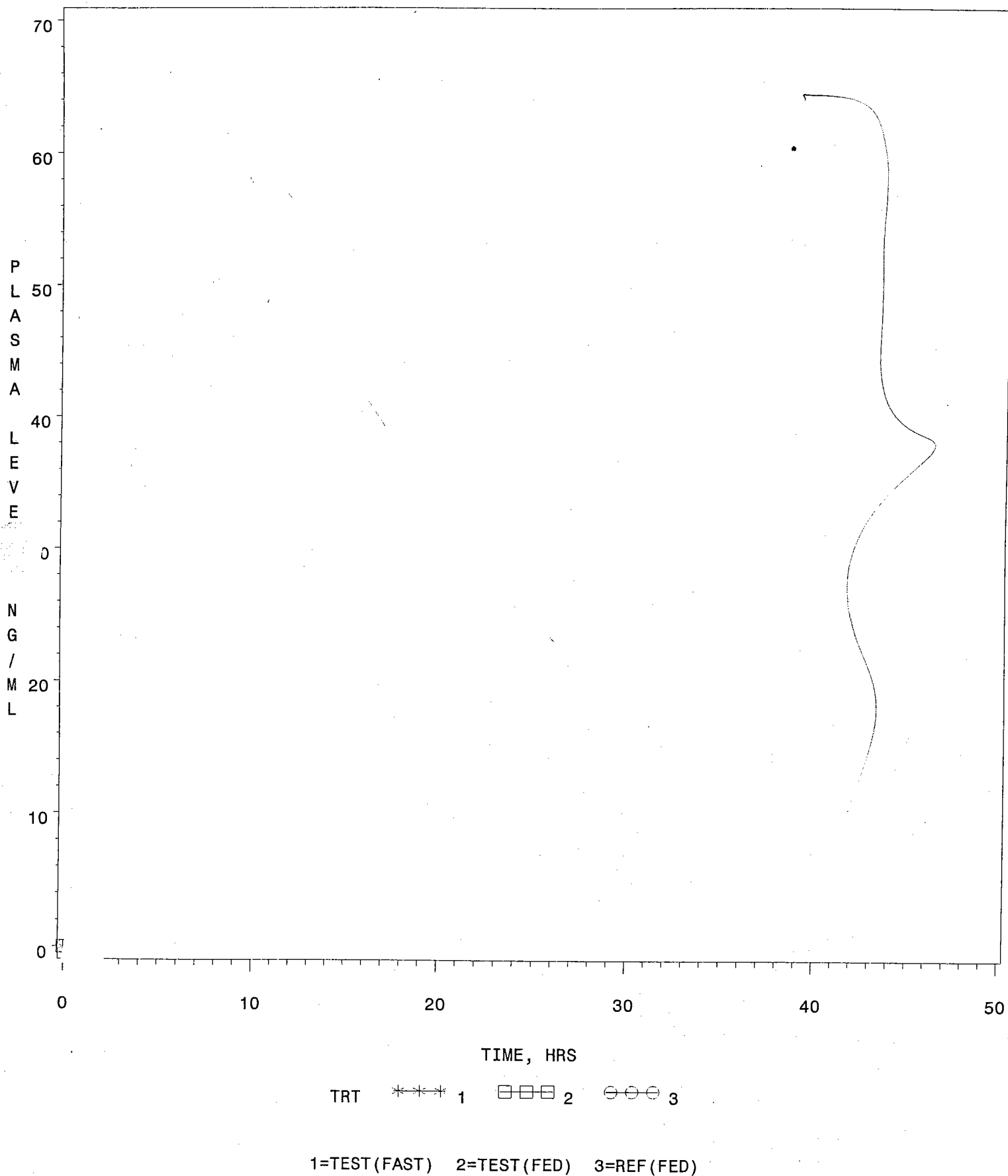


FIG 6. PLASMA DESACETYLDILTIAZEM LEVELS

DILTIAZEM HYDROCHLORIDE ER CAPSULES, 360 MG, ANDA #75-401

UNDER FASTING/NONFASTING CONDITIONS

DOSE=1 X 360 MG

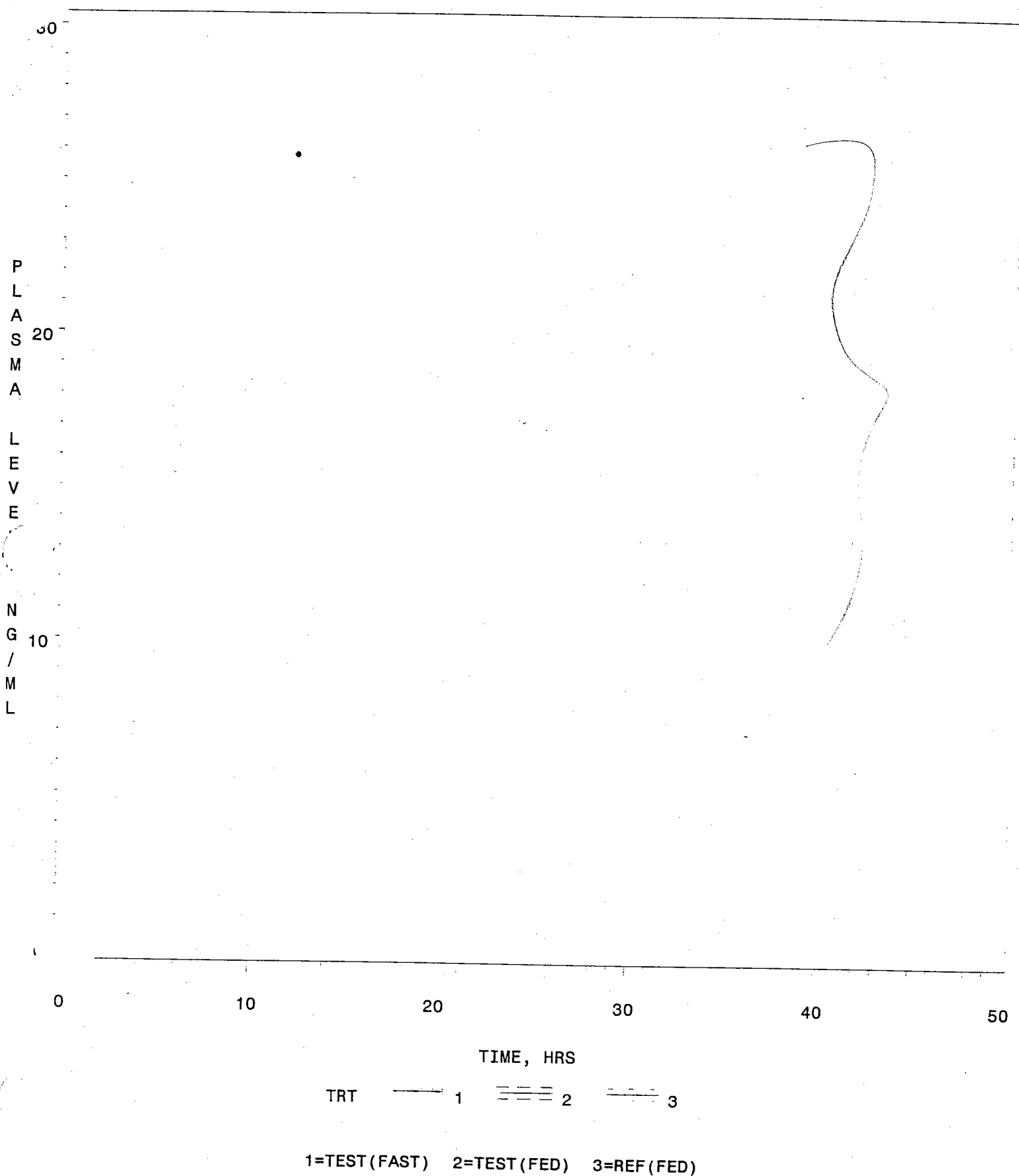
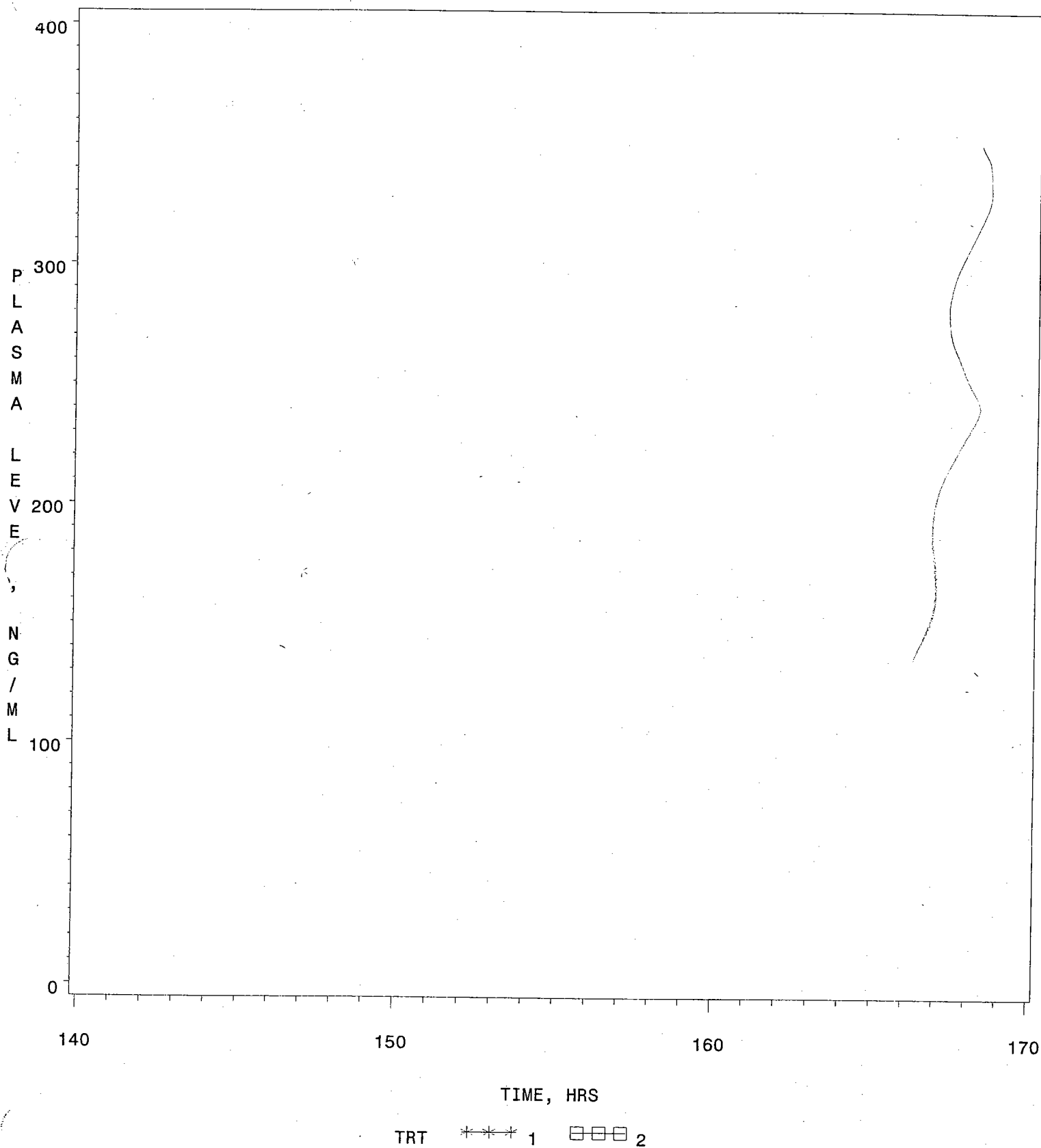


FIG 7. PLASMA DILTIAZEM LEVELS

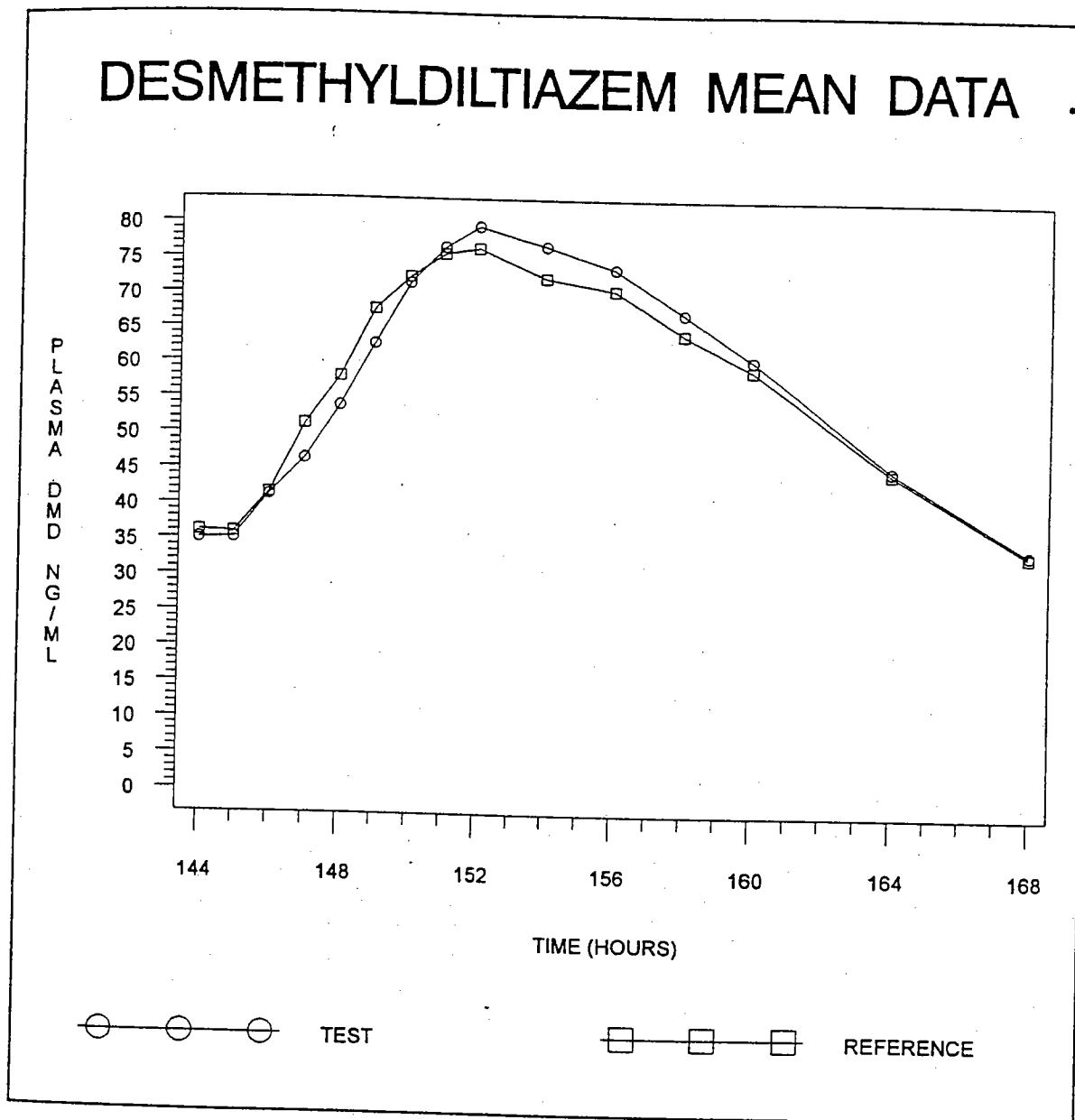
DILTIAZEM ER CAPSULES, 360 MG, ANDA #75-401
UNDER STEADY-STATE CONDITIONS
DOSE=360 MG ONE TIME/DAY FOR 6 DAYS AND ONCE PER 7TH DAY



1=TEST PRODUCT(ANDRX) 2=REFERENCE PRODUCT(BIOVAIL)

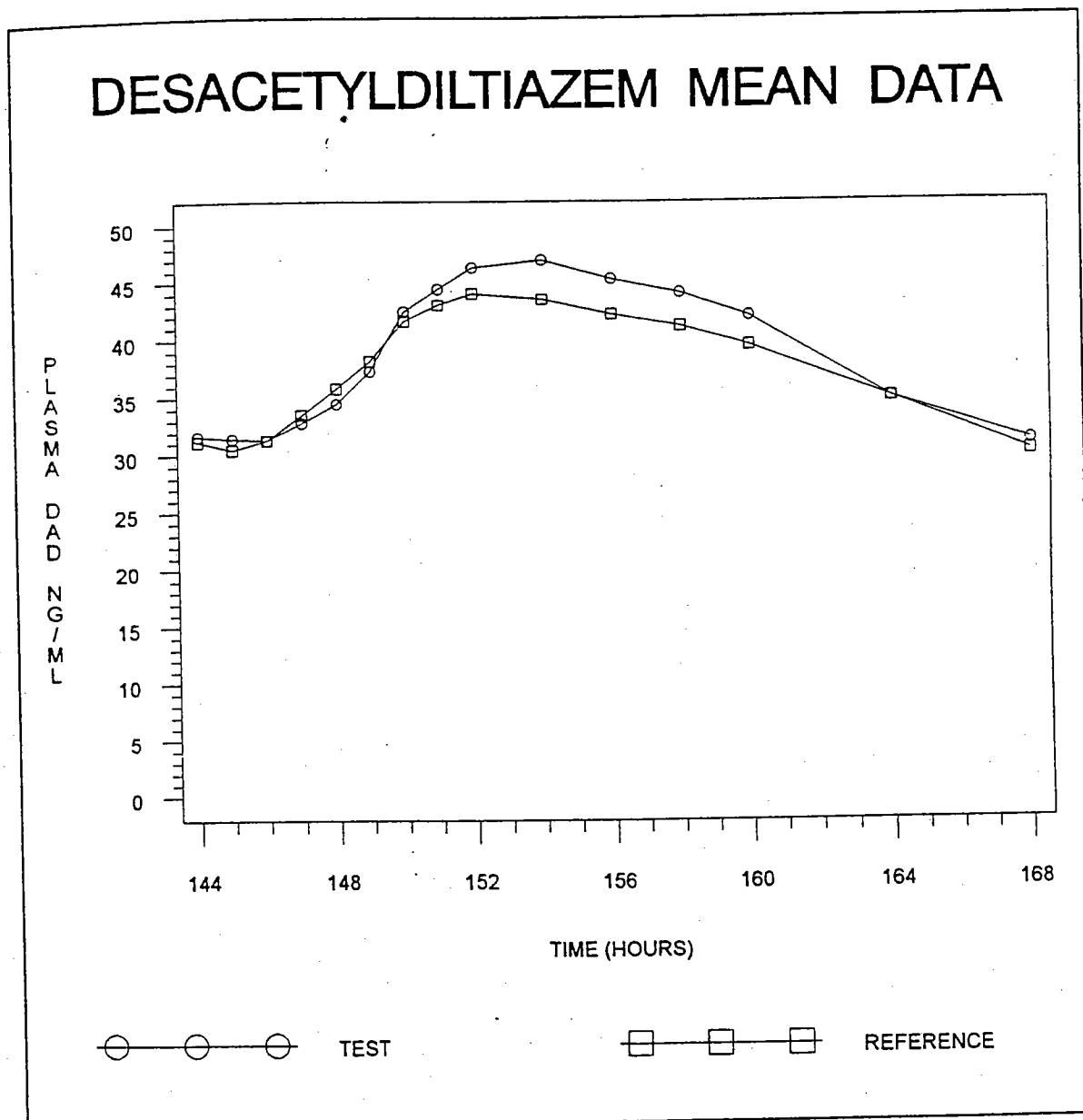
DILTIAZEM 360 MG CAPSULE MULTIPLE DOSE STUDY
ANDRX P97-504
STATISTICAL REPORT

Figure 8 Linear Plot of Mean Plasma Desmethyldiltiazem Concentrations vs Time



DILTIAZEM 360 MG CAPSULE MULTIPLE DOSE STUDY
ANDRX P97-504
STATISTICAL REPORT

Figure 9 Linear Plot of Mean Plasma Desacetyldiltiazem Concentrations vs Time



**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75-401

**ADMINISTRATIVE
DOCUMENTS**

RECORD OF TELEPHONE CONVERSATION

I called Andrx and spoke to Jacqueline Davis concerning ANDA 75-401. A tentative approval summary was recently done for this application. We are still awaiting OPDRA's finding on the suitability of the proposed trade name

The application cannot be fully approved until this issue is resolved. Two errors were discovered in the chemical name as seen in the DESCRIPTION section of the insert. I informed the firm of these errors and let them know that they could make the changes when they submit the FPL PI before final full approval. Ms. Davis agreed to this. She also inquired about the proposed trade name. I told her that we had not received word yet.

**APPEARS THIS WAY
ON ORIGINAL**

DIVISION OF LABELING AND PROGRAM SUPPORT

DATE

March 29, 2000

ANDA NUMBER

75-401

IND NUMBER

TELECON

INITIATED BY	MADE
APPLICANT/	X BY
SPONSOR	TELE.

X FDA	IN
	PERSON

PRODUCT NAME

Diltiazem HCl ER Capsules

FIRM NAME

ANDRX

**NAME AND TITLE OF
PERSON WITH WHOM
CONVERSATION WAS HELD**
Jacqueline Davis
Reg. Affairs

TELEPHONE NUMBER

(954) 321-5229

SIGNATURE

Adolph Vezza

Adolph Vezza 3/29/00

FAN

4.1

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 3, 2000

TO: Director, Investigations Branch
Minneapolis District Office
240 Hennepin Avenue
Minneapolis, MN 55401-1912

and

Director, Investigations Branch
Baltimore District Office
900 Madison Avenue
Baltimore, MD 21201-2199

FROM: C.T. Viswanathan, Ph.D. *MS Kelly for*
Associate Director (Bioequivalence)
Division of Scientific Investigations (HFD-48)

SUBJECT: FY2000 Data Validation Inspection, Bioresearch
Monitoring, Human Drugs, CP 7348.001
CANCELLATION

RE: ANDA 75-401

DRUG: Diltiazem HCl Extended Release Capsules

SPONSOR: Andrx Pharmaceuticals, Inc.

This memo requests that you cancel the audit and inspection of the following bioequivalence studies, which had been requested by the attached memorandum. The audit is no longer required.

Study #1: P97-502, A Relative Bioavailability Study of Diltiazem TZ 360 mg Capsules Versus Tiazac under Fasting Conditions.

Study #2: P97-503, A Limited Food Effects Study of Diltiazem TZ 360 mg Capsules.

Study #3: P97-504, A Multiple Dose Relative Bioavailability Study of Diltiazem TZ Capsules Versus Tiazac under Fasting Conditions.

Peter

Clinical Site: _____

Analytical Site: _____

**APPEARS THIS WAY
ON ORIGINAL**

CC:

HFA-224

HFD-45/Lepay

HFD-48/Fujiwara/O'Shaughnessy(2)/CF

HFD-615/Fan/Beers-Block

HFR-CE250/Glasgow

HFR-CE850/Matson

Draft: JAO 3/3/00

Edit: MKY

DSI:5317;0:\BE\assigns\bio75401.doc

Memorandum to the Record

ANDA: 75-401

DRUG: Diltiazem Hydrochloride Extended-release Capsules USP,
(Once-a-Day Dosage), 120 mg 180 mg, 240 mg, 300 mg and
360 mg

SUBJECT: Request for Reclassification to Minor Amendment dated
April 28, 2000 and June 26, 2000..

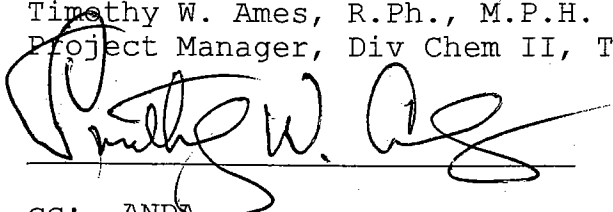
FIRM: ANDRX Pharmaceuticals, Inc.

DATE: August 10, 2000

Regarding these requests, MAJOR amendment was deemed appropriate at the time of issuance due to requiring a new bio study. Upon the submission of the study waiver request (April 28, 2000), the request for the bio sprinkle study was immediately reviewed by the Division of Bioequivalence and denied. Upon submission of the completed bio study sprinkle study (June 26, 2000), the review was begun immediately upon receipt, as though it were a priority review, due to the short queue within the Division of Bioequivalence. Therefore, reclassification to a Minor amendment was not considered.

The CMC portion of the application had already been found acceptable, prior to the issuance of the 4/13/00 NA MAJOR. As this is the CMC reviewer's next original assignment in queue, no further action with regard to the reclassification is warranted as per the Deputy Division Director, V.Sayeed.

Timothy W. Ames, R.Ph., M.P.H.
Project Manager, Div Chem II, Team 8, OGD



cc: ANDA
Division file (1)
HFD-641/VSayeed

File: V:\FIRMSAM\ANDRX\MEMOS\75401mem.doc

ANDA APPROVAL SUMMARY

ANDA: 75-401 DRUG PRODUCT: Diltiazem Hydrochloride ER Capsule, USP

M: Andrx Pharmaceuticals Inc.

DOSAGE FORM: Capsule

STRENGTH: 120 mg, 180 mg, 240 mg, 300 mg and 360 mg

CGMP STATEMENT/EIR UPDATE STATUS:

CGMP certification is satisfactory (See Page 9162).

EIR update : EER acceptable on 3-31-00.

BIO STUDY: Satisfactory.

See Bio. Review by K.R. Dhariwal on 7-12-2000. The dissolution testing was conducted using _____

The formulation of 120, 180, 240 and 300 mg capsules is proportionally similar to 360 mg capsules which underwent bioequivalency testing. The dissolution testing results on 120, 180, 240, 340 and 360 mg capsules are acceptable. The waiver of in vivo bioequivalence requirements for 120, 180, 240 and 300 mg capsules are granted.

Bio. dissolution specifications:

Time	Specification
2hr	NMT _____
4hr	_____
8hr	_____
12hr	NLT _____
16hr	NLT _____

VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

Not required, USP product.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?:

Containers used in the stability testing are the same as described in the container section.

Container 30's	75 cc, white round HDPE bottle _____ _____ _____ _____	_____	_____ _____ _____ _____ _____ _____ _____
Container 1000's	1887 cc white, round, HDPE bottle _____ _____	_____	_____ _____ _____

Closure	38 mm white — CRC		
Closure	cap		
	89 mm — cap		

LABELING:

Satisfactory on 5-9-2000.

STERILIZATION VALIDATION (IF APPLICABLE):

NA

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):

Diltiazem Hydrochloride ER Capsules , 360 mg, batch # 700R001 is compared to the listed drug Tiazac. A waiver of in vivo bioavailability testing for the Diltiazem Hydrochloride ER Capsules USP, 120 mg, 180 mg, 240 mg and 300 mg was requested and granted.

The size of the bio batch was _____ tablets(lot #700R001).

Firm's source of NDS OK : Yes _____; DMF _____

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):

For 120 mg Capsules	_____ Capsules, lot # 696R001
For 180 mg Capsules	_____ Capsules, lot # 697R001
For 240 mg Capsules	_____ Capsules, lot # 698R001
For 300 mg Capsules	_____ Capsules, lot # 699R001
For 360 mg Capsules	_____ Capsules, lot # 700R001

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?:

For 120 mg Capsules:	_____ Capsules
For 180 mg Capsules:	_____ Capsules
For 240 mg Capsules:	_____ Capsules
For 300 mg Capsules:	_____ Capsules
For 360 mg Capsules:	_____ Capsules

Manufacturing process is the same as bio.stability.

CHEMIST: S. Basaran

S. Basaran 9/11/00

DATE:8-17-2000

Team Leader: U. Venkataram

DATE:8-18-2000

v:\firmsam\andrx\ltrs&rev\75401APR.SUM.DOC

RECORD OF TELEPHONE CONVERSATION

I spoke to Jacqueline Davis of the firm today about ANDA 75-401 (Diltiazem ER Capsules). Their proposed trade name for this product has been sent to OPDRA for evaluation. She had some questions for me: (1) What firm firm wants to change the proposed trade name (a) before approval - send in new labeling which would be sent to OPDRA (b) after approval - send in prior approval supplement with new name and labeling which would be sent to OPDRA. (2) What if firm drops the proposed trade name and goes with the established name (a) before approval - send in new labels and labeling without the trade name (b) after approval - send in the new labels and labeling without the trade name in an annual report. (3) How long does it take to review a proposed trade name? I told her I didn't know.	DATE January 28, 2000						
I told her that the two tables in the PI had print which is too small and that before full approval the firm would have to send in a new PI correcting this deficiency.	ANDA NUMBER 75-401						
APPEARS THIS WAY ON ORIGINAL	IND NUMBER						
APPEARS THIS WAY ON ORIGINAL	TELECON						
APPEARS THIS WAY ON ORIGINAL	<table border="0"> <tr> <td>INITIATED BY</td> <td>MADE</td> </tr> <tr> <td>X APPLICANT/ SPONSOR</td> <td>X BY TELE.</td> </tr> <tr> <td>X FDA</td> <td>IN PERSON</td> </tr> </table>	INITIATED BY	MADE	X APPLICANT/ SPONSOR	X BY TELE.	X FDA	IN PERSON
INITIATED BY	MADE						
X APPLICANT/ SPONSOR	X BY TELE.						
X FDA	IN PERSON						
APPEARS THIS WAY ON ORIGINAL	PRODUCT NAME Diltiazem ER Caps (Once-a-Day Dosage)						
APPEARS THIS WAY ON ORIGINAL	FIRM NAME ANDRX						
APPEARS THIS WAY ON ORIGINAL	NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD Jacqueline Davis Reg. Affairs						
APPEARS THIS WAY ON ORIGINAL	TELEPHONE NUMBER (954) 321-5229						
APPEARS THIS WAY ON ORIGINAL	SIGNATURE Adolph Vezza <i>Adolph Vezza 1/28/00</i>						

DIVISION OF LABELING AND PROGRAM SUPPORT

E L E C T R O N I C M A I L M E S S A G E

Sensitivity: COMPANY CONFIDENTIAL

Date: 09-Jan-2001 02:59pm EST

From: Krista Scardina
SCARDINAK

Dept: HFD-610

Tel No: FAX t-

TO: Rosemarie Wiseman *

(WISEMANR)

TO: Edward Washington*

(WASHINGTON)

TO: Wayne Green *

(GREENW)

Subject: ANDA 75-401

Hello

Could you please make the following piece a new correspondence for bio instead of amendment:

ANDA 75-401 Diltiazem by Andrx

Letter date: January 5, 2001

Thanks

Krista

APPEARS THIS WAY
ON ORIGINAL

ANDA APPROVAL SUMMARY

ANDA: 75-401 DRUG PRODUCT: Diltiazem Hydrochloride ER Capsule, USP

FIRM: Andrx Pharmaceuticals Inc. DOSAGE FORM: Capsule

STRENGTH: 120 mg, 180 mg, 240 mg, 300 mg and 360 mg

CGMP STATEMENT/EIR UPDATE STATUS:

CGMP certification is satisfactory (See Page 9162).

EIR update: EER acceptable on 10-9-02. _____ ending
_____ inspection in _____

BIO STUDY: Satisfactory; Reviewed by K.R. Dhariwal

- ◆ Bio study conducted under fasting conditions for 360 mg EXC, lot # 700B006A is satisfactory
- ◆ Bio study conducted under non- fasting conditions for 360 mg EXC, lot # 700B006A is satisfactory.
- ◆ Bio study conducted under fasting conditions for 240 mg EXC, lot # 698B006B is satisfactory.
- ◆ The sprinkling biostudy for the 360 mg EXC, lot# 700B006A is satisfactory
- ◆ Currently, the DOB is withholding their comments on the proposed dissolution specification (_____) pending our review of the dissolution data. We have found the firm's justification for using _____ in place of _____ as the dissolution medium acceptable. We will be recommending to DOB that they accept firm's proposal for the dissolution specifications. The formulation of 120, 180, 240 and 300 mg capsules is proportionally similar to 360 mg (lot#700B006) capsules that was used to establish bioequivalency. The dissolution testing results on 120, 180, 240, 340 and 360 mg capsules are acceptable. The waiver of in vivo bioequivalence requirements for 120 (lot#696B006), 180 (lot#696B007), 240 (lot#149B042) and 300 (lot#699B005)mg capsules are granted.

Dissolution specifications:

<u>Time</u>	<u>Specification</u>
2hr	NMT _____
4hr	_____
8hr	_____
12hr	NLT _____
16hr	NLT _____

The DOB has recommended that the firm should use _____ for _____ dissolution studies and not _____

VALIDATION -(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

Not required, USP product.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN
CONTAINER SECTION?:

Containers used in the stability testing are the same as described in the container section. The package size is 30's, and 1000's counts.. Stability data and protocol are acceptable. Expiration date is granted for 24 months and is supported by stability data.

LABELING:

Satisfactory on 3-26-2003. Update labeling is pending for review

STERILIZATION VALIDATION (IF APPLICABLE):

NA

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):

Diltiazem Hydrochloride ER Capsules, 360 mg, batch # 700B006 is compared to the listed drug Tiazac. A waiver of in vivo bioavailability testing for the Diltiazem Hydrochloride ER Capsules USP, 120 mg, 180 mg, 240 mg and 300 mg was requested and granted.

The size of the bio batch 360 mg, lot #700B006, was capsules

Firm's source of NDS OK: Yes (DMF# . DMF# reviewed by S.Basaran on 10-17-02 and found satisfactory.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):

For 120 mg Capsules: Capsules lot # 696B006
For 180 mg Capsules: Capsules lot # 697B007
For 240 mg Capsules: Capsules lot # 698B006
For 300 mg Capsules: Capsules lot # 699B005
For 360 mg Capsules: Capsules lot # 700B006

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?:

For 120 mg Capsules: Capsules
For 180 mg Capsules: Capsules
For 240 mg Capsules: Capsules
For 300 mg Capsules: Capsules
For 360 mg Capsules: Capsules

The proposed manufacturing process is the same as that used for the bio and stability batches.

CHEMIST: S. Basaran, Ph.D.

DATE:1-15-2003

Team Leader: U. Venkataram, Ph.D.

DATE:1-17-2003

U. V. Venkataram
4/7/03

V:\Firmsam\Andrx\LTRS&REV\75401APRSUM_SB.DOC

Telephone Conversation Memorandum

ANDA: 75-401

DRUG: Diltiazem Hydrochloride ER Capsules, 120 mg, 180 mg,
240 mg, 300 mg and 360 mg

FIRM: Andrx Pharmaceuticals, Inc.

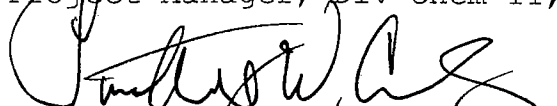
PERSONS INVOLVED: Diane Servello, Andrx
Tim Ames, FDA

PHONE NUMBER: 954-432-4412

DATE: December 1, 1999

Firm was contacted to relate the new interim dissolution method and specifications. Firm was requested to incorporate the new specifications into the finished product release and stability protocol specifications and submit the revised specifications as a telephone amendment.

Timothy W. Ames, R.Ph., M.P.H.
Project Manager, Div Chem II, Team 8, OGD



cc: ANDA 75-401
Division file (1)

File: V:\firmsam\andrx\telecons\75401tc1.doc

RECORD OF TELEPHONE CONVERSATION

I called the firm today and left a message concerning the PI and the proposed trade name for this unapproved ANDA. Jacqueline Davis called me back later in the day. I told her that the quality of the PI submitted 1-14-00 was very poor and requested that it be improved. She said that they would have the font size enlarged and send in the revised PI by FedEx tomorrow (1-20-00) morning.

I also mentioned to her that their proposed trade name "Taztia XT" would be reviewed. She asked how often does the Labeling and Nomenclature Committee meet and I told her that it was no longer in existence but that there is a newly formed group in the FDA which continuously reviews proposed proprietary names and consequently the review process would probably not take as long as previously. She was happy to hear it.

**APPEARS THIS WAY
ON ORIGINAL**

DIVISION OF LABELING AND PROGRAM SUPPORT

DATE

January 19, 2000

ANDA NUMBER

75-401

IND NUMBER

TELECON

INITIATED BY	MADE
X APPLICANT/ SPONSOR	X BY TELE.

X FDA	IN PERSON

PRODUCT NAME

Taztia XTTM
(diltiazem HCl ER
capsules - once-
a-day dosage)

FIRM NAME

ANDRX

**NAME AND TITLE OF
PERSON WITH WHOM
CONVERSATION WAS HELD**
Jacqueline Davis
Reg. Affairs

TELEPHONE NUMBER

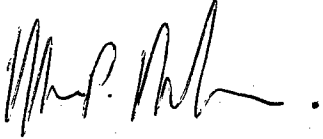
(954) 581-7500

SIGNATURE

Adolph Vezza

Adolph Vezza 1/19/00

RECORD OF TELEPHONE CONVERSATION

I called Andrx and talked to Dave Gardner concerning their ANDA for Diltiazem ER caps. This is a generic copy of Biovail's Tiazac. I informed Mr. Gardner that the patent holder/NDA holder, Biovail Labs has contacted OGD and stated that Andrx has submitted a notice of patent non-infringement to them before the citizen petition requesting a change in the listed drug had been approved by FDA. I explained to Mr. Gardner that per 21 CFR 314.95(b) Andrx can not send the notice of non-infringement until it receives from FDA an acknowledgement letter for their ANDA. I further instructed Mr Gardner that Andrx would have to re-send the notice of patent non-infringement once they receive the acknowledgemnt for this ANDA. Mr Gardner said he understood and would comply with our request. APPEARS THIS WAY ON ORIGINAL	DATE
	August 14, 1998
	APPLICATION NUMBER
	75-401
	IND NUMBER
	TELECON
	INITIATED BY MADE — APPLICANT/ X BY SPONSOR TELE.
	XFDA — IN PERSON
PRODUCT NAME	
Diltiazem ER Caps	
FIRM NAME	
Andrx	
NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD	
Dave Gardner Reg Affairs	
TELEPHONE NUMBER	
954-587-1054	
SIGNATURE	
	

(Peter)

E L E C T R O N I C M A I L M E S S A G E

Date: 17-Aug-1998 11:03am EDT
From: William Rickman
RICKMAN
Dept.: HFD-615 MPN2 113
Tel No: 301-827-5862 FAX 301-594-0174

TO: Doug Sporn

(SPORND)

Subject: RE: Biovail's Tiazac

Doug,

Here is a summary of the events surrounding the Andrx submission of a generic version of Biovail's Tiazac (diltiazem HCl ER caps):

-The "orange book" had the 360 mg strength Tiazac product designated as the RLD since it was a single source reference drug.

-We subsequently removed this RLD designation due to the lower strengths of Tiazac that were duplicates of therapeutic inequivalent NDAs.

-Andrx submitted an ANDA for the 360 mg strength (later amended to include the lower strengths). Product development and the BE study were started when the orange book had designated the 360 mg Biovail Tiazac product as the RLD.

-Andrx submitted a CP requesting we designate the entire spectrum of Tiazac strengths as RLDs.

-Andrx made a PIV patent certification in their ANDA and provided notice to the patent holder (Biovail) before they got an acknowledgement letter. The regs state that notice can not be given until applicant receives from FDA an acknowledgement letter, 314.95(b). Andrx was notified by phone on 8/14/98 that they would have to resend the notice of noninfringement after they have rec'd an acknowledgment letter.

-Andrx's CP requesting Tiazac as RLDs was approved on July 31, 1998.

-Andrx submitted a copy of the petition approval letter to their ANDA on August 10, 1998.

Acknowledgement letter will cite the August 10th date as date acceptable for filing.

Peter

Telecon

Date: 081098

Time: 1000 H

ANDA #: 75-401

Firm: Andrx Pharmaceuticals

Drug: Diltiazem Hydrochloride Extended-release Capsules, 120 mg,
180 mg, 240 mg, 300 mg and 360 mg

Participants: Gregg Davis, FDA and Jacqueline Davis, Andrx

Phone #: 954-321-5229

Agenda:

I called Jacqueline Davis and asked for an additional piece of information to make the application complete for filing. To be in compliance with 21 CFR 314.94(a)(3)(iii), the application must contain a copy of FDA's correspondence approving the citizen petition. She said she will fax the info and follow with a hard copy.

APPEARS THIS WAY
ON ORIGINAL

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75-401

CORRESPONDENCE



*Labeling review
drafted 3/24/03
G. Vega*

March 18, 2003

Gary Buehler, Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT

N/A

FPL

RE: ANDA #75-401; Taztia™ (Diltiazem Hydrochloride Extended-release Capsules, USP), 120 mg, 180 mg, 240 mg, 300 mg and 360 mg Final Printed Labeling

Dear Mr. Buehler:

Reference is made to FDA's facsimile dated March 14, 2003 providing labeling comments for the above mentioned application (facsimile attached). Reference is also made to our March 17 letter to the FDA requesting permission to implement the recommended changes post-approval.

Comment:

The "sun" image as it appears in front of the proprietary name may be construed to be the letter "O" since the proprietary name also contains a modifier (XT) in a similar color. The "sun" image also contains "rays" that cover some of the first letter "T" in the proprietary name and interfere with the appearance of the proprietary name. Delete the "sun" image to increase the prominence of the proprietary name.

Response:

We have removed the "sun" image so as not to cause interference with the appearance of the proprietary name.

Comment:

The "ONCE DAILY" phrase that appears in conjunction with the proprietary name should be deleted. It not only distracts from the visual appearance of the proprietary name, but also is redundant to the "ONCE-A-DAY DOSAGE" state on the principal display panel.

Response:

We have deleted the phrase "ONCE DAILY" which appeared above the proprietary name.

Comment:

The large "XT" design covers approximately 50% of the total area of the label. This "XT" design distracts from the prominence of the proprietary name. DMETS recommends deleting the design as it obscures the readability of the name.

Response:

The "XT" design has been deleted.

RECEIVED

MAR 20 2003

OGD / CDER

Comment:

DMETS recommends moving the dosage strength to be directly beneath the proprietary and established name and away from the net quantity statement.

Response:

The dosage strength box has been moved to be directly beneath the proprietary and established name.

Comment:

DMETS recommends increasing the prominence of the phrase "ONCE-A-DAY DOSAGE".

Response:

We increased the font size and made the statement bold to increase prominence.

Comment:

DMETS recommends increasing the prominence of the dosage strength on the 180 mg container label. This may be accomplished with a different background color in the boxed area.

Response:

We feel that by moving the dosage strength box out of the green border area that the prominence of the 180 mg strength box can be seen clearer.

Comment:

DMETS recommends using a different background color to display the dosage strength for either the 300 mg or 360 mg container label. Both the 300 mg and 360 mg dosage strengths will be placed next to each other on the pharmacy shelf. The similarity between the red and maroon colors may cause the bottles to be inadvertently interchanged and lead to medication errors.

Response:

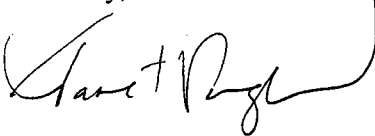
To avoid possible medication errors, we have changed the dosage strength box on the 360 mg container label from red to black with reverse white lettering. This will clearly distinguish the 360 mg strength from the 300 mg strength container (the dosage strength box for the latter strength is purple).

In this regard, we have enclosed the following:

1. Twelve copies of container label for the 30, 90, and 1000 count labels. (Six copies are included with the archival copy and six copies are included with the review copy.)
2. In accordance with 21 CFR 314.94(a)(8)(iv), a side-by-side comparison, annotating the revisions to our labeling is included.

Should you have any questions or comments concerning this submission, please contact the undersigned at (954) 358-6125.

Sincerely,



Janet Vaughn
Assoc. Director of Regulatory Affairs

RECEIVED

MAR 20 2003

OGD / CDER



ANDA #75-401

Diltiazem HCl Extended-Release Capsules, USP (Taztia XT™)
120, 180, 240, 300, and 360 mg

NEW CORRESP

NC

VIA FACSIMILE AND FED EX

March 17, 2003

Mr. Gary Buehler
Director, Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, Maryland 20855

RECEIVED

MAR 20 2003

Re: Request to Implement Labeling Changes Post-Approval

OGD / CDER

Dear Mr. Buehler:

Reference is made to your facsimile dated March 14, 2003 (labeling deficiencies) for the above referenced application. Andrx recognizes the Agency's concern regarding potential confusion and medication errors due to labeling similarities across our product line, as we have employed the same template for our three diltiazem hydrochloride extended-release products (Diltia XT, Cartia XT and Taztia XT). We appreciate the Agency's recommendations for the container label and we agree that these changes could help to minimize potential errors, thus improving patient safety, as they would help to distinguish the Taztia XT from the other diltiazem products.

Consequently, Andrx hereby agrees to make all the changes identified in the March 14, 2003 facsimile. We have already provided a PDF file by email of the revised label to Adolf Vezza, Labeling Reviewer, OGD, for his review. If OGD has any further comments on the revised labeling, please let us know. We will make any necessary changes. If the revised container labeling is satisfactory as is, please let us know and we will immediately submit final printed labeling.

However, we respectfully request that the Agency permit us to implement these changes post approval. In support of this request, we cite the following:

1. Andrx's two other diltiazem hydrochloride extended-release products, Diltia XT and Cartia XT, were approved by the Agency and have been marketed with the same template in question, since October 1997 and July 1998, respectively. The Agency has never communicated any potential safety concerns with respect to these marketed products and we are unaware of any confusion that has arisen as a result of similarities in our container labels. In fact, we believe that by implementing brand names, and various colors, rather than using just the generic name, has helped to differentiate these once daily Diltiazem HCl

ER products, which in many cases have the same dosage strength but are therapeutically equivalent to different reference listed drugs, thereby avoiding possible medication errors.

2. The proposed proprietary name, "Taztia XT", was found acceptable by OPDRA in April 2000, and final printed labeling was requested at that time, signifying an acceptance of the template used for our container labels. Due to revisions in the innovator's insert, the insert for Andrx's drug product has undergone various changes, but the Agency has never expressed a concern regarding the design of the template used for the container labels. In fact, the application was first tentatively approved on September 29, 2000 with the proposed container labels, and again on May 14, 2001. Additionally, all promotional material, which included pictures of our container labels, was found acceptable by DDMAC in April 2001.
3. In anticipation of final approval of the ANDA, and having never received any comments from the Agency regarding the template used for our container labels since submission of the draft labels (approximately 3 years), Andrx has manufactured and packaged the following launch quantities of the drug product using the container labels we believed were approved by the Agency:

Dosage	Item Code	Lot Number	Bottle Count
<i>30 count package size</i>			
120 mg	696-30	696C001A	—
	696-30	696C002C	—
180 mg	697-30	697C001	—
	697-30	697C002A	—
240 mg	698-30	698C001	—
	698-30	698C002	—
300 mg	699-30	699C001	—
	699-30	699C002A	—
360 mg	700-30	700C003	—
	700-30	700C004	—
<i>90 count package size</i>			
120 mg	696-90	696C002B	—
	696-90	696C003	—
	696-90	696C004	—
180 mg	697-90	697C002B	—
	697-90	697C003	—
	697-90	697C004	—
240 mg	698-90	698C003	—
	698-90	698C004	—
	698-90	698C005	—
	698-90	698C006	—
300 mg	699-90	699C002B	—
	699-90	699C003	—
	699-90	699C004	—
360 mg	700-90	700C002	—

Dosage	Item Code	Lot Number	Bottle Count
	700-90	700C005	—
	700-90	700C006	—

We anticipate the launch quantities would be exhausted in the market place in approximately one (1) month.

A change in the label at this time, as the Agency recommends, would effectively delay the public's access to the first and only generic for Tiazac® and also impose significant financial hardship on Andrx, as the launch quantities would need to be re-packaged and re-labeled. If FDA does not permit such a post-approval change, the Agency's action would frustrate the objective of the Hatch-Waxman Amendments of making bioequivalent, cost-saving generic products available to the public as quickly as possible.

Accordingly, we respectfully request that the FDA permit Andrx to launch the already packaged and labeled launch quantities of the drug product. Again, we hereby commit to implement the March 14th recommended changes for the next production quantities of the drug product that are manufactured. Granting of this request will be beneficial to the American consumer, within the letter and spirit of the Hatch-Waxman Amendments, and would prevent a severe financial hardship on Andrx.

Should you have any questions or comments concerning this submission, please contact the undersigned at (954) 358-6125 (phone) or (954) 358-6350 (facsimile).

Sincerely,



Janet Vaughn
Associate Director, Regulatory Affairs

Cc: Wm. Peter Rickman
Stan Shepardson
Adolph Vezza

75-401 (11.1)

ANDA (See Attachment)

Andrx Pharmaceuticals, L.L.C.
Attention: William Stahovec
4955 Orange Avenue
Ft. Lauderdale, FL 33314

Dear Sir:

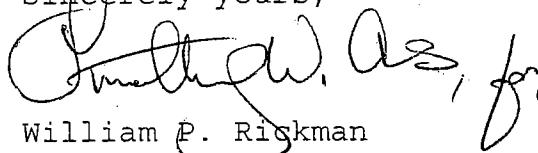
7 — We acknowledge receipt of your communications dated
January 8, 2003, submitted as required by the provisions
of Regulation 21 CFR 314.72(a) and Section 505(k) of the
Federal Food, Drug and Cosmetic Act for the abbreviated
new drug applications (ANDA) for the drug products listed
in the attachment.

Your letter details the transfer of ownership of the ANDAs
from Andrx Pharmaceuticals, Inc. to Andrx Pharmaceuticals,
L.L.C.

Pursuant to 21 CFR 314.72(b), the new owner shall advise FDA
about any change in the conditions of the pending applications.

The material submitted is being retained as part of your
applications.

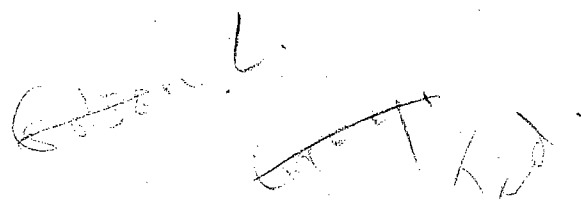
Sincerely yours,



William P. Rickman
Director

Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment



ANDADrug Products

40-441	Codrix (Acetaminophen and Codeine Phosphate Tablets, 500 mg/30 mg)
40-488	Codrix (Acetaminophen and Codeine Phosphate Tablets, 500 mg/60 mg)
40-493	Hydrocodone Bitartrate and Acetaminophen Tablets, 5 mg/500 mg
• 40-494	Hydrocodone Bitartrate and Acetaminophen Tablets, 7.5 mg/750 mg
40-495	Hydrocodone Bitartrate and Acetaminophen Tablets, 10 mg/660 mg
75-401	Taztia XT™ (Diltiazem Hydrochloride Extended-release Capsules) 120 mg, 180 mg, 240 mg, 300 mg and 360 mg
75-990	Loratadine Orally-Disintegrating Tablets, 10 mg
76-049	Quinapril Hydrochloride Tablets, 5 mg, 20 mg, and 40 mg
76-159	Glipizide Extended-release Tablets, 10 mg
76-172	Metformin Hydrochloride Extended-release Tablets, 500 mg
76-208	Loratadine and Pseudoephedrine Sulfate Extended-release Tablets, 5 mg/120 mg
76-267	Benazepril Hydrochloride Tablets, 5 mg, 10 mg, 20 mg, and 40 mg
76-334	Norgestimate and Ethinyl Estradiol Tablets, 0.250 mg/0.035 mg
76-335	Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215mg/0.035 mg and 0.250 mg/0.035 mg
76-336	Mirtazapine Tablets, 15 mg, 30 mg, and 45 mg
76-342	Benazapril Hydrochloride and Hydrochlorothiazide Tablets, 5 mg/6.25 mg, 10 mg/12.5 mg, 20 mg/12.5 mg and 20 mg/25 mg



January 8, 2003

Gary Buehler,
Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP

NC

Dear Mr. Buehler,

Pursuant to 21 CFR 314.72, Andrx Pharmaceuticals, Inc. has enclosed letters notifying the agency of change of ownership of its abbreviated new drug applications ("ANDAs"). Ownership of the ANDAs are being is being transferred from Andrx Pharmaceuticals, Inc. to Andrx Pharmaceuticals, L.L.C. For your convenience, please find below a complete list of the ANDAs being transferred.

ANDA

No.

PRODUCT

75-401 Taztia XT (Diltiazem HCl) 120 mg, 180 mg, 240 mg, 300 mg, 360 mg
40-443 Acetaminophen and Codeine Phosphate Tablets, 300 mg/15 mg, 300 mg/30 mg,
and 300 mg/60 mg
75-416 Naproxen Sodium ER Tablets, 375 mg
75-706 Loratadine & Pseudo ER Tablets 10 mg/240 mg

40-441 Codrix (Acetaminophen and Codeine Phosphate Tablets, 500 mg/30 mg)
40-447 Codrix (Acetaminophen and Codeine Phosphate Tablets, 500 mg/15 mg)
76-179 Tamoxifen Citrate Tablets, 10 mg and 20 mg

75-990 Loratadine Orally-Disintegrating Tablets 10 mg
76-208 Loratadine & Pseudo ER Tablets 5 mg/120 mg
76-334 Norgestimate and Ethinyl Estradiol Tablets, 0.250 mg/0.035 mg

76-267 Benazapril HCl Tablets, 5 mg, 10 mg, 20 mg, and 40 mg

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- 76-342 Benazapril HCl and Hydrochlorothiazide Tablets, 5 mg/6.25 mg, 10 mg/12.5 mg, 20 mg/12.5 mg, and 20 mg/25 mg
- 76-335 Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg /0.035 mg, 0.215 mg /0.035 mg, and 0.250 mg /0.035 mg
-

- 76-172 Metformin HCl XR Tablets 500 mg
- 76-159 Glipizide ER Tablets 10 mg
- 76-049 Quinapril HCl IR Tablets, 20mg/40 mg and 5 mg, and 10 mg
-

- 40/488 Codrix (Acetaminophen and Codeine Phosphate Tablets, 500 mg/60 mg)
- 40-495 Hydrocodone Bitartrate and Acetaminophen Tablets, 10 mg /660 mg
- 40-494 Hydrocodone Bitartrate and Acetaminophen Tablets, 7.5 mg /750 mg
- 40-493 Hydrocodone Bitartrate and Acetaminophen Tablets, 5 mg /500 mg
- 76-336 Mirtazapine Tablets, 15 mg, 30 mg, and 45 mg
-

- 75-961 Metformin HCl Tablets, 500 mg, 850 mg, and 1000 mg
- 75-604 Potassium Chloride Extended-release Tablets, 10 mEq and 20 mEq
- 74-752 Cartia XT® (Diltiazem HCl Extended-release Capsules, 120 mg, 180 mg, 240 mg, and 300 mg)
- 75-347 Omeprazole DR Capsules, 10 mg, 20 mg, and 40 mg
- 75-270 Ketoprofen Extended-release Capsules, 100 mg, 150 mg and 200 mg
- 74-852 Diltia XT ® (Diltiazem HCl Extended-release Capsules, 120 mg, 180 mg, and 240 mg)
- 75-829 Etodolac Extended-release Tablets, 400 mg and 500 mg

Please do not hesitate to contact me at (954) 358-6124, if you have any further questions.

Sincerely,
ANDRX PHARMACEUTICALS, INC.



William Stahovec
Associate Director of Regulatory Affairs



January 7, 2003

NEW CORRESP

NC

Gary Buehler
Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: Re: ANDA 75-401; Taztia XT (Diltiazem HCl) 120 mg, 180 mg, 240 mg, 300 mg, and 360 mg

Dear Mr. Buehler:

We refer to the abbreviated new drug application ("ANDA") listed above. Pursuant to §314.72, Andrx Pharmaceuticals, Inc. is notifying the agency of a change in ownership for this ANDA. The change in ownership is effective as of December 13, 2002.

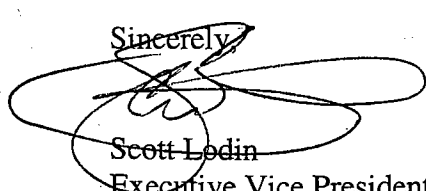
All rights to this ANDA have been transferred to:

Andrx Pharmaceuticals L.L.C.
4955 Orange Avenue
Ft Lauderdale, FL 33314
Attention: Janet Vaughn, Senior Manager of Regulatory Affairs
Phone: (954) 358-6100 or (954) 358-6125 (direct line)
Fax: (954) 358-6350

Andrx Pharmaceuticals, Inc. certifies that the new owner has a complete copy of this ANDA. A separate letter will be sent to your office by Andrx Pharmaceuticals, L.L.C. with a signed 356H form containing (1) a commitment to abide by the agreements, promises and conditions contained in this application; (2) the date the change in ownership is effective; and (3) a statement that a complete copy of the application is in their possession.

Please do not hesitate to contact me at (954) 585-1751 if you require additional information.

Sincerely,



Scott Lodin

Executive Vice President and General Counsel

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December 10, 2002

Gary Buehler, Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT

N/AH

FPL

RE: ANDA #75-401; Taztia™ (Diltiazem Hydrochloride Extended-release Capsules, USP), 120 mg, 180 mg, 240 mg, 300 mg and 360 mg Final Printed Container Labels

Dear Mr. Buehler:

As per Adolph Vezza telephone request, we are enclosing final printed container labels for the above product. Draft container labels were originally submitted in our labeling amendment dated January 14, 2000 which are identical to the final printed containers labels submitted herein.

In this regard, we have enclosed the following:

1. Twelve copies of container label for the 30, 90, and 1000 count labels. (Six copies are included with the archival copy and six copies are included with the review copy.)

Should you have any questions or comments concerning this submission, please contact the undersigned at (954) 358-6125.

Sincerely,
ANDRX PHARMACEUTICALS, INC.

A handwritten signature in black ink, appearing to read "Janet Vaughn", is written over a horizontal line.

Janet Vaughn
Sr. Manager of Regulatory Affairs

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ANDA #75-401

Diltiazem HCl Extended-Release Capsules, USP (Taztia XT™)
120, 180, 240, 300, and 360 mg

November 22, 2002

ORIG AMENDMENT

Nham

Mr. Gary Buehler
Director, Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, Maryland 20855

RE: MINOR AMENDMENT – CMC COMMENTS

Dear Mr. Buehler:

Reference is made to your facsimile dated November 6, 2002 (CMC comments) for the above referenced application (copy attached). Pursuant to 21 CFR 314.120, Andrx Pharmaceuticals is submitting a minor amendment to this ANDA that provides a complete response to all the deficiencies listed in the facsimile.

Response To Chemistry, Manufacturing And Controls Deficiencies

A. Chemistry Deficiencies:

1. Regarding the manufacturing process:

You have submitted executed batch records and stability data in support of your claim that the

[]

- a. The RSD of many dissolution data ranges is rather high (up to —). For example, see stability data sheet on page 485. Please explain.

Response

High variability of the dissolution data is observed during the first few hours of dissolution where there is a low concentration of released drug. This is not unexpected and is inherent in any process where measurement of low drug concentrations is required. As the submitted data indicates, the variability decreases as drug release progresses.

- b. The dissolution results are not consistent across strengths, lots or packaging configurations. Please explain.

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Response

Although the data appears to be inconsistent, the variability is within the accepted ranges recommended by the Division of Bioequivalence.

- c. The dissolution averages are within specification, but in many instances the individual values are above the upper limit. It is not clear whether you are using the USP Acceptance Table. If so, please specify number of samples used.

Response

The acceptance criteria for drug release are based on the USP Acceptance Table. The stability data provided under **Tab 1** specifies the number of samples tested for drug release.



3. Regarding the dissolution medium:

You have withdrawn your earlier assertion that — provides for a more discriminating medium for the observation of the curing phenomenon. In this amendment you have provided data that you purport to demonstrate that the — and buffer medium provide similar profiles. We however, believe that this is not so. In this regard:

- a. At 4-hour and 8-hour time points, the dissolution in — is lower than that in —. Is this due to the pH of the medium? Please explain.
- b. The range of dissolution values in — medium (for example, — at 8 hours for the 30 count package) is larger than the — medium (for example, — for the 30-count package) during the — (page 656). Please explain.
- c. Use of — medium may result in more out of specification lots due to the generally high dissolution rates observed in this medium. Please discuss.

Response

We concur with the Agency that at the 4-hour and 8-hour time points, the dissolution value in is lower than in . This is clearly due to the pH of the medium. We also agree that during the equilibration period, the range of dissolution values at the 8-hour timepoint is indeed larger in than in the . At the 4-hour timepoint, however, the range of dissolution values is larger in the than in .

The equilibration period is more clearly defined at the 4-hour timepoint in the medium and in fact, our studies to determine the required equilibration period were conducted in this medium. Dissolution testing of the optimized product beyond the equilibration period has been performed in . We have shown that once equilibration has occurred, dissolution of the optimized product stored under various stability conditions consistently meets the current acceptance criteria recommended by the Division of Bioequivalence. At each timepoint, the average drug released is approximately at the midpoint of the recommended ranges.

4. We note that the expiration date is calculated from the date of manufacture of the active . It is not clear if the stability test points are calculated from the date of manufacture of the active or the date of release? Please explain.

Response

The stability test points are calculated from the date the product is .

5. As noted in our previous letter, we may request full term data for establishing the expiration dating for this product.

Response

We acknowledge that the Agency may request full term data for establishing the expiration dating for this product. However, we maintain that the data we have already generated clearly support the proposed expiration-dating period.

Response

copy) of the final printed labeling are provided under Tab 4.

- B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. **You have submitted 48-month stability data for the old bio batches (lot # 699R001A) to establish the curing phenomenon. We have not evaluated this data as the proposed process is different from the process used in the manufacture of the old batches.**

Response

We note and acknowledge that the Agency has not evaluated the 48-month stability data for the old bio batches.

2. **The dissolution specifications are under review and the final specification will be established by the Division of Bioequivalence.**

Response

We note and acknowledge that the dissolution specifications are under review and the Division of Bioequivalence will establish the final specification.

3. **Please submit available controlled room temperature stability data.**

Response

The available controlled room temperature stability data is provided under Tab 2.

4. **A satisfactory compliance evaluation for the firms referenced in the ANDA is required for approval. The Establishment Evaluation Request (EER) is pending.**

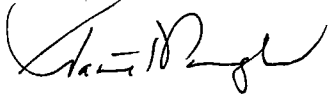
Response

We note and acknowledge that a satisfactory compliance evaluation for the firms referenced in the ANDA is required for approval and that the Establishment Evaluation Request (EER) is pending.

Andrx Pharmaceuticals, Inc. certifies that a Field Copy of this amendment was submitted to the Florida District Office. That field copy is a true copy of the information contained in this amendment.

Should you have any questions or comments concerning this amendment, please contact me at (954) 358-6125 (Tel.) or 954-358-6350 (Facsimile).

Sincerely,



Janet Vaughn

Sr. Regulatory Affairs Manager

Redacted 3

10/29/22
1hr

Page(s) of trade

secret and /or

confidential

commercial

information



NAH
Bio has dup
copy.
Asher 10-10-02

ANDA #75-401
Diltiazem HCl Extended-Release Capsules, USP (Taztia XT™)
120, 180, 240, 300, and 360 mg

September 30, 2002 ~~BIOAVAILABILITY~~

Mr. Gary Buehler
Director, Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, Maryland 20855

ORIG AMENDMENT

N/AB

Re: Bioequivalency Amendment

Dear Mr. Buehler:

Reference is made to your facsimile dated September 11, 2002 regarding the above referenced application (copy attached). Pursuant to 21 CFR 314.120, Andrx Pharmaceuticals is amending this application by responding to the listed deficiencies.

Fasting study on the 360 mg capsules:

1. Sample numbers 6.07.4, 6.08.4, 10.05.1, [10.06.1] 12.04.3, 12.05.3, 16.08.1, 16.09.1 were coded IA and were reassayed for diltiazem, desacetyldiltiazem, and desmethyl diltiazem. However, these samples do not seem to meet the definition of 'IA' given in SOP DH 8.2 (vol. 10.3, page 0433). Please provide the justification for reassaying these samples and using the reassay values.

Response:

An error in one step of the extraction procedure occurred for the eight listed samples, requiring a _____ of the plasma samples. Because of this error, although the samples were analyzed, the concentrations were never calculated and thus, no 'initial' values were reported. A 'reassay' of these eight samples was then performed.

According to _____ terminology (as given in SOP DH 8.2, vol. 10.3, page 0433 (Tab 1)), a result obtained when a plasma sample is re-extracted is referred to as a "reassay" value, regardless of whether a "first" value was obtained or not. As there were no initial values, the 'reassayed' values are the only values that were obtained for samples 6.07.4 and 6.08.4; 10.05.1 and 10.06.1; 12.04.3 and 12.05.3; 16.08.1 and 16.09.1.

Certified copies of the form "____ Procedures" for these samples are provided under Tab 2. These forms indicate where the analyst noted the errors (at Step 14) in the extraction procedure with regard to the aforementioned samples. As indicated in the Notes section of the forms in Tab 2, the samples were inadvertently pooled and were thus immediately coded "IA" for "incomplete analyses".

Therefore, as discussed above, the "reassay" value is the only value that was obtained for these samples.

2. Please provide potency and content uniformity data of the reference product.

Response:

Potency and content uniformity data for the reference product, Tiazac™ (Diltiazem HCl Extended Release) Capsules, 360 mg, Biovail's lot #010912, is provided under Tab 3.

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3. The size of the bio batch and that of the largest lot planned for full production is not given.

Response:

Strength (mg)	Theoretical Biobatch size (no. of caps)	Theoretical Commercial batch size (no. of caps)
360		

Fasting study on the 240 mg capsules:

1. Please clarify if the clinical study was conducted in _____ (page 4, vol. 10.13; page 1518, vol. 10.15) or in _____ (page 1523, vol. 10.15).

Response:

The clinical portion of the study was done at the _____

2. Please provide potency and content uniformity data of the test and reference products.

Response:

Potency and content uniformity data for the reference product, TiazacTM (Diltiazem HCl Extended Release) Capsules, 240 mg, Biovail's lot #010807, is provided under Tab 3.

3. The size of the bio batch and that of the largest lot planned for full production is not given. The manufacture date of the test product should be provided.

Response:

The theoretical batch sizes of the biobatch and the proposed commercial production batch are as follows:

Strength (mg)	Theoretical Biobatch size (no. of caps)	Theoretical Commercial batch size (no. of caps)
240		

The biobatch was manufactured September 11, 2001.

Sprinkling study:

1. In the fed study, one subject (#22) had diltiazem C_{max} T/R ratio of 0.362 but the results were not considered enigmatic. Please explain why these results were not considered enigmatic whereas the similar results obtained in the sprinkling study (subject #21) were considered enigmatic.

Response:

In the fed study (R02-046), although the results from Subject #22 after Brand dosing appear enigmatic, the subject presented no apparent clinical reasons and was not deemed an outlier. Therefore Subject #22 in the fed study (R02-046) was not removed from the final data set. Whereas in the sprinkling study (R02-428), clinical reasons were presented (viral illness/medication ingestion prior to and/or during Period 2; Statistical Report, page 5) to consider the results for Subject #21 to be enigmatic and therefore a repeat study (A02-428) with this subject and 3 control subjects was performed. The results of the repeat study confirmed that the results for

Subject #21 in R02-428 (after Brand formulation dosing) were enigmatic, and Subject #21 was subsequently removed from the final data set.

2. Please clarify if the clinical study was conducted in _____ page 3, vol. 10.19; page 1433, vol. 10.22) or in _____ (page 478, vol. 10.20).

Response:

The clinical portion of the study was done at the _____

Dissolution:

Please provide volumes, compositions and molarities of the dissolution media used in the dissolution testing.

Response:

Dissolution testing is conducted in _____
The _____ is comprised of a solution of _____

Formulation:

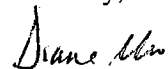
The quantities of active _____ ingredients given in the master formula on page 75 vol. 9.1 differ from that given in the original application. Please provide comparative quantitative composition of all strengths of your drug product.

Response:

Reference is made to the September 19, 2002 telephone conversation with Dr. Nina Nwaba (OGD-Bioequivalence (BE) Project Manager) and the BE reviewer in which Andrx was instructed that in response to this comment, Andrx need only submit a comparative composition table of all strengths of the drug product and compare the original ANDA batches to the batches provided in the May 2002 amendment. **Tab 4** includes a table of the theoretical composition of the capsules based on 100% potency of the ER _____ as well as a comparison of the theoretical (target) capsule fill weights versus the actual fill weights (based on the actual potency of the ER _____) used for both the ANDA batches and the new batches. Please note that no changes have been made to the formulation/composition since the original ANDA was submitted. However, per the approved batch record, the capsule fill weight requires adjustment based on the assay of the ER _____

We look forward to a prompt review of the submitted information, and approval of this application. Please do not hesitate to contact me at 954-358-6114 if you require any additional information.

Sincerely,



Diane Servello
Sr. Director of Regulatory Affairs



June 7, 2002

Mr. Gary Buehler
Director, Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, Maryland 20855

UC
NEW CORRESP

Re: ANDA No. 75-401 (TaztiaTMXT - Diltiazem HCl Extended-Release Capsules,
120, 180, 240, 300, and 360 mg) – TECHNICAL CORRECTION

Dear Mr. Buehler:

As discussed in our correspondence dated October 5, 2001, Andrx Pharmaceuticals, Inc. (Andrx) discovered that the batches of TaztiaTM XT Capsules which it manufactured with _____

As a result of this discovery, our May 22, 2002 submission advised that all batches of TaztiaTM XT Capsules would be manufactured with a _____ Nevertheless, in preparing our May 22, 2002 submission, we noticed that our controlled correspondence dated December 10, 2001, had an incorrect statement with regard to the number

All batches of TaztiaTM XT Capsules that were manufactured with a _____ have been rejected, and will not be sold.

Please do not hesitate to contact me at 954-358-6114 if you require any additional information.

Sincerely,

Diane Servello

Diane Servello
Sr. Director of Regulatory Affairs

RECEIVED

JUN 10 2002

OGD / CDER

*Noted
D. Shepperson
6/24/02
Shawn to
S. Baseman
for review*

*7/5/02
6/15/02*



May 22, 2002

NAB

ORIGINAL

Mr. Gary Buehler
Director, Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, Maryland 20855

Re: ANDA No. 75-401 (TaztiaTMXT - Diltiazem HCl Extended-Release Capsules, 120, 180, 240, 300, and 360 mg) – BIOEQUIVALENCE AMENDMENT

Dear Mr. Buehler:

Reference is made to your letters dated March 5 and 12, 2002 concerning the above-referenced product. Pursuant to 21 CFR 314.120 Andrx Pharmaceuticals, Inc. is amending this application by responding to all the listed deficiencies.

Simultaneously with this letter, Andrx Pharmaceuticals, Inc. ("Andrx") is submitting a CMC amendment, providing complete responses to the CMC deficiencies communicated to Andrx in a letter dated March 20, 2002. As more completely explained in that letter, Andrx discovered that

_____ was used in the manufacturing process. Andrx investigated those failures and identified the problem as the being the _____ for its product, and through its correspondence of October 23 and November 5, 2001 attempted to explain the cause of the problem through _____ between two different strengths of its _____ product; one of which failed and one of which passed. Following additional investigation and the agency's continued concern about whether an appropriate _____ was established, Andrx determined (and orally communicated to the agency) that it would only manufacture its product using the same _____ used to manufacture its original biobatches, and performed additional bioequivalence testing of that _____ product. Accordingly, Andrx hereby requests that the _____ data submitted to this application on October 23 and November 5, 2001 be withdrawn, and is hereby submitting additional bioequivalence studies demonstrating that our _____ product is bioequivalent to the RLD.

Accordingly, please see the following for our responses:

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March 5, 2002 letter - Bioequivalency Deficiencies

Comment 1

You state that the diltiazem hydrochloride capsules that you provided to Biovail were from the validation lots. The manufacturing process differed from the original ANDA bio-batches in the _____, which affected the dissolution and hence the failure to show bioequivalence to the 240 mg capsules of the RLD. However, since the same _____ are used for all strengths, why did the 120 mg capsules study pass but the 240 mg capsule study fail the dissolution and bioequivalence testing?

Response:

An investigation of these failures was conducted, and the results are described more fully in the

[REDACTED]

Comment 2

1

[REDACTED]

Response:

[REDACTED]

bioequivalent to the RLD.

Comment 3:

release rates. The dissolution profiles of these two strengths are similar ($f_2 =$ _____)

Response:

Our product is bioequivalent to the test.

Comment 4:

Response:

As we are withdrawing the data submitted to this application on October 23 and November 5, there is no need to supply further dissolution data in reference to the above comment.

Comment 5:

Response:

As described in our response to Comment 1, the 240 mg capsules supplied to Biovail were made

March 12, 2002 letter - Bioequivalency Deficiencies

Comment:

The bioequivalence studies and the dissolution testing proposed by you on March 5, 2002 are acceptable. However, please note that since the manufacturing process of the test product is

determined to be significantly different from the one submitted originally, a sprinkling study on the proposed highest strength is also requested for the approval of the product.

Response:

As discussed in our March 5, 2002 letter, Andrx is submitting the following data for your review:

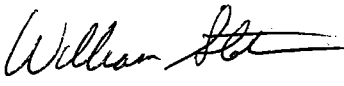
1. Dissolution profiles for 120 mg, 180 mg, 240 mg, 300 mg and 360 mg capsules [both Taztia XT™ (Andrx) and Tiazac® (Biovail)] in the following media:
 - pH — (Exhibit 1)
 - pH — Exhibit 2)
 - pH — Exhibit 3)
 - pH — Exhibit 4)
 - — (Exhibit 5)
2. F₂ factors calculated, comparing: (Exhibit 6)
 - 120 mg vs. 360 mg
 - 180 mg vs. 360 mg
 - 240 mg vs. 360 mg
 - 300 mg vs. 360 mg
3. Results of ongoing stability studies on the original ANDA biobatches and the validation batches produced with the optimized process in October 2001. These include the two lots used in the new bioequivalence studies (240 mg – 698B006 and 360 mg – 700B006). The optimized process includes the 4 ~~period~~ and the 30-day equilibration period. (Exhibit 7)
4. Reports of the long-term stability of diltiazem and its metabolites in human plasma are included for each of the four new bioequivalence studies in **Exhibit 8**.
5. Final report of bioequivalence study (study no. R02-045):
Diltiazem hydrochloride 360 mg capsules (Andrx) vs. Tiazac 360 mg capsules (Biovail); Single dose fasting in 40 healthy subjects; Randomized, 4 period, 2 sequence, crossover, replicate design; Measurement of diltiazem, desmethyldiltiazem and desacetyldiltiazem to 48 h. (**Appendix A, Volumes 2 through 8**)
6. Final report of bioequivalence study (study no. R02-046):
Diltiazem hydrochloride 360 mg capsules (Andrx) vs. Tiazac 360 mg capsules (Biovail); Single dose fed in 24 healthy subjects; Randomized, 2 period, 2 sequence, crossover design; Measurement of diltiazem, desmethyldiltiazem and desacetyldiltiazem to 48 h. (**Appendix B, Volumes 9 through 12**)
7. Final report of bioequivalence study (study no. R02-206):
Diltiazem hydrochloride 240 mg capsules (Andrx) vs. Tiazac 240 mg capsules (Biovail); Single dose fasting in 40 healthy subjects; Randomized, 4 period, 2 sequence, crossover,

replicate design; Measurement of diltiazem, desmethyldiltiazem and desacetyldiltiazem to 48 h. (**Appendix C, Volumes 13 through 18**)

8. Final report of bioequivalence study (study no. R02-428 and A02-428):
Diltiazem hydrochloride 360 mg capsules (Andrx) vs. Tiazac 360 mg capsules (Biovail);
Single dose fasting sprinkling study in 40 healthy subjects; Randomized, 4 period, 2
sequence, crossover, replicate design; Measurement of diltiazem, desmethyldiltiazem and
desacetyldiltiazem to 48 h. (**Appendix D, Volumes 19 through 24**)

Andrx believes that the data presented in this amendment, along with the data included with the CMC amendment being submitted simultaneously, clearly demonstrate that by using a 40-hour and a 30-day equilibration period, the resulting product is bioequivalent and has a stable dissolution rate. We look forward to a prompt review of the submitted information, and approval of this application. Please do not hesitate to contact me at 954-358-6114 if you require any additional information.

Sincerely,

for 

Diane Servello
Director of Regulatory Affairs



May 22, 2002

NAC

ORIG AMENDMENT

Mr. Gary Buehler
Director, Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, Maryland 20855

Re: ANDA No. 75-401 (TaztiaTMXT - Diltiazem HCl Extended-Release Capsules, 120, 180, 240, 300, and 360 mg) – MAJOR AMENDMENT - CMC

Dear Mr. Buehler:

Reference is made to your letter dated March 20, 2002 concerning the above-referenced product. Pursuant to 21 CFR 314.120 Andrx Pharmaceuticals, Inc. is amending this application by responding to all the listed deficiencies.

Please note that a bioequivalence amendment is being submitted simultaneously with this amendment, providing complete responses to the bioequivalence deficiencies communicated to Andrx in letters dated March 5 and 12, 2002. The bioequivalence amendment includes in-vivo dissolution data and final reports from four new bioequivalence studies.

Accordingly, please see the following for our responses:

Comment 1

Please submit the revised master batch records and executed batch records for the strengths used in the new bioequivalence studies and for those strengths for which a biowaiver is requested. The product strengths should be manufactured using different batches of active — All laboratory controls including revised dissolution method, accelerated and room temperature stability data and other pertinent Chemistry, Manufacturing and Controls information are to be submitted. Because your studies showed that, for this product, changes in the dissolution rate are observed from room temperature studies but not from the accelerated studies, long term room temperature stability data is necessary to establish a tentative expiration date.

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Response:

Enclosed, please find the following:

1. A revised master batch record for "Diltiazem HCl Extended-release (TZ)" (Code #151). Please note that optimization of the process involved only the extended-release stage. The manufacturing parameters for the active process remain unchanged from the master batch records submitted with the original ANDA. (**Exhibit 1**)
2. Executed batch records for batches of each of the five strengths produced with the optimized process. The product strengths were produced using different batches of active and extended-release as shown in the following table:

Table 1. Test Batches

STRENGTH	CAPSULE BATCH NUMBER	EXTENDED-RELEASE BATCH NUMBER	ACTIVE BATCH NUMBER	LOCATION OF EXECUTED BATCH RECORD IN THIS AMENDMENT

3. Certificates of analysis for each of the five capsule batches listed above are included as **Exhibit 7**.
4. We have enclosed stability data from batches produced with the optimized process and our original ANDA biobatches as **Exhibit 8**, as follows:

Table 2a. Available stability data – 120 mg

BATCH NUMBER	STABILITY CONDITION	PACKAGE SIZE	LAST TIMEPOINT TESTED

Table 2b. Available stability data – 180 mg

[illegible]

Table 2c. Available stability data – 240 mg

BATCH NUMBER	STABILITY CONDITION	PACKAGE SIZE	LAST TIMEPOINT TESTED

Table 2d. Available stability data – 300 mg

BATCH NUMBER	STABILITY CONDITION	PACKAGE SIZE	LAST TIMEPOINT TESTED

BATCH NUMBER	STABILITY CONDITION	PACKAGE SIZE	LAST TIMEPOINT TESTED

5. As demonstrated by the long-term studies (48 months) of controlled room temperature stability from our original ANDA biobatches, the drug release from Taztia XT remains very stable after the equilibrium is reached. (The equilibrium is discussed in more detail in our response to Comment 3 below)

Comment 2

The critical parameters identified in your optimization studies affect the _____ efficiency of the process, which determines the extended release characteristics of the product. Please submit _____ efficiency data on the process for the test batches requested in 1). For comparison, please also submit the _____ efficiency data on the process submitted in the ANDA.

Response

Please see **Exhibit 10** for a report showing the _____ efficiency of the test batches listed in Table 1 above in comparison with the original ANDA batches.

Comment 3

You have indicated that, after the completion of the _____ process, the _____ In addition to this _____, there is an equilibration period during which the product dissolution at the 4-hour time point continues to increase. Because the _____ process affects the product dissolution profile and, by inference, Diltiazem bioavailability, please address the following issues:

- i. *Please characterize the process responsible for the observed equilibration – e.g. continued curing of the _____ or some other mechanism. Provide and discuss the study results leading to your conclusions, including the parameters/characteristics studies and the test/procedures used for the analysis of measurement.*

As outlined in our Master Batch record included as Exhibit 1 (Product Code number 151),

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**Page(s) of trade
secret and /or
confidential
commercial
information**

change in dissolution between the 3-month and 6-month test intervals, clearly demonstrating that once equilibrium is reached, the dissolution remains stable.

Since we have demonstrated that a 30-day period _____ is sufficient to allow completion of the equilibration process, the in-vitro drug release will remain unchanged throughout the shelf life of the product. In addition, the new bioequivalence studies (which are being submitted simultaneously with this amendment) were conducted more than 30 days after _____. Thus, the studies were conducted on batches that were properly equilibrated. The study results show that after equilibration, the product is bioequivalent to the RLD.

iv. Please clarify how this equilibration period affects the schedule for product release and distribution, and product expiration dating.

Response:

As stated previously, _____ batches will be held for 30-days to permit completion of the equilibration process. After the 30-day period, the batches will be tested by our QC laboratory and released for distribution. The expiration-dating period will be calculated from the beginning of the manufacturing cycle, which is the date the active _____ were produced.

Comment 4

Because you have indicated that using _____ as the dissolution medium obscures the effect caused by the _____ equilibrium phenomenon, we recommend that the _____ medium be used for your product dissolution test.

Response

Andrx Pharmaceuticals respectfully acknowledges the agency's recommendation that the dissolution test be conducted in _____. In our December 12, 2000 amendment, Andrx indicated that _____ obscured the _____ equilibrium phenomenon. However, after reviewing all of the data collected as of today, we believe that our original statement was incorrect. Our current data show that the _____ medium does not obscure the _____ equilibrium phenomenon. Indeed, the onset of the equilibration process is clearly evident equally in both _____ and _____ after _____.

To demonstrate this fact, we have enclosed dissolution data for Taztia XT 360 mg capsules, lot #700C001. In this study, dissolution testing was conducted at weekly intervals using both _____ and _____. The results show that the dissolution behavior in both media is almost identical. However, a greater increase in the 4th hour dissolution value is seen with the _____. (Exhibit 14)

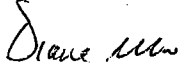
Therefore, we propose to continue the use of _____ as the dissolution medium for product release and stability monitoring

Andrx believes that the data presented in this amendment, along with the data included with the bioequivalence amendment being submitted simultaneously, clearly demonstrate that by using a

Taztia XT™ (Diltiazem HCl Extended-release Capsules); ANDA 75-401

_____ and a 30-day equilibration period, the resulting product is bioequivalent and has a stable dissolution rate. We look forward to a prompt review of the submitted information, and approval of this application. Please do not hesitate to contact me at 954-358-6114 if you require any additional information.

Sincerely,



Diane Servello
Sr. Director of Regulatory Affairs

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February 1, 2002

Via Facsimile (Hand Delivery on February 4, 2002)

Gary J. Buehler
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place (HFD-600)
Rockville, Maryland 20855

CONFIDENTIAL
Contains Data
Subject to Protective
Order

Re: ANDA 75-401 (Taztia™ Diltiazem HCl Extended-Release Capsules, 120, 180, 240, 300, and 360 mg) – Renewed Request that the Patent Certification for this Application be Reissued

Dear Mr. Buehler:

On September 28, 2001, Biovail submitted information documenting that Andrx Pharmaceuticals intended to market a drug pursuant to the above-referenced abbreviated new drug application (ANDA) that was different than the drug product originally described in the ANDA. Therefore, Andrx was seeking approval of a product formulation that had never been the subject of a patent certification under 21 U.S.C. § 355(j)(2)(A)(vii). Biovail has neither received a new notice of patent certification from Andrx nor a response from your office. In the meantime, however, further production of records in ongoing litigation between Biovail and Andrx now provides vastly more evidence in support of the view that the existing patent certification in ANDA 75-401 is inaccurate. Indeed, Biovail's interpretation of the evidence is that the product described by ANDA 75-401 is unapprovable and that a new application for a redesigned product is needed. Recent document production by Andrx and deposition testimony have revealed to Biovail that the staff of the Office of Generic Drugs has confirmed many of the same deficiencies that Biovail has noted. Until a new patent notification has been received, however, Biovail will continue to provide you with the benefit of its analysis of deficiencies noted in materials submitted to you by Andrx as they come to our attention.

As you are no doubt aware, on January 2, 2002, Biovail filed a Citizen Petition (Docket No. 02P-0001), which recommends a procedure that FDA should adopt to help maintain the

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integrity of patent certifications when amendments are submitted during the FDA approval process. That petition also identified that publicly disclosed information regarding ANDA 75-401 revealed the potential for product changes affecting the accuracy of a patent certification were viewed by that applicant as capable of implementation without even providing advance notice to FDA, let alone to the holder of the NDA for the reference listed drug or to the patent holder. We urge your support for favorable FDA action on that petition.

Comment Regarding Andrx letter dated October 5, 2001

In a letter dated October 5, Andrx Pharmaceuticals, Inc., purports to respond to comparative bioavailability data conducted at Biovail's request and which have been previously submitted to you. That letter continues the tradition Andrx established with its original ANDA filing of ignoring, disguising, or misrepresenting data that are unfavorable. The letter chronicles Andrx's unsuccessful attempts to develop a production-scale manufacturing procedure that can consistently produce an in-specification product. What the October 5 letter lacks is any clear evidence that Andrx understands what is causing its manufacturing problems or that it has data documenting that the problems have been resolved.

Andrx also takes the opportunity to urge FDA to ignore the Biovail data on policy grounds. This argument is specious and ironic. The protective order governing Biovail's access to all of the data Biovail has submitted was specifically amended to authorize Biovail to share data with FDA (a copy of the Order is attached to this letter.) Andrx's hypothesis that data submitted by an applicant are more reliable than other data is false. In fact, there is a rich and sorry history of generic drug applicants submitting fraudulent data to FDA to obtain approvals. Indeed, FDA's data integrity requirements grew out of that experience. FDA has audited the study conducted by Biovail's Contract Research Division (CRD). Biovail prefers to let the integrity of the data speak for itself.

As discussed in detail below, during the past nine months Biovail has made numerous submissions which, in its opinion, unequivocally document that Andrx has deliberately and persistently taken steps to hide from FDA the fact that the product described by ANDA 75-401 is poorly designed and cannot be manufactured to meet specification. This strategy resulted in FDA issuing a tentative approval on September 29, 2000. When Andrx came to realize that it could not manufacture product that met specification – even when it tried to replicate the conditions used for the batch which demonstrated bioequivalence to Tiazac at the 360 mg dosage – it proposed an amendment dated December 12, 2000¹, to change the dissolution method

¹ While that amendment characterizes the failing results of the USP test procedure as an artifact and postulates advantages to adopting a _____ dissolution medium, the non-correlation between *in vivo* and *in vitro* results documented at Exhibit 7 to the Declaration of Dr. Mathiowitz contained in Biovail's October 11 submission exposures that the "advantages" postulated by Andrx have been contradicted by data.

by which the specifications would be measured to one that is more "forgiving." Biovail has since established that the new dissolution method, which has never been validated with Taztia™, is so "forgiving" it is incapable of predicting whether the product will perform in a manner that is bioequivalent to the reference listed drug, Tiazac®. Nonetheless, FDA issued a second tentative approval on May 14, 2001.

Andrx has long had reason to know that ANDA 75-401 was filed prematurely.

The 360 mg dose samples manufactured by Andrx and used for the bioequivalence study in its ANDA were manufactured in an irreproducible manner.² The fact that the batch was found to be bioequivalent to Tiazac was an unfortunate accident from Andrx's perspective because it falsely suggested that a successful product design had been established. Reproducing the accidental bioequivalence of this batch was further confounded by the a lack of evidence that the product met USP specifications when manufactured; the ANDA reported apparent compliance with USP criteria only because the USP test data submitted in the application was not performed until months after manufacture was complete.³ Andrx later admitted that this product was unstable as manufactured since its absorption of _____ altered its rate of dissolution.⁴ Subsequent admissions confirm this same product failed the new proposed dissolution method (using _____ as a dissolution media) when it was manufactured.⁵

² See pp. 009355-56 of ANDA 75-401 (Tab P of Biovail's May 10, 2001, submission). The batch record for Lot 151R001 reports that the extremely critical _____

³ The failure to conduct testing shortly after completion of manufacturing was cloaked in an obfuscatory note at page 009695 of the original ANDA, the significance of which can only be appreciated in light of subsequent events. The USP dissolution method using _____ was first proposed in the *Pharmacopeial Forum* in January 1997, a full year prior to manufacture by Andrx of the product used for the biostudy. As disclosed in the Technical Report that accompanied Andrx's December 12 amendment to NDA 75-401, Andrx hoped from the start to have the _____ dissolution method applied to its product. It did perform timely initial testing of the product manufactured for the biostudy with this method. One incentive to file the ANDA with the untimely conducted (and, hence, irreproducible) USP dissolution results is that the biostudy batch apparently failed to meet specifications using the _____ dissolution media.

⁴ See paragraph 2.2 at page 004 of the December 12, 2000, amendment to ANDA 75-401.

⁵ This was first brought to FDA's attention at page 10 of the evaluation of Andrx data submitted to Mr. Buehler on May 10, 2001, citing page 0000023 of Exhibit E (the December 12, 2000, amendment to ANDA 75-401).

It is equally important to note that all batches produced by Andrx, whether pilots or scaled up, show an early period of dissolution instability from 3 weeks to 3 months due to inappropriate process conditions. This is particularly significant given that the pivotal bioequivalence study was run, without proper analysis, only DAYS after the product was

As noted above, Andrx struggled unsuccessfully to scale up its process during calendar year 2000, and concluded that rather than actually fix the problems with its manufacturing process by correcting a faulty product design, it would redefine success by proposing an alternate dissolution test method in a December 12 amendment to its ANDA. This was not an optional submission by Andrx solely for the purpose of accommodating changes required by scale up; it was a mandatory filing because Andrx's long and unsuccessful validation program had proven it could not successfully produce a compliant batch even at the original scale used to make product for the bioequivalence study.⁶ Given the admissions contained in the December 12, 2000, amendment, the original application was clearly unapprovable for production at any scale.

The alternate *in vitro* dissolution test proposed by Andrx is completely inadequate to predict the *in vivo* performance of its product. Biovail's October 11, 2001, submission contained an expert opinion of Dr. Edith Mathiowitz explaining the inappropriateness of a _____ from a scientific standpoint and contained a plot of blood levels from various dosage strengths of Taztia™ as a function of the 8-hour dissolution results for the product at Exhibit 7. The correlation, such as it is, shows that the _____ dissolution test method tends to provide the same dissolution result regardless of how the product performs *in vivo*. FDA's request that Andrx perform a post approval equilibration study⁷ suggests that some concern about the Andrx manufacturing methods and the reliability of the dissolution test method existed at FDA.

The consequences of Andrx's non-rigorous approach to process design and product development came to the fore when Taztia™ samples provided to Biovail in the course of patent infringement litigation were subjected to separate bioequivalence testing by Biovail's CRD and Anapharm. Both facilities confirmed that the 240 mg dosage strength reached a C_{max} level that was significantly above the maximum level for bioequivalence.

⁶ Andrx Report "Scale Up Report for Diltiazem HCl Extended-Release Capsules (TZ), page 5 of 6 for Batch 151A003, Batch Record Revision No. 2. This was submitted to Mr. Buehler as Exhibit E of Biovail's August 21, 2001, submission. Also, Andrx Investigation Report No. 00-054 "Out of Specification Results, DI Water Dissolution-Diltiazem HCl ER Pellets (TZ), Product Code # 151. This is Exhibit C of the August 21, 2001, submission.

⁷ Exhibit S of Biovail's August 21, 2001 submission is a copy of Andrx's commitment to perform the requested study.

Andrx's own records document the adoption of manufacturing process changes that result in a product different than that described in the original ANDA. The changes envision manufacturing outside of the ranges previously disclosed to FDA. Even with these manufacturing changes, it is likely that the final product will remain highly variable. At the very least, the significance of the changes requires that new certifications be submitted for all listed patents, since the product that Andrx now plans to market is substantially different from that which it originally certified to FDA and provided notification of to Biovail.

Andrx's response to the above and its plea for FDA to move forward with approval of all of the dosage strengths of Taztia™ is contained in a letter to Mr. Gary Buehler dated October 5, 2001. It is more of the same. Footnote 1 of that correspondence is every bit as obfuscatory as the note contained in the original ANDA (see footnote 4 of this letter). According to Andrx, the reason that all of the above can be ignored is that: *"the batch from which the Taztia samples were drawn failed to meet dissolution specifications and, thus, would not be expected to demonstrate bioequivalence to Tiazac upon testing."* As if that explains it all. Indeed, it just underscores that a fundamental design deficiency exists because a 120 mg dosage strength product produced under virtually identical conditions appeared to be both bioequivalent and more stable.

Andrx claims that the 240 mg batch met specifications (presumably using the inappropriate, but tentatively approved, _____ dissolution test) when manufactured, but was grossly out of specification 3 months later and so would be expected to fail bioequivalence testing. It follows, of course, that if this product were approved, patients taking it before the 3 month test results were in, and the necessary recall effected, should expect to experience blood levels of diltiazem substantially higher than if they had taken Tiazac®. Rather than find that disclosure reassuring, it should be seen as further confirmation of the lack of control that Andrx has over its product and process.⁸ An alternate explanation for the failing result emerges from dissolution data generated by _____ on individual capsules of the 120 mg dosage strength Taztia™. The data demonstrate what appears to be a significant lack of blend uniformity.⁹ A Citizen Petition (Docket No. 00P-1199), which questions the

⁸ Andrx reports in its October 5 letter that the mean four hour dissolution value for Lot No. 698B001 in May 2000 was 44%; the mean four hour dissolution value in late January was 34%. Validation Report for the Diltiazem HCl Extended-Release Capsules (TZ) 120, 180, 240, 300, and 360 mg. Document No. PVR-055, Table 7, page 15 of 23. This report was included as Exhibit F of Biovail's August 21, 2001, submission. A change in dissolution of more than _____ at the 3 month time point is evidence of a serious design problem given that the batch record for the failing batch is not significantly different than that of batches which appear to remain stable for more than 3 months.

⁹ See p 7/16 of the _____ "1099 Tiazac®, Dissolution, Comparison 2001-03-09 Report. Sample #5 of the 120 mg capsule performs significantly different from the other 5
(continued ...)

appropriateness of bioequivalence waivers for lower dosage strengths when products are composed of multiple bead populations with intentionally different dissolution characteristics, has been pending at FDA since March 16, 2000. Taztia™ is composed of populations with intentionally different dissolution characteristics. The data suggest that Andrx's manufacturing methods do not achieve

In the meantime, Biovail makes a number of observations which raise further doubts as to the credibility of the incomplete explanations that Andrx provides:

1. Clinical dosing (March 10 and March 15) for the bioequivalence test done at CRD occurred about two months after the 240 mg capsules were manufactured; clinical dosing (April 23 and April 30) for the bioequivalence test done at occurred when the capsules were still less than 4 months old. In May, when Andrx completed the 3 month stability analysis which it asserts showed failure, the capsules were more than 4 months old. Despite the instability reported by Andrx, however, the test results from CRD and are remarkably similar. CRD ($C_{max} = 136.28\%$); ($C_{max} = 137.427$).

These observations are consistent with the absence of a correlation between *in vivo* and *in vitro* performance when a is used for the dissolution test. They are also consistent with the possibility that the "stability failure" was really the result of sampling a stable product with non uniform distribution of the populations. We note that it was the product that was constantly under Andrx's custody and control that exhibited dramatic changes in dissolution over time. The consistency of the CRD and results do not support the allegation of mishandling.

2. In footnote 1 of its October 5 letter, Andrx discloses its awareness that its process validation studies have not been successful. Indeed, it reports that its product is "extremely sensitive to even small changes" in process parameters associated with application of the which controls the extended release properties of the While it then asserts that it has reverted to processing parameters identical to the parameters used for the production of the original biobatches, it concedes that one of the important

(...continued)

samples. The final, corrected copy of this report was submitted as Enclosure 2 of a letter to Krista Scardina in FDA's Division of Bioequivalence dated October 5, 2001.

_____ has been changed. The absence of a specification for dew point and significant dew point variations during production of the original biobatch, together with the disruptions to the spray coating process that occurred means that reversion to "identical" processing parameters is impossible. Its subsequent claim of stability at the 30-month time point only refers to the original biobatch.

3. The on-going stability studies on the original ANDA biobatches cannot possibly show that the product manufactured with Andrx's optimized process is stable at the 30-month time point since the so-called optimized process was still being developed as of October 5, 2001 and had not even been recognized as necessary 30 months ago. In light of the "extreme sensitivity" and the unexplained dramatic stability failure of the 240 mg dose batch, extrapolating stability from the original irreproducible biobatch is unjustified. Should Andrx ever succeed in validating a manufacturing process at any scale, a stability study longer than 3 months will be necessary to confirm that the existing stability problems have been resolved.
4. The October 5 letter concedes that Andrx intends to ignore the requirement of the May 14, 2001 tentative approval letter to provide "[u]pdated information related to the labeling or chemistry, manufacturing and controls data, or any other change in the conditions outlined in this abbreviated application" when it believes the application may be considered for final approval. The representation by Andrx that it was going to advise FDA of changes to its chemistry, manufacturing and control procedures pursuant to FDA guidance for SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation (SUPAC-MR) is an erroneous application of the guidance. To appreciate the error of Andrx's interpretation, it is important to recognize that FDA does not approve the material on which bioequivalence data contained in an ANDA is generated, it approves the manufacture of future batches when it is convinced that the data before it reliably establishes how such future production will perform. While scale up issues commonly require adjustments to manufacturing procedures, the SUPAC-MR Guidance presumes that the process being scaled is one that yields a stable, reproducible product. Process adjustments addressed by the SUPAC-MR Guidance are those which are often necessary to reestablish a stable, reproducible product at the new scale. It would be a serious breach of FDA's responsibility under the Federal Food, Drug, and Cosmetics Act

(FFDCA) for FDA to issue an approval to Andrx and, thereby, authorize Andrx to conduct, post-approval, the product development that it failed to complete prior to filing its ANDA.

5. The incentive to be the first filer of an ANDA are well established. An FDA approval of Taztia™ based on the application that Andrx has filed will simply encourage more hastily prepared, incompletely researched and unapprovable first-filed applications.

Comment Regarding Andrx letter dated November 5, 2001, Amendment to NDA 75-401

On November 5, 2001, Andrx submitted an analysis by Dr. Polli which Andrx represented to FDA as establishing a _____ with internal and external predictability for a dissolution test method based on a _____ medium. Biovail has retained an independent expert to review Dr. Polli's report. This critique will be completed shortly and will be forwarded to assist OGD in assessing the Andrx submission. The preliminary conclusion of Biovail's expert, Dr. Young, is that Dr. Polli's analysis falls short of what Andrx has represented.

Comment Regarding Andrx letter dated December 11, 2001

On January 15, 2002, Biovail received a communication from Andrx to the FDA, dated December 11, 2001 that essentially concedes the truth of everything that Biovail has been communicating to the FDA concerning Andrx's inability to reliably and reproducibly produce a "bioequivalent" product to Biovail's extended-release diltiazem hydrochloride product Tiazac.

In this critical document, Andrx admits the following:

"[A]ll batches produced under the validation study started in January 2001 were rejected. This decision was made because *evidence showed that the manufacturing process could not consistently produce a product that met all specifications.*"

Exhibit A, p. AX-463P 029518 (emphasis added).

Andrx claims, in this document, to have achieved a set of "optimized" conditions for manufacture of its alleged bioequivalent product. Andrx alleges that the following conditions are _____

Exhibit A, AX-463P 029519. According to this document:

Id.

Andrx then claims that these "optimized" low processing parameters "correspond to the conditions used to produce the original ANDA biobatches." Exhibit A, AX-463P 029521. One important point needs to be made here. Of the two "biobatches" made pursuant to the original ANDA, namely 151R001 and 151R002, only lot number 151R001 was ever administered to humans to demonstrate alleged bioequivalence to Tiazac. This lot differs in substantial ways from the allegedly "optimized" processing parameters proposed by Andrx in its December 11, 2001 correspondence to the FDA, as shown below.

The spray rate for Part A of the controlled release process for lot number 151R001 ranged from [redacted]. See Exhibit B, "Key Batch Parameters."¹¹ The "optimized" parameter has a range of [redacted], with a target of [redacted]. The rate for Part B of this process, for lot number 151R001, ranged from [redacted]. The "optimized" parameter was set at a range of [redacted], with a target of [redacted]. The rate for Part C of this process, for lot number 151R001, ranged from [redacted]. The "optimized" parameter was set at a range of [redacted], with a target of [redacted].¹²

¹⁰ Andrx had previously prepared validation batches based on other "optimized" conditions, only to later learn that "five of these batches failed the 4-hour dissolution specification after 3 months on room temperature stability." Exhibit A, AX-463P 029518.

¹¹ These values were calculated based on the amount of controlled release [redacted] onto the active [redacted] (in grams) per unit time, as those values are reported in the executed batch record for lot number 151R001. See Tab P of Biovail's May 10, 2001, submission.

¹² In the December 11, 2001 correspondence, Andrx justifies its statements about the similarity between the original ANDA parameters and the "optimized" parameters by reference to Table 7 of that correspondence, on page AX-463P 029552. This table apparently combines processing parameters for both lots 151R001 and 151R002, thus seeming to suggest that the original ANDA parameters are the same as the "optimized" process. Biovail submits that the only relevant original ANDA processing parameters are those that were used to make the only

(continued ...)

What should be readily apparent is that not a single ~~one~~ rate parameter actually used to make the only batch Andrx ever administered to human beings to allegedly demonstrate bioequivalence to Tiazac, namely lot number 151R001, ever rose to any of the "optimized" ~~rate~~ rate parameters.

With respect to another "optimized" processing parameter, the dew point during ~~the~~ Andrx claims that this parameter is optimally set at ~~the~~. Two critical observations must be made with respect to this parameter. First, this processing parameter was never specified in the original ANDA, nor has it been specified in any amendments submitted to the FDA (at least as far as Biovail can determine).¹³

Second, and most critically, the dew point values for original ANDA lot number 151R001 that was actually administered to human beings to demonstrate bioequivalence, *was always higher than* ~~the~~. In short, the original ANDA processing parameters used to make lot number 151R001 did not have a "low" dew point (as defined by Andrx in Exhibit A for its "optimized" processing parameters) and did not have a ~~low~~ rate (as defined by Andrx for its "optimized" process).

Andrx has also provided additional information, in its December 11, 2001 submission, that demonstrates Andrx's wishful thinking that its most recent "optimized" process "correspond[s] to the conditions used to produce the original ANDA biobatches." Andrx sets for a "Comparison of Processing Times for Extended-Release ~~the~~ for Taztia XT ANDA Batches, the First Validation Batches of 2001, and the Current Validation Batches." Exhibit A, AX-463P 029529. A cursory glance shows that there is nothing that corresponds between the "current" "optimized" parameters and the process used to make lot 151R001. Every processing parameter listed on this table differs substantially between the ANDA biobatch and the latest "optimized" batches. Lot 151R001 was "preconditioned" for 10 minutes, more than three times longer than the 3 minute precondition for the "Current Validation." The ~~process~~ process time for Part A was ~~for~~ for the ANDA biobatch, as opposed to the ~~longer~~ longer time (about ~~for~~ for the "Current Validation." The spray process time for Part B is approximately ~~longer~~ longer in the "Current Validation" compared to the ANDA biobatch (about ~~currently~~ currently, versus ~~the~~

(...continued)

batch that Andrx ever administered to human beings to demonstrate alleged bioequivalence, namely batch number 151R001.

¹³ Surely the addition of a new processing parameter would require that Andrx submit an amendment to the FDA setting forth this new parameter, as well as a justification for this parameter as it relates to the original ANDA process.

¹⁴ See Tab P of Biovail's May 10, 2001, submission.

minutes for the ANDA biobatch); the _____ rate process for Part C is about _____, longer in the "Current Validation" (about _____ currently, compared to _____ for the ANDA biobatch). The initial _____ times are twice as long under the most recent "optimized" parameters compared to the ANDA biobatch (_____ for the ANDA biobatch, compared to about _____ under the "optimized" conditions).

In this table, Andrx also disingenuously sets forth, in separate footnotes, the target _____ rates for the ANDA batches and the most recent "optimized" validation batches. The _____ rate ranges for Parts A and C do not overlap. The upper limit for the target _____ rate for Part A in the ANDA as originally submitted is _____; the lower limit for the "optimized" Part A _____ rate is _____ % increase. Likewise, the upper target _____ rate for Part C of the original ANDA process is set at _____ whereas the lower limit for the "optimized" Part C _____ rate is set at _____.

In fact, analysis of the data in this table demonstrates that there is much more similarity between Andrx's previously failed "optimized" validation and the current "optimized" validation. Given this high degree of similarity between a previous failed "optimized" process and the current "optimized" process, and the virtual absence of similarity between the original ANDA process and the current "optimized" process, it is difficult to understand Andrx's confidence that the present "optimized" process will not be the same dismal failure as its earlier "optimized" process. Like the blind men and the elephant, Andrx is groping around different parts of its hopelessly befuddled process and hoping that its pronouncement that the process is now "optimized" is the truth. Its own data proves that Andrx has fixed nothing.

The critical conclusion is that there has never been a human study performed with samples of Andrx's product made pursuant to this "optimized" process. Because there has never been a demonstrable *in vitro-in vivo* correlation of Andrx's product made by this "optimized" process, ***there is no evidence whatsoever that Andrx's "optimized" process results in a product that is bioequivalent to Tiazac.***

Despite this critical lack of evidence, Andrx proclaims that it has yet again "optimized" its processing parameters, even though the last time Andrx declared its processing parameters optimized, "five of these ["optimized" validation] batches failed the 4-hour dissolution specification after 3 months on room temperature stability." Exhibit A, AX-463P 029518.

In the face of this dubious history, Andrx prepared an additional fifteen validation lots based upon the most recent "optimized" processing parameters. *Id.* at AX-463P 029522. These fifteen lots were also placed on room temperature stability, with a two-week sampling interval. *Id.* According to Andrx, room temperature stability data from these fifteen new validation lots "duplicate the room temperature stability results obtained for lot 696X013, the experimental lots produced with the optimized results." *Id.* According to Andrx:

“[i]n all these lots, the 4-hour dissolution values increased slightly from the initial values (room temperature curing process), but reached a plateau within four to six weeks. All of these batches remain within the approved dissolution specifications for the product.”

Id.

First, the room temperature stability results for experimental lot 696X013 (purportedly made pursuant to the latest “optimized” parameters) must be examined. As shown in Exhibit B (AX-463P 023178), a plot of the dissolution mean values for the 4-hour time point over time for experimental lot 696X013, the dissolution values never achieve a plateau.

Moreover, the 3-month room temperature data demonstrate that lot 696X013 exhibits significant variability in dissolution results at the 4-hour time point. According to the raw data, three different measurements on two different days in two different labs gives three different results. Exhibit B, AX-463P 023184. For example, QC (Quality Control), on October 23, 2001, measured dissolution at 4 hours for lot 696X013 stored at room temperature for 3 months, and obtained values ranging from 29 to 40, with an average (calculated) of 35, and a standard deviation (calculated) of 3.7. Two days later, the same laboratory measured the same lot, and obtained values ranging from 31 to 36, with an average of 34 and a standard deviation of 2.9. On October 23, 2001 (the same day as the first QC measurements), the analytical research (AR) lab conducted the same measurements on the same lot, and obtained results ranging from 31 to 38, with an average of 32.5 and a standard deviation of 1.8.

In other words, the allegedly stable lot 696X013 showed actual dissolution results after 3 months of room temperature storage that ranged from a low of only 3 percentage points higher than the time 0 results shown on Exhibit B) to a high of 14 percentage points higher than the time 0 results). The scatter plot on Exhibit B shows the high variability of these dissolution results, belying any claim that this product has reached a “plateau” within four to six weeks.

As for the validation lots made with the most recent “optimized” parameters, even without the raw data it is apparent that there is no “plateau” within this four to six week time period. For example, lot 696B006C has gone from a 4-hour dissolution value of 25 at time zero to 37 after 45 days (more than 6 weeks’ time), with a line that is ever-increasing. Exhibit A, AX-463P 029523. In the Andrx parlance, the ΔR for this lot is already — after only 1.5 months! Similarly, lot 697B005C displays a ΔR of — after 1.5 months, with no indication that the values have reached a plateau after that time. Exhibit A, AX-463P 029523. Lots 698B006A and 698B006C display ΔR values of approximately — percent after almost 10 weeks, and then apparently *decrease* approximately one week later. AX-463P 029525. The values for these two lots never plateau, much less plateau within four to six weeks.

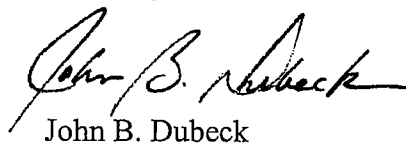
Nevertheless, this plain fact does not prevent Andrx from asserting that "[i]n all these lots, the 4-hour dissolution values increased *slightly* from the initial values." According to Andrx's usage of the word "slightly," a change from a dissolution value of 25 to 37 in six weeks' time (lot 696B006C), a change of 12 percentage points (which is a percentage change of almost 50% in 45 days) means the "values increased slightly" over this time period.

* * *

Despite Andrx's protestations to the contrary, its efforts to rush FDA to grant an inappropriate approval simply underscores the inconsistencies in its ANDA and its desperation to hide them. The simple fact is that ANDA 75-401 is unapprovable for any dosage strength because Andrx has failed to document it is capable of manufacturing any product at any scale that meets all of the applicable specifications and maintains compliance with such specifications for more than a few months. The above conclusion follows despite the completely inappropriate use of an unvalidated dissolution method that is designed to minimize the effect of manufacturing variability.

In closing, please note that this document contains confidential information of both Andrx and Biovail and should therefore be maintained by FDA as confidential pursuant to 21 C.F.R. § 20.61. Except for the data from the publicly available Andrx letter dated October 5, 2001, references to Andrx data are based upon documents which were produced to Biovail in connection with litigation between the companies and are subject to a protective order. Enclosed with this letter are two Orders by Linnea R. Johnson, Chief United States Magistrate Judge for the United States District Court for the Southern District of Florida, relating to the relevant litigation between Biovail and Andrx. Pursuant to the second Order, FDA is free to receive and consider the materials submitted without regard for the provisions contained in the original protective order. FDA must maintain the disclosure as confidential pursuant to 21 C.F.R. § 20.61.

Sincerely,



John B. Dubeck

Enclosures (Exhibits A and B)

cc: Kevin M. Fain, Esq. – FDA Office of the Chief Counsel
(cover letter only) (via facsimile)

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF FLORIDA

CASE NO. 01-6194-CIV-DIMITROULEAS
MAGISTRATE JUDGE JOHNSON

ANDRX PHARMACEUTICALS, INC.,

Plaintiff,

v.

BIOVAIL CORPORATION,

Defendant,

and

TOMMY G. THOMPSON, Secretary, U.S.
Department of Health and Human Services,
BERNARD A. SCHWEITZ, D.V.M., Ph.D.,
Acting Principal Deputy Commissioner, U.S.
Food and Drug Administration, and U.S. FOOD
AND DRUG ADMINISTRATION,

Additional Defendants.

ORDER MODIFYING THE PROTECTIVE ORDERS

Having reviewed Defendant Biovail Corporation's Emergency Motion to Modify the March 9, 2001 Protective Orders previously entered in this case, and determined that the circumstances here warrant modification of (i) the March 9, 2001 general Protective Order and (ii) the second order of the same date relating to certain Taztia samples (collectively referred to herein as the "Protective Orders"),

IT IS HEREBY ORDERED, that the Protective Orders are modified as follows:

1. Notwithstanding any contrary provision in the Protective Orders the Food and Drug Administration ("FDA"), and its employees, agents and attorneys, shall have access to material designated "Confidential" in this case, provided that any material disclosed to FDA in accordance with this Order shall be maintained as confidential by FDA pursuant to 21 C.F.R. § 20.61. Material designated "Confidential" may be used for purposes of assessing the bioequivalence of Taznia.

2. Except with respect to the limited disclosure of information permitted pursuant to this Order, the Protective Order shall remain in full force and effect.

SO ORDERED in chambers in Fort Lauderdale, Broward County, Florida on this

2 day of ^{May} April, 2001.


WILLIAM P. DIMITROFF Linn R. Johnson
UNITED STATES DISTRICT JUDGE
MAGISTRATE

APPEARS THIS WAY
ON ORIGINAL

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF FLORIDA

CASE NO. 01-6194-CIV-DIMITROULEAS/JOHNSON

ANDRX PHARMACEUTICALS, INC.,

Plaintiff,

vs.

BIOVAIL CORPORATION,

Defendant,

and

TOMMY G. THOMPSON, et al,

Additional Defendants.

ORDER

THIS CAUSE is before the Court on Defendant Biovail Corporation's Emergency Motion to Modify the Protective Orders, filed April 17, 2001 and Plaintiff's Cross-Motion for Further Sanctions (Docket Entry No. 125). This Court has reviewed the pleadings filed incident to this matter and is otherwise duly advised. Accordingly, it is hereby

ORDERED AND ADJUDGED as follows. Defendant Biovail Corporation's Emergency Motion to Modify the Protective Orders, filed April 17, 2001 is **GRANTED** and Plaintiff's Cross-Motion for Further Sanctions (Docket Entry No. 125) is **DENIED**.

This Court agrees with Biovail that good cause has been shown for modification of the Protective Order. Andrx has already agreed to allowing the FDA access to the released information. For the reasons stated in the motion and the reply memorandum in support, it only stands to reason that the FDA be allowed access to all material designated

"confidential" in this case. There is, after all, no confidentiality concerns as the modified Protective Order, attached hereto, conditions such disclosure on the requirement that the FDA maintain any such disclosures as confidential pursuant to 21 C.F.R. § 20.61.

Andrx's Motion for Sanctions is denied. For the reasons set forth in Biovail's Reply Memorandum this Court finds no additional violation of the Protective Order. This Court is satisfied that Biovail's use of Andrx's confidential information was "solely for purposes of prosecuting or defending this action" and therefore in compliance with the Protective Order. As for Biovail's previous violation of the Protective Order, Andrx cannot establish that it has been harmed by the previously made inadvertent, now contained disclosures.

DONE AND ORDERED on May 2, 2001, in Chambers, at West Palm Beach, Florida.


LINNEA R. JOHNSON
CHIEF UNITED STATES MAGISTRATE JUDGE

CC: The Honorable William P. Dimitrouleas
Matthew Triggs, Esquire
Michael A. Cardozo, Esquire
Ronald S. Rauchberg, Esquire
Nancy Kilson, Esquire
Gerald J. Houltihan, Esquire
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*NOT ADMITTED IN D.C.
*RESIDENT BRUSSELS

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May 14, 2001

NEW CORRESP

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Via Messenger

Gary J. Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place (HFD-600)
Rockville, Maryland 20855

Re: ANDA 75-401



Noted. NAI.
Bm ybel
5/30/01

Dear Mr. Buehler:

Enclosed please find two documents that were inadvertently omitted from our submission on Thursday, May 10, 2001. They are an Order issued by Linnea R. Johnson, Chief United States Magistrate Judge for the United States District Court for the Southern District of Florida in the Andrx Pharmaceuticals, Inc. v. Biovail Corporation and Tommy G. Thompson proceedings. The second is an Order Modifying the Protective Orders previously issued in Andrx Pharmaceuticals v. Biovail Corporation (Case No. 01-6194-CIV, S.D. Fla). Pursuant to the modification, FDA is free to receive and consider the materials previously submitted without regard for the provisions contained in the original protective order. FDA needs to maintain the disclosure as confidential pursuant to 21 C.F.R. § 20.61.

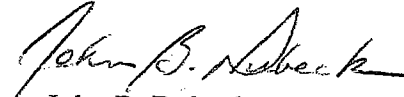
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Gary J. Buehler
May 14, 2001
Page 2

KELLER AND HECKMAN LLP

We have enclosed 15 copies to be inserted into the binders that were sent to you last week. If you have any questions, please give me a call.

Cordially,


John B. Dubeck

Enclosure

cc: Kevin Fain, Esq.
Kim Dettelbach, Esq.
William Peter Rickman
Timothy Ames
Dale P. Conner
Emma R. Singleton



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TELECOMMUNICATIONS
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May 10, 2001

NEW CORRESP
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(202) 434-4125
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Via Messenger

Gary J. Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place (HFD-600)
Rockville, Maryland 20855

Re: ANDA 75-401

Dear Mr. Buehler:

Enclosed is Biovail Corporation's evaluation of Andrx Pharmaceutical Incorporated's submissions in support of its ANDA 75-401. Biovail's evaluation demonstrates that Andrx is unable to manufacture a product that is consistently bioequivalent to Biovail's Tiazac, the reference product, and that Andrx has made misleading submissions to FDA, and therefore the Andrx ANDA should not be approved by FDA.

Biovail requests a meeting with FDA to focus on the technical issues addressed in Biovail's evaluation. The following individuals would participate in the discussion at such a meeting on Biovail's behalf: Paul Maes, Vice President, Pharmaceuticals, of Biovail's subsidiary, Biovail Technologies, Inc., and Gerald Vince and Russell Rutledge of AAC Consulting Group, Inc. Also attending would be Kenneth Cancellara, Biovail's Senior Vice President and General Counsel, John Dubeck of Keller and Heckman LLP, and Ron Rauchberg of Proskauer, Rose LLP. We suggest that a meeting be scheduled as soon as possible. Biovail will endeavor to make its representatives available to attend on whatever date FDA proposes.

Please note that the enclosed evaluation contains the confidential information of both Andrx Pharmaceuticals, Incorporated and Biovail Corporation and should therefore be maintained by FDA as confidential pursuant to 21 C.F.R. § 20.61. A copy of the May 2, 2001 Order Modifying Protective Order entered by United States Magistrate Judge Linnea R. Johnson



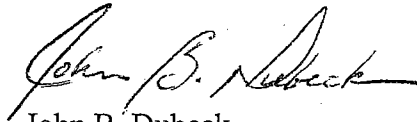
Handwritten notes:
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Noted. NAT.
B. M. G. M.
5/30/01

Gary J. Buehler
May 10, 2001
Page 2

KELLER AND HECKMAN LLP

entered in Andrx Pharmaceuticals Incorporated v. Biovail Corporation, et al, (S.D. Fla. Case No. 01-6194-Civ.), permitting FDA to receive Andrx confidential information provided that it is maintained as confidential pursuant to 21 C.F.R. § 20.61, is enclosed.

Respectfully submitted,



John B. Dubeck

cc: William Peter Rickman
Dale P. Conner
Timothy W. Ames
Emma R. Singleton

APPEARS THIS WAY
ON ORIGINAL



VIA FEDERAL EXPRESS

April 13, 2001

Gary Buehler,
Acting-Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NC NAI
NEW CORRESP
9/20-APR-2001
Hugues S. Land

PATENT AMENDMENT

ANDA 75-401 – Taztia XT (Diltiazem HCl ER Capsules)

Dear Mr. Buehler:

Andrx Pharmaceuticals, Inc. ("Andrx") is amending the above referenced application to provide documentation of the required patent notification and notice of receipt, as well as a copy of a complaint filed against Andrx.

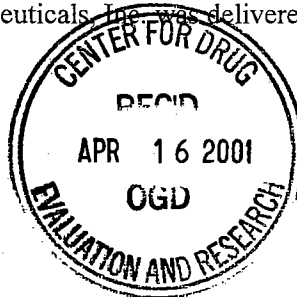
Documentation of Notification /Notices of Receipt:

In accordance with 21 CFR 314.95(b), Andrx certifies that:

- i. the required notices of certification of non-infringement of patent 6,162,463 were provided by U.S. Postal Service Express Mail, return receipt requested to each person identified under §314.95(b) (i.e. Biovail Corporation, Biovail Laboratories, Inc. and DOV Pharmaceuticals, Inc.)
- ii. the notices met the content requirements under §314.95(c).

Return receipts and/or US Postal Service "Tracking and Delivery Confirmation" reports are enclosed as follows:

- A US Postal Service return receipt was requested for the notice sent to Biovail Laboratories, Inc., however, none was returned to Andrx. Instead, we have provided a copy of The US Postal Service Express Mail "Tracking and Delivery Confirmation" for this notice (Tracking #EK824041655US), showing delivery of the notice on February 20, 2001.
- The US Postal Service does not provide return receipts for Canadian addresses, therefore, this service was not available for the notice sent to Biovail Corporation. However, the "Tracking and Delivery Confirmation" for this notice (Tracking #EK824041647US) shows delivery on February 22, 2001.
- A return receipt postcard and the Tracking and Delivery Confirmation" (Tracking #ET292479909US) shows that the notice sent to DOV Pharmaceuticals, Inc. was delivered on February 22, 2001.



Page Two
ANDA 75-401; Patent Notice
April 13, 2001

Copy of Complaint::

A copy of the patent infringement complaint filed against Andrx Pharmaceuticals, Inc. by Biovail Laboratories, Inc (Case #01-6548) is attached.

Should you have any questions concerning this information, please contact me at (954) 585-1412.

Sincerely,



Diane Servello
Director, Regulatory Affairs

**APPEARS THIS WAY
ON ORIGINAL**

File: 75-401

KING & SPALDING

1730 PENNSYLVANIA AVENUE, N.W.
WASHINGTON, D.C. 20006-4708
TELEPHONE: 202/737-0600
FACSIMILE: 202/626-3787

DIRECT DIAL:

Please file in latest
open annual volume

75-401

April 4, 2001

VIA FACSIMILE

Gary Buehler, Acting Director
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

NEW CORRES
NC

Re: Andrx Corporation -- Additional Information in Support of Request for
Immediate Final Approval of Taztia™ XT (ANDA 75-401)

Dear Mr. Buehler:

We respectfully submit the following additional information in support of the request of Andrx Corporation ("Andrx") for immediate final approval of Andrx's drug product Taztia™ XT (diltiazem hydrochloride extended-release capsules; ANDA 75-401). Andrx made that request by letter to you dated March 30, 2001.

Andrx's letter sets forth several strong bases upon which the Food and Drug Administration ("FDA") should conclude that Biovail Corporation's ("Biovail") listing of U.S. Patent No. 6,162,463 ("the '463 Patent") as covering the approved drug Tiazac® should apply only to ANDAs filed after March 26, 2001, if at all. Among other reasons, FDA has determined that Biovail's January 8, 2001 declaration was inadequate because it did not employ the text required by 21 C.F.R. § 314.53(c)(2)(i). See Letter from Ralph Lillie to John Dubeck, Esq. (March 23, 2001). Biovail did not make a declaration using the required language until March 26, 2001 -- i.e., more than 3 months after the patent issued.

We note that FDA's own "Patent Submission Sample Format," which the agency posted on its website almost a year ago on April 25, 2000, makes clear that FDA regards 21 C.F.R. § 314.53(c)(2)(i) as mandating use of the language prescribed by regulation. A copy of FDA's Sample Format is attached for your reference. It is unmistakable that, amid the "suggestions," "shoulds," and "options" that appear throughout the Sample Format, FDA chose to present the

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US):

B. The following declaration statement is required by 21CFR 314.53. If any of the submitted patents have Composition/Formulation or Method of Use claims, it should be submitted for each patent that contains composition/formulation or method of use claims.

The undersigned declares that the above stated United States Patent Number _____ covers the composition, formulation and/or method of use of _____ (name of drug product). This product is:

- ___ currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act)

OR

- ___ the subject of this application for which approval is being sought.)
-

Signed:

Date:

Title (optional):

Telephone Number (optional):

The above information should be submitted to the NDA with the original application or as correspondence to an existing NDA. For patents issued after the NDA is filed or approved, the applicant is required to submit the information within 30 days of the date of issuance of the patent.

To expedite publication in the *The Orange Book*,* the above information may be provided to the Division of Data Management and Services at the address below. You may also contact the Division of Data Management and Services directly at (301)827-5467 regarding listing of patent information.

Mailing address: (US Mail)

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Data Management and Services
Information Services Team
HFD-93
5600 Fishers Lane
Rockville, MD 20857

Gary Buehler, Acting Director
March 30, 2001
Page 2

following statement -- in large boldface type -- with regard to the patent listing declaration required by 21 C.F.R. § 314.53(c)(2)(i):

The following declaration statement is required by 21 C.F.R. 314.53. If any of the submitted patents have Composition/Formulation or Method of Use claims, it should be submitted for each patent that claims composition/formulation or method of use claims.

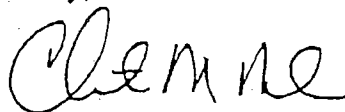
Printout from <http://www.fda.gov/cder/orange/patdecl.htm> at 2 (emphasis added.) FDA then repeats the specific declaration language prescribed by § 314.53(c)(2)(i).

FDA's regulations are clear. Section 314.53(c)(2)(i) states that, for a patent to be effectively listed, an applicant "*shall submit* the following declaration." 21 C.F.R. § 314.53(c)(2)(i) (emphasis added). FDA's March 23, 2001 letter to Biovail confirmed, "[f]or FDA to list the '463 patent for Tiazac (NDA # 20-401), Biovail *must submit* a signed declaration which reads as follows: [quoting the regulations]." (Emphasis added.)

The improper January 8 listing by Biovail was ineffective vis-à-vis Andrx's ANDA, and Andrx should not be further delayed as a result of the late declaration filed on March 26, 2001.

Thank you for your consideration of this additional information. Andrx sincerely appreciates FDA's prompt review of the company's request for immediate approval.

Sincerely,



Christina M. Markus

Attachment

cc: Mr. Donald B. Hare, Office of Generic Drugs (HFD-604)
Kevin Fain, Esq., Office of the Chief Counsel (GCF-1)

Scott Lodin, Esq.
Andrx Corporation

Louis M. Solomon, Esq.
Solomon, Zauderer, Ellenhorn, Frischer & Sharp

Eugene M. Pfeifer, Esq.



March 14, 2001

Handwritten:
Ruth A. Jones
NA I
4/2/01

**VIA FACSIMILE AND
OVERNIGHT DELIVERY**

Mr. Gary Buehler
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

Handwritten: NC
NEW CORRESP

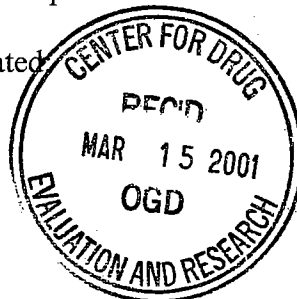
Re: ANDA 75-401 — Taztia™ XT Capsules (Diltiazem Extended-Release Capsules USP) 120 mg, 180 mg, 240 mg, 300mg, and 360 mg

Dear Mr. Buehler:

Andrx Pharmaceuticals, Inc. ("Andrx") hereby reiterates its request that FDA immediately act to remove U.S. Patent 6,162,463 from the Orange Book listing for Tiazac, and approve Andrx's pending ANDA No. 75-401.

Delisting by FDA is fully within the statutory and regulatory authority of the agency. It would *not* embroil the agency in patent disputes. Rather, it would send an important message that the Orange Book listing regime administered by FDA will not be subject to unscrupulous manipulation by NDA applicants and that FDA will act swiftly to protect the interests of ANDA holders and the public. In this case, delisting can be accomplished solely on the basis of public admissions made by the NDA holder itself.

Biovail's subsequent public admissions reveal that its January 8, 2001 certification to this agency in support of listing the '463 patent was false and misleading. In that certification, Biovail's Chairman Eugene Melnyk stated



The undersigned declares that Patent No. 6,162,463 *covers a formulation* of the drug diltiazem hydrochloride *which is sold under the tradename Tiazac*. This product is *currently approved* under Section 505 of the Federal Food, Drug and Cosmetic Act.

The declaration purposefully departs from the more precise and clearly unambiguous declaration required at 21 CFR 314.53(c)(2), which should have stated:

The undersigned declares that Patent No. [6,162,463] covers *the* formulation . . . of [Tiazac.] This product is currently approved (emphasis added)

Frankly put, the Melnyk declaration was a calculated deception. It was intended to deceive and mislead, and it accomplished its purpose of delaying the approval of the Andrx product. Only through the litigation Andrx initiated was Biovail forced to provide the agency with the details necessary to defend the validity of its position. See our prior letter dated February 1, 2001. Biovail's January 8 certification was false, and the continued listing of that patent is contrary to established FDA practice and precedent. Nor should Biovail now, three weeks after publicly stating it wanted to discuss this matter further with the agency, be allowed to correct or justify its prior misrepresentation, presumably based upon activities undertaken or completed during the interim between its original listing and the date of that meeting.

Biovail now seeks to justify its listing because, it claims, the '463 patent covers a product that Biovail is currently manufacturing, albeit not selling. Its problem is that the formulation and process for manufacturing under the patent are not approved. See enclosed declaration of Robert Jerussi. Continued listing of this patent is contrary to the FDA's long-established policy, articulated over 10 years ago in *Pfizer v. FDA*, 753 F.Supp. 171 (D. Md. 1990), that only patents that cover the approved drug product may properly be listed in the Orange Book. That case quoted FDA as confirming: "A patent for a formulation that has never

been approved may not be listed by FDA” (753 F. Supp. at 174). We and FDA are not at odds here. In the instant matter, FDA and the Department of Justice have represented to a Federal District Court that:

[B]y virtue of Biovail’s own statements, FDA is now of the view that the ’463 patent does not claim the approved drug product as required by the statute and therefore cannot be listed in the Orange Book for Tiazac. (Fed. Defs. Notice of Change in Position at 3) When queried by the Court, your counsel also informed the Court that the FDA was “prepared unilaterally to delist the patent” (Tr. at 4-5).

Biovail does not, because it cannot, dispute that its revised formulation and process are not approved. To the contrary, it suggests that the revisions do not require approval because they somehow fall within the scope of its currently approved NDA. This is nonsense, quite apart from the fact that by its terms, the ’463 patent covers a novel product different from the product explicitly approved in the NDA. As Dr. Jerussi’s declaration illustrates, the FDA’s standing policies make clear that changes such as Biovail describes can only be implemented through a prior approval supplement. For example, the *Guidance for Industry: SUPAC-MR: Modified Release Solid Oral Dosage Forms* (September 1997) explains that for a manufacturing process change such as Biovail proposes to implement — a “change in the type of process used in the manufacture of the product” (Guidance at 26), “a manufacturing process that is not identical in every respect to the original manufacturing process used in the approved application” (Guidance at 25) — is classified as a major change, which requires not only a prior approval supplement, but also a single-dose bioequivalence study to prove that the new version is equivalent to the original. The Guidance gives as an example of a major change (at 26). Clearly, Biovail’s proposed

change — involving the replacement of some of the
the Tiazac capsule with ;

Similarly, the November 1999 *Guidance for Industry: Changes to an Approved NDA or ANDA* also precludes Biovail from marketing its proposed new version of Tiazac without prior FDA approval. That document specifically identifies “[c]hanges that may affect the controlled (or modified) release, metering or other characteristics (e.g. particle size) of the dose delivered to the patient” as an example of a major change that cannot be made without a prior approval supplement (Guidance at 12). Obviously, Biovail’s decision to replace some of the is a change that may affect the controlled release characteristics of the product. At the very least, it is a change that *permits*, but does not *require*, addition of the to the capsules. Accordingly, implementing the proposed change would require relaxing an acceptance criterion for Biovail’s final product — yet another example of a change that specifically requires the filing of a prior approval supplement (1999 Guidance at 17).

Congress empowered FDA to list any patent that “claims the drug for which the applicant submitted the application . . . and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in manufacture, use, or sale of the drug.” 21 U.S.C. § 355(b)(1). It did so for several reasons: first, to preclude the listing of patents that do not claim the approved drug; second, to prevent the listing of patents that cannot reasonably be asserted in an infringement case against an ANDA applicant; and third, to establish a reference listed drug as a fixed entity that a generic applicant should seek to emulate and with respect to which it must file certifications.

Continued listing of the '463 patent defeats the goals expressed in the statute. Clearly the '463 patent does not claim Tiazac, as approved. Second, Andrx cannot be said by any stretch of imagination to infringe the '463 patent. Perforce, infringement cannot reasonably be asserted because Tiazac is not covered by the patent, and because Andrx seeks to make a delayed release preparation equivalent to Tiazac, as approved, and not a combination of delayed release and immediate release such as covered by the patent. Third, continued listing of the patent would undermine the objective in the statute that there be a known and approved entity as the reference listed drug — not some ephemeral thing that can undergo metamorphosis at the unfettered whim of one seeking to stymie competition.

Finally, while we recognize the reluctance of FDA to become involved in patent related issues, you are not here confronted with any arcane issue. On its face, the patent does not cover Tiazac as approved. Even if you do not read the patent, the formulation and process Biovail has admitted to using recently, in order to fabricate a basis to list the '463 patent, is clearly not what FDA approved. Biovail intentionally has misrepresented facts to FDA in its declaration, to the effect that the integrity of the NDA regulatory system has been sullied. It is not conceivable to us that such abuse of the patent listing system would be tolerated by FDA.

Up until now, the courts have been willing to grant FDA latitude based on your repeated representations that you lack the expertise to make fine distinctions in this area. For that treatment to continue, FDA must demonstrate that it will act responsibly and not abuse the discretion the courts grant it. If you fail to act in a case involving outright deceit in support of a clearly improper listing, you will jeopardize the “favored position” you now occupy. Put another way, if FDA will allow itself to be lied to, with no ramifications, then the deference the courts have been willing to give FDA’s gatekeeper function will not be allowed to continue.

In summary, there is no support for Biovail's claim that its listing of the '463 patent is proper. The listing is invalid, and the agency should immediately remove it from the Orange Book. Because the patent was not properly listed within 30 days of the date of its issuance as required by 21 U.S.C. § 355(c)(2), it cannot preclude final FDA approval of Andrx's ANDA.

In concluding that Andrx had not shown a likelihood of success in establishing that it had a private right of action to compel Biovail to delist the '463 patent, Judge Dimitrouleas expressly stated that "[i]t is the FDA's job to determine whether to list or delist a patent" (March 6 Order at 9). Whether or not the FDA is capable of addressing or resolving every dispute that might arise over whether a patent should be listed, it cannot shirk its responsibility to take action in those cases in which it is able to make a determination. As your counsel correctly told the District Court:

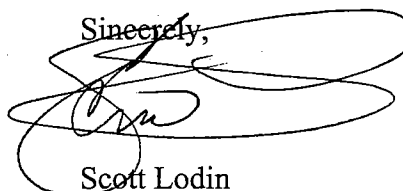
[W]hen an NDA holder in a lawsuit makes subsequent representations that show on their face that the patent which allegedly claims the approved drug product at issue actually claims a different, unapproved, formulation of the product, then it is proper and necessary for the agency to reconsider the listing of the patent. (Fed Defs. Change of Pos. at 3-4)

It is our understanding that FDA has previously taken the initiative both to refuse to list patents, as in the *Pfizer* case, where the NDA holder's submission did not support it, and also to delist patents when it has concluded that the listing was not proper, as in the case of several of the patents that were previously listed for bupropion. In that case Glaxo Wellcome had secured the listing of several method-of-use patents covering unapproved uses of bupropion, marketed by Glaxo Wellcome as Wellbutrin for the treatment of depression. The six patents at issue covered an array of unapproved uses, including, among others, treatment of

psychosexual dysfunction, reduction of cholesterol, and attention deficit disorder. Applicants seeking generic approvals complained, and in late 1998, public criticism surfaced in the trade press. *See* The Pink Sheet, 1998 WL 8442250 at 1 (Oct. 26, 1998) (noting that according to the Generic Pharmaceutical Industry Association, the listing of these patents was an “abuse”). The Agency, following communication with Glaxo Wellcome, delisted the patents.

FDA was correct in July 1998, when it concluded “that it would not be in the public interest to have Tiazac shielded from direct generic competition”. However, the simple fact here is that, unless the FDA delists the patent, Andrx will be forced to engage in a second round of patent litigation with Biovail — litigation that Biovail has already stated will take at least 30 months (*see* Biovail’s Mem. in Opp. to Motion for Expedited Discovery Schedule, dated March 12, 2001, at 7). And then, of course, unless the agency acts swiftly and decisively now, there will be absolutely nothing to stop Biovail from listing yet another bogus patent, and starting the process of delay all over again. All the while, consumers will be prevented from buying Andrx’s lower-priced generic product. That cannot be the result Congress intended, nor cannot it be the result the FDA should be a party to.

Sincerely,

A handwritten signature in black ink, appearing to be "Scott Lodin", is written over a large, loopy, handwritten "S" or "L" that spans across the signature line and the name below.

Scott Lodin
Vice President and General Counsel

Enclosure

cc: Eugene M. Pfeifer, Esq.



ANDA 75-401

Taztia XT (Diltiazem HCl Extended-release Capsules USP)

March 13, 2001

Gary Buehler, Acting Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NC
NEW CORRESP

*Therapeutic
NAI
4/2/01*

Re: PATENT AMENDMENT

Dear Mr. Buehler:

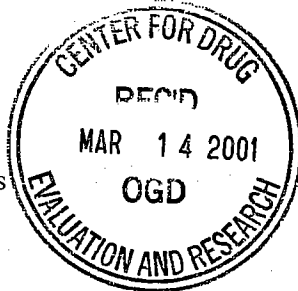
Reference is made to a March 12, 2001 telephone communication between Bonnie McNeal of the Office of Generic Drugs and Diane Servello of Andrx Pharmaceuticals, Inc. ("Andrx"). Per Ms. McNeal's request, Andrx is providing the Agency with a copy of the February 13, 2001 decision of the United States Court of Appeals for the Federal Circuit with respect to United States Patent No. 5,529,791 ("the '791 patent"). The Appeals Court affirmed the earlier District Court decision that Andrx does not infringe the '791 patent.

Should you have any questions concerning this submission, please contact the undersigned at (954) 585-1412 (telephone) or (954) 587-1054 (fax).

Sincerely,

Diane Servello

Diane Servello
Director, Regulatory Affairs



ANDA 75-401

Taztia XT (Diltiazem HCl Extended-release Capsules USP)

February 28, 2001

Gary Buehler, Acting Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

OTC AMENDMENT
FPL
FA

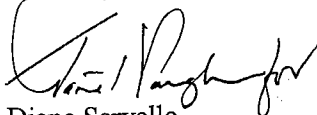
Re: Request for Additional Copies of Patient Outsert

Dear Mr. Buehler:

Please refer to the February 27, 2001 telephone conversation between Bonnie McNeal, Project Manager of the Office of Generic Drugs and Janet Vaughn of Andrx Pharmaceuticals, in which Ms. McNeal requested additional copies of the final printed labeling (package insert). Four copies of the final printed labeling were originally submitted in our April 28, 2000 amendment. An additional twelve (12) copies of the final printed package insert is enclosed.

Should you have any questions concerning this submission, please contact the undersigned at (954) 585-1412 (telephone) or (954) 585-1848 (fax).

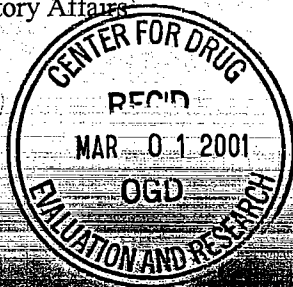
Sincerely,



Diane Servello
Director, Regulatory Affairs

DS/jad

Enclosure(s)



ANDA 75-401

Taztia XT (Diltiazem HCl Extended-release Capsules USP)

February 16, 2001

Gary Buehler, Acting Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: FAX AMENDMENT - Patent Certification

Dear Mr. Buehler:

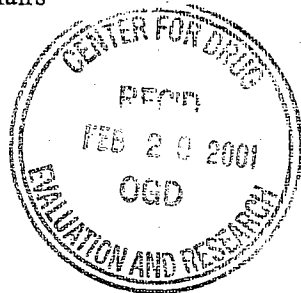
Reference is made to your facsimile dated February 2, 2001 for the above referenced application. We are amending the application to provide a patent certification to patent #6162463, which expires on April 28, 2018.

Should you have any questions concerning this submission, please contact the undersigned at (954) 585-1412 (telephone) or (954) 587-1054 (fax).

Sincerely,

Diane Servello

Diane Servello
Director, Regulatory Affairs





January 5, 2001

Gary Buehler, Acting Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW COPY 133P

**RE: ANDA 75-401; Taztia XT (Diltiazem HCl Extended-release Capsules USP)
Additional Information for CMC/Bioequivalence Minor Amendment**

Dear Mr. Buehler:

Reference is made to our CMC/Bioequivalence Minor Amendment submitted on December 12, 2000, providing for a change in the dissolution medium used in the testing of this product. Andrx Pharmaceuticals, Inc. ("Andrx") is herewith providing additional information for the Agency's review with regard to our request for a change in the dissolution medium from _____ to _____.

We have attached copies of dissolution profiles generated in media of various pHs. These data were submitted previously in the bioequivalence section of our original ANDA. The data include dissolution results for the 360 mg strengths of both the Andrx product and the Reference Listed Drug ("RLD"), Tiazac®. As shown by the data, the Andrx formulation for this product is pH-independent, as demonstrated by the fact that the dissolution profiles in each of the media are consistent with each other. Indeed, the sustained-release _____ used in our formulation, _____ is intended to be pH-independent. The enclosed data also demonstrate that the formulation for Tiazac® is less pH-independent, as shown by the different dissolution profiles in the various media.

Andrx believes that the pH-independence of our formulation provides more evidence that our product uses a different drug delivery system than the RLD. This provides a greater reason why the dissolution method for our product needs to be different than the method approved for the RLD.

Andrx Pharmaceuticals, Inc. certifies that a true copy of this amendment was sent to the Florida District Office as a Field Copy.

We look forward to your prompt review of the submitted information.

Sincerely,

A handwritten signature in cursive script, appearing to read "Diane Servello".

Diane Servello
Director of Regulatory Affairs





ANDA #: 75-401, Taztia XT™, (Diltiazem Hydrochloride Extended-release Capsules),
120 mg, 180 mg, 240 mg, 300 mg and 360 mg

December 15, 2000

Gary Buehler,
Acting-Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP

RE: General Correspondence

Dear Sir:

This letter is to inform you that the administrative offices of Andrx Pharmaceuticals, Inc. have relocated to a new address. Please direct all future correspondences pertaining to the above referenced ANDA to the following address and/or contact persons:

Andrx Pharmaceuticals, Inc.
4955 Orange Drive
Fort Lauderdale, Florida 33314

Diane Servello, *Director of Regulatory Affairs*
Telephone: (954) 585-1412

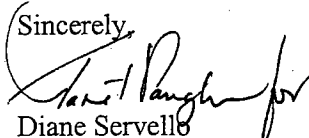
Janet Vaughn, *Manager of Regulatory Affairs*
Telephone: (954) 585-1665

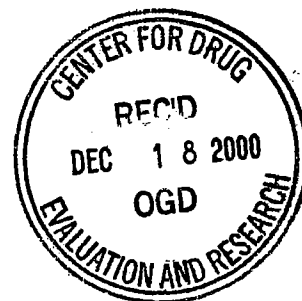
Facsimile: (954) 587-1054

Please note that the manufacturing site for the drug product has not changed. The new address for the administrative offices is contiguous with the manufacturing site.

Should you have any questions or comments concerning these changes, please contact Janet Vaughn at the above telephone number.

Sincerely,


Diane Servello
Director, Regulatory Affairs





ORIG AMENDMENT

N/AM

December 12, 2000

Gary Buehler, Acting Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

**RE: ANDA 75-401; Taztia XT (Diltiazem HCl Extended-release Capsules USP)
Consideration for Final Approval - CMC/Bioequivalence Minor Amendment**

Dear Mr. Buehler:

Reference is made to your letter dated September 29, 2000, tentatively approving this abbreviated new drug application (ANDA). Andrx Pharmaceuticals, Inc. ("Andrx") is submitting this amendment to notify the Agency of circumstances that may affect the date of final approval for this application. This correspondence also includes a **minor CMC/Bioequivalence amendment** describing a revision to the current dissolution method contained in this application.

Circumstances that may affect the date of final approval:

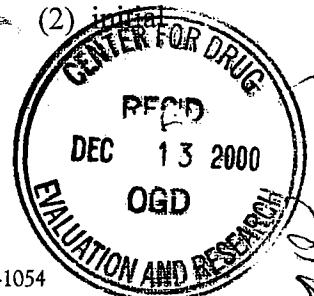
As required by 21CFR 314.95(b), Andrx submitted patent notices to the patent holders and the NDA holder of the Reference Listed Product, Tiazac®. Based on the information contained in our October 16, 1998 patent amendment, Andrx believes that the thirty-month stay of final approval will expire on February 11, 2001.

Please note however that on December 4, 2000, the Court of Appeals heard oral argument on the NDA holder's appeal of the lower court order stating that our ANDA product did not infringe the NDA holder's patent. We believe that the appellate court's order will be issued within the month of December 2000, before the expiration of thirty-month stay of final approval in February 2001. A copy of the final order will be submitted to the Agency as soon as the court decision has been reached.

CMC/Bioequivalence amendment

Andrx recently discovered a problem with the current dissolution method for this product. The problem needs to be resolved before we can produce commercial launch quantities for this product.

The current dissolution method and specifications, tentatively approved by OGD on September 29, 2000, for (1) the in-process extended-release (ER) (2) initial product release and (3) stability testing are as follows:



<u>Time point</u>	<u>Specification</u>
2 hours	Not more than
4 hours	
8 hours	
12 hours	Not less than
16 hours	Not less than

This dissolution method differs from the method initially used by Andrx to test our ANDA batches, which used a paddle speed of _____ as the dissolution medium. The change in our dissolution method from _____ buffer to _____ was made as a result of a new method that was published in the *Pharmacopeial Forum* shortly before our ANDA was submitted, rather than any problems with our product and the original method.

During the scale-up of this product for commercial introduction, we discovered that the initial dissolution profile of the ER _____, when tested using _____ as the dissolution medium, is approximately _____ slower at the 8 hour dissolution time point than ER _____ that have been equilibrated with ambient moisture conditions. This phenomenon only occurs when the product is tested using _____ as the dissolution medium, as opposed to the _____ medium originally used for dissolution testing of our ANDA batches.

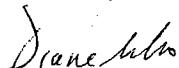
We are not requesting any change to the dissolution time points or specifications in this amendment. The only changes to the dissolution method being requested at this time are (1) the replacement of _____ with the original _____ buffer dissolution medium and (2) change of the paddle speed from _____

A report describing the dissolution problem, accompanied by supporting data is enclosed for your review.

Andrx Pharmaceuticals, Inc. certifies that a true copy of this amendment was sent to the Florida District Office as a Field Copy.

We look forward to your prompt review of the submitted information.

Sincerely,



Diane Servello
Director of Regulatory Affairs

ORIG AMENDMENT

N/FA

Sent by Facsimile to 301-443-3839

September 18, 2000

Gary Buehler, Acting Director
Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

**RE: ANDA 75-401; Diltiazem Extended-Release Capsules USP (Once-a-Day Dosage)
120 mg, 180 mg, 240 mg, 300 mg and 360 mg**

FACSIMILE AMENDMENT

(Hard copy to follow by Federal Express)

Dear Mr. Buehler:

As a follow-up to a telephone call from Dr. U. Venkataram on September 14, 2000, we are herewith amending this application to provide revised specification sheets for the finished drug product.

The specification sheets have been revised to provide specifications reflecting the significant figures described in the USP monograph for "Diltiazem HCl Extended-release Capsules". Please see the following pages for copies of the revised specification sheets for each of the five strengths.

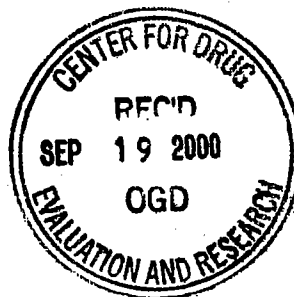
Andrx Pharmaceuticals, Inc. certifies that a true copy of this amendment was sent to the Florida District Office as a Field Copy.

Please direct any questions concerning this submission to the undersigned at (954) 327-4412 (telephone) or (954) 587-1054 (fax).

Sincerely,

Diane Servello

Diane Servello
Director, Regulatory Affairs



Sent by Facsimile to 301-443-3839

ORIG AMENDMENT

September 12, 2000

NAC

Gary Buehler, Acting Director
Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: **ANDA 75-401; Diltiazem Extended-Release Capsules USP (Once-a-Day Dosage)
120 mg, 180 mg, 240 mg, 300 mg and 360 mg**

FACSIMILE AMENDMENT

(Hard copy to follow by Federal Express)

Dear Mr. Buehler:

As a follow-up to a telephone call from Dr. U. Venkataram on September 11, 2000, we are herewith amending this application to provide revised specification sheets for the finished drug product.

The specification sheets have been revised to include two identification tests (as required by the USP). The specifications have also been updated to include the capsule imprint information in the "Appearance" section.

Andrx Pharmaceuticals, Inc. certifies that a true copy of this amendment was sent to the Florida District Office as a Field Copy.

Please direct any questions concerning this submission to the undersigned at (954) 327-4412 (telephone) or (954) 587-1054 (fax).

Sincerely,

Diane Servello

Diane Servello
Director, Regulatory Affairs





June 26, 2000

Gary Buehler, Acting Director
Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

NDA ORIG AMENDMENT
BIOAVAILABILITY

N/AB
N/AC

RE: ANDA 75-401; Taztia™ XT Capsules (Diltiazem HCl Extended-Release Capsules USP), 120 mg, 180 mg, 240 mg, 300 mg and 360 mg

BIOEQUIVALENCY AMENDMENT

and

REQUEST FOR CLASSIFICATION TO MINOR AMENDMENT

Dear Mr. Buehler:

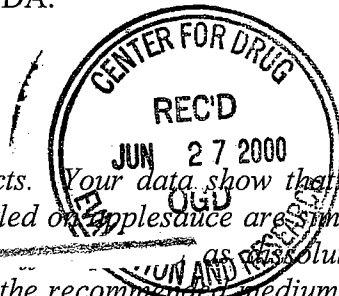
Your facsimile dated June 9, 2000 (copy attached) denied the request Andrx Pharmaceuticals, Inc. ("Andrx") submitted on April 28, 2000 for a waiver of the sprinkle study on Taztia XT™, but did not fully respond to all of the comments set forth in our letter (copy attached). We also note that we have not yet received (nor did we expect) a response to our June 15, 2000 correspondence waiving the court decision "finality protection provided by FDA's interpretation of Hatch-Waxman Amendments and requesting immediate final approval of the referenced ANDA following the Agency's determination that Taztia XT is bioequivalent to Tiazac®.

Pursuant to 21 CFR 314.120, Andrx is amending its ANDA to respond to the *Bioequivalence* comments included in your June 9, 2000, and is reiterating its requests for classification of this amendment as a minor amendment and for final approval of its ANDA.

I. Bioequivalence response:

FDA Comment:

You state that _____ is used in the test and reference products. Your data show that the dissolution profiles of intact capsules and capsule contents sprinkled on applesauce are similar when the tests are conducted using _____ medium. You did not compare the dissolution in water, which is the recommended medium for the test product. However, it is the current practice of the Division of Bioequivalence to request an additional sprinkling bioequivalence study when the dosage and administration section of the labeling describes administration of the product sprinkled on food. Therefore your waiver request for sprinkling bioequivalence study on diltiazem hydrochloride ER 360 mg capsule is denied.



Response:

We have completed a single-dose bioequivalence study, comparing the Andrx product to Tiazac, when sprinkled over applesauce. The following information is included with this amendment:

Exhibit 1: Certificates of analysis for the test and reference products used in this study, including assay and dissolution.

Exhibit 2: A printout and diskette containing the data files from this study. (The diskette is included in the archival copy only).

Exhibit 3: The final report for the study, entitled "A relative bioavailability study of 360 mg Diltiazem Extended-Release Capsules under fasting conditions" (*PRACS Study #R00-272*).

The study results demonstrate that Taztia XT™ is bioequivalent to Tiazac® when the —, are administered with applesauce.

We note that these results are consistent with the in-vitro data included with our April 28, 2000 amendment. As the agency will see, the dissolution profiles of the two products in — and — are very similar (*See Figures 1 through 4 with accompanying tables*), and in-vitro data successfully predicted the outcome of the bioequivalence study included with this amendment. Taking gastric emptying time and GI motility into consideration, Andrx correctly anticipated that the biostudy results would be somewhere between the previous results obtained from our fasting and food challenge studies. This is confirmed by comparing the AUC and Cmax values from all three studies comparing Taztia XT™ to Tiazac® when the products were administered under (1) fasting conditions, (2) with applesauce and (3) after a high-fat breakfast (*See Table 1*).

Andrx continues to believe that the necessity for additional "sprinkle" bioequivalence studies is questionable, when fasting and food challenge studies have already been conducted, and that the "need" for these studies is generally as a result of innovator firms' attempt to delay generic competition. The agency should not reward innovator firms who resort to this tactic by requiring an ANDA applicant to conduct additional time-consuming studies that provide duplicative information.

II. Request for Classification to a Minor Amendment:

Your April 13, 2000 request that Andrx conduct a new "sprinkle" bioequivalence study, and revise our labeling for this product, was the result of a recent voluntary change in the labeling of the Reference Listed Drug (RLD), Tiazac®. The primary objective of that change, which allows the sprinkling of extended-release — over applesauce, was to further delay the marketing of Andrx's bioequivalent product. The requirement to conduct a new "sprinkle" bioequivalence study has effectively delayed the public's access to the first and only generic for Tiazac. By classifying this response as a minor amendment, FDA will expedite its internal review and approval of our ANDA, and thereby better achieve the objective of the Hatch-Waxman Amendments of making bioequivalent products available to the public. Biovail Corporation

International, the NDA holder for Tiazac, should not be rewarded for its pattern of tactics intended to delay the introduction of the Andrx product.

Our April 28, 2000 letter set forth additional facts concerning the innovator's attempt to delay competition and further support this request for reclassification.

III. Request for Waiver of Finality Protection

Our June 15, 2000 letter advised the agency that Andrx has received a favorable court decision in our patent infringement suit with Biovail, and requested a waiver of the court decision "finality" protection implicit in the current FDA policy regarding court decisions (which does not apply to ANDAs submitted before March 2000). Andrx knows that this waiver is not authorized by the agency's guidance but, as set forth in our letter, believes it to be both consistent with the agency's stated position and the Hatch Waxman Amendment's objective of making bioequivalent products available to the public at the earliest prudent opportunity.

Should you have any questions concerning this submission, please contact the undersigned at (954) 327-4412 (telephone) or (954) 587-1054 (fax).

Sincerely,

Diane Servello
Director of Regulatory Affairs



June 15, 2000

Gary Buehler, Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

NEW CORRESP

NC
30 months does not
expire until 2001
NAT
6/28/00

Re: **ANDA 75-401 -- Taztia™ XT Capsules (Diltiazem Extended-Release Capsules USP) 120 mg, 180 mg, 240 mg, 300 mg, and 360 mg**

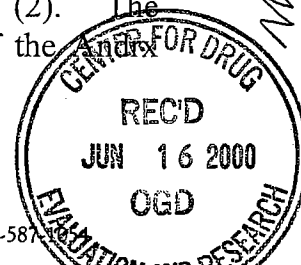
**WAIVER OF COURT DECISION "FINALITY" PROTECTION
AND REQUEST FOR IMMEDIATE FINAL APPROVAL**

Dear Mr. Buehler:

Andrx Pharmaceuticals, Inc. ("Andrx") is willing to waive the "finality" protection to which it is entitled under 21 C.F.R. § 314.107(e), as interpreted by Food and Drug Administration ("FDA") prior to March 2000, and hereby requests that FDA grant immediate final approval of the referenced abbreviated new drug application.

BACKGROUND FACTS

In August 1998, following FDA's acceptance of the referenced ANDA as filed, Andrx sent the requisite Paragraph IV certification to Biovail Corporation International and others having an interest in the approved new drug application ("NDA") for Tiazac® (collectively, "Biovail"). Biovail received the Paragraph IV certification, and in September 1999, within the statutorily prescribed 45-day period, commenced a lawsuit claiming that the Andrx product infringed United States Patent No. 5529791 (the "'791 Patent") which had been listed in the Orange Book as covering the reference listed drug, Tiazac®. 21 U.S.C. § 355 (j) (5) (B) (iii); 21 C.F.R. § 314.107(f) (2). The commencement of that suit prevents FDA from granting final approval of the Andrx



ANDA until the expiration of the thirty month period beginning when Biovail received Andrx's Paragraph IV Certification or "on the date of the court decision" that the Biovail patent is invalid or was not infringed by the Andrx product, whichever is earlier. 21 U.S.C. § 355 (j) (5) (B) (iii).

On March 6, 2000, the United States District Court for the Southern District of Florida determined that Taztia XT™ Capsules do not infringe the '791 Patent. A copy of the Order finding the '791 patent not infringed is Attachment A. Biovail has appealed this decision to the United States Court of Appeals for the Federal Circuit and has taken a series of other steps to delay final FDA approval of the marketing of Taztia XT.

Andrx believes the patent infringement suit initiated by Biovail has no merit and was initiated and continues to be maintained on appeal solely in an effort to delay the marketing of Taztia XT™. In light of this, and other unique circumstances involving this product, Andrx is willing to waive its right to receive a final and unappealable decision in its patent litigation before it is required to market its product. The right to delay the marketing of an ANDA product while patent litigation is ongoing is implicit in the statute and has long been recognized by FDA's interpretation of the term "court", when used in §355 (j) (5) (B) (iii) (I).

FDA recognition of the Andrx waiver (i) is consistent with the intent and objective of the Hatch Waxman Amendments to "make available more low cost generic drugs" as soon as possible; (ii) will not disrupt any legally cognizable interest of Biovail, (iii) is consistent with FDA's present interpretation of the term "court" and "decision of a court", and (iv) does not conflict with any of "retroactive" effect concerns expressed by the courts which have addressed this subject and recognized by FDA's recently issued guidance. H.R. Rep. No. 98-857, pt. 1, at 14 (1987).

I. PRELIMINARY ISSUES

A. ANDA 75-401 Is Subject To FDA's Historical Definition Of "Court Decision"

ANDA 75-401 was submitted to FDA, and the agency's review was essentially complete, long before issuance of the opinion of the United States District Court for the

District of Columbia in Mylan Pharmaceuticals Inc. v. Shalala¹ and FDA's publication of its related guidance document.² Consistent with applicable law and FDA policy, therefore, FDA's historical regulation defining "court decision" (21 C.F.R. § 314.107(e)) continues to govern ANDA 75-401. See Court Decision Guidance at 4 (new definition of "court decision" will be applied only to certain ANDAs submitted after publication of FDA's guidance document). According to that regulation, Andrx is entitled to await a final appellate court decision without any negative impact on either the product approval or Andrx's entitlement to 180 days of generic market exclusivity.

Andrx strongly endorses FDA's policy of generally applying the new interpretation of "court decision" on a prospective basis only. The Mylan Court and FDA have both correctly recognized that the new interpretation may dramatically change the value of Paragraph IV certifications. Retroactive application would unfairly penalize ANDA applicants (including Andrx) that relied, in good faith, on the government's longstanding regulatory interpretation.³ For this very reason, administrative agencies

¹ 81 F. Supp.2d ____ (D.D.C. 2000) ("Mylan"). In Mylan, the District Court held 21 C.F.R. § 314.107(e) (i.e., the "finality" protection) to be invalid, on the basis that it is inconsistent with the meaning of the phrase "a decision of a court" in section 505(j)(5)(B)(iv) of the Federal Food, Drug, and Cosmetic Act ("FDC Act"), 21 U.S.C. § 355(j)(5)(B)(iv). The Court held that "a decision of a court" should be construed to include patent decisions of United States district courts, regardless of whether a decision is appealed. This decision was followed recently in the consolidated cases Mylan Pharmaceuticals Inc. v. Henney, Civ. Action No. 99-cv-862 (D.D.C. March 31, 2000) and Pharmachemie v. Henney, Civ. Action No. 99-cv-801 (D.D.C. March 31, 2000) (collectively "Pharmachemie") (a vacated district court decision that had found a patent invalid is a "decision of a court" under the FDC Act).

² "Guidance for Industry: Court Decisions, ANDA Approvals, and 180-Day Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act" (March 2000) ("Court Decision Guidance"); see 65 Fed. Reg. 16922 (March 30, 2000).

³ FDA reaffirmed its adherence to 21 C.F.R. § 314.107(e) as recently as August 1999. See, 64 Fed. Reg. 42873, 42879 (Aug. 6, 1999). Andrx agrees with FDA that § 314.107(e) was a permissible and reasonable interpretation of the FDC Act that guaranteed a meaningful exclusivity benefit related to Paragraph IV certifications. 59 Fed. Reg. 50338, 50352 (Oct. 3, 1994) ("Beginning the 180-day exclusivity period before the resolution of the appeals process would render the exclusivity valueless to a prudent applicant who delayed marketing until the issues were resolved on appeal"). As the

generally are prohibited from applying new rules retroactively. Bowen v. Georgetown Univ. Hosp., 488 U.S. 204 (1984); see also Clark-Cowitz Joint Operating Agency v. FERC, 826 F.2d 1074, 1082-83 (D.C. Cir. 1987) (en banc) ("the longer and more consistently an agency has followed one view of the law, the more likely it is that private parties have reasonably relied to their detriment on that view").

FDA's longstanding policy of regulating ANDAs pursuant to rules in effect at the time of filing also supports general application of the new "court decision" definition on a prospective basis only. See, e.g., Serono v. Shalala, 158 F.3d 1313, 1322 (D.C. Cir. 1998) (upholding FDA's decision to apply regulations that were in effect when an ANDA was filed, rather than regulations promulgated two years later).

At the same time, the right being protected by FDA's prospective only application of the regulation belongs to Andrx. Given the unique circumstances of this matter, Andrx wishes to be able to waive that right in a manner consistent with the Hatch-Waxman Amendments and for an end entirely in the public interest.

B. Limited Scope Of Waiver

The waiver addressed by this letter is limited in scope: Andrx desires to waive the court decision finality protection with regard to ANDA 75-401 only. Andrx does not waive any specific protection that applies to other Andrx ANDAs currently pending before, or that may later be received by, FDA.

Andrx was the first company to file an ANDA containing a Paragraph IV certification for Tiazac® and, therefore, is the only company entitled to waive the court decision "finality" protection. Neither Biovail nor another ANDA applicant can waive Andrx's entitlement to the protection of court decision "finality" regarding its Taztia XT™ application.⁴

agency is well-aware, the penalties for patent infringement are potentially great (including possible liability for treble damages). 35 U.S.C. § _____. To date, Andrx is not aware of any firm -- itself included -- that has been willing to market a generic drug product before a favorable trial court decision has become final and non-appealable.

⁴ Under the precedent first established in Granutec, Inc. v. Shalala, 1998 U.S. App. LEXIS 6685 (4th Cir. April 3, 1998) (unpublished opinion), a subsequent ANDA filer could secure a relevant "court decision" in a case not involving Andrx. See also 64 Fed. Reg. at 42879. However, even in such a case, the subsequent filer could not waive or

A waiver of court decision finality protection must be made voluntarily and affirmatively by the qualifying applicant. FDA should not infer that any eligible ANDA applicant has waived its right to await a final, non-appealable court decision before beginning to market a drug product. Rather, the agency must require an express written statement (such as this letter) that demonstrates knowledge and voluntary relinquishment of the valuable protection that is being surrendered.

ANDRX'S WAIVER IS PERMISSIBLE AND BENEFICIAL

A. Andrx Is Harmed By Not Being Able To Market Its Non-Infringing Product Immediately

Andrx has pursued marketing approval for Taztia XTTM since 1998. Andrx developed a product that does not infringe the '791 patent covering Tiazac[®] and, when nonetheless sued by Biovail for patent infringement, obtained a United States District Court decision so stating. Although Biovail has appealed that decision in an effort to delay the marketing of Taztia XTTM, Andrx fully expects the Federal Circuit to uphold Andrx's victory on appeal.

Andrx has worked diligently to ensure that all substantive requirements for marketing have been satisfied. The established bioequivalence requirements for this product were satisfied in January 2000, and Andrx had been repeatedly advised by the agency that tentative approval of its ANDA would be received in February 2000. However, due to a last minute amendment to the Tiazac[®] labeling, which Andrx believes was specifically intended to delay the marketing of Taztia XTTM, Andrx was required to conduct new "sprinkling" bioequivalence studies in competition with Tiazac[®]. Biovail also sought to delay the marketing of Taztia XTTM by commencing a lawsuit against FDA in the United States District Court for the District of Maryland and by filing a Citizen Petition seeking to prevent FDA's approval of the Andrx ANDA without additional testing not required by the applicable guidance or justified by any scientific rationale.

Once Andrx satisfies the scientific requirements for approval of its ANDA, Andrx will be financially harmed by not being able to market its product. Every day that Taztia

limit Andrx's entitlement to await a final, non-appealable court decision before going to market.

XTTM is kept off the market, Andrx loses sales and market share. Andrx desires to initiate commercial marketing of Taztia XTTM as soon as possible and is willing to assume the risk that its product will later be determined to infringe the '791 patent. As discussed below, no legitimate interest of Biovail will be harmed or affected by the agency's approval of this waiver by Andrx.

B. Waiver Of Court Decision "Finality" Protection Is Consistent With The Hatch-Waxman Amendments

Andrx estimates that Biovail's appeal of the District Court decision might require up to eighteen months to achieve final resolution. If this time-frame proves accurate, the thirty-month period prescribed by the statute will expire before the conclusion of the appellate process. Thus, there is a significant likelihood that Andrx will at that time be faced with the decision of launching its product "at risk."

While most companies are loath to incur this risk, a confluence of factors have caused Andrx to be willing to commence marketing Taztia XTTM before finality in its patent litigation is achieved. First, prior to the submission of its ANDA, Andrx received a clear and unambiguous opinion from its patent counsel to the effect that any claims of patent infringement which might be brought by Biovail would be baseless. Second, the United States District Court opinion confirmed and upheld Andrx's legal position, as set forth in that opinion of counsel, on every aspect of the case in which it made a determination. The Court's well-reasoned opinion will, in our view, be upheld on appeal. Third, based upon the projected remaining period of the appeal process, the \$170 million in annual Tiazac® sales and Andrx's financial position at this time, Andrx believes that marketing Taztia XTTM, before achieving "finality" in the patent litigation, is an acceptable business risk. Moreover, through the use of a unique insurance policy Andrx believes it has been able to secure, following years of effort, Andrx believes it can even further reduce this risk.

Andrx's commercial marketing of Taztia XTTM will also enable subsequently approved generic products to enter the market sooner than otherwise would be the case⁵.

⁵ As the first ANDA applicant to have filed a Paragraph IV certification concerning Tiazac®, Andrx is entitled to 180 days of generic market exclusivity. Under the applicable regulation, there are only two triggers for this 180-day period: (1) when Andrx initiates commercial marketing of its product or (2) when the appellate court confirms that the patent is invalid, unenforceable, or would not be infringed by Andrx's marketing.

Neither the FDC Act nor FDA's implementing regulations prohibit a generic manufacturer that has successfully defended patent infringement litigation at the district court level from waiving its right to the protection of a final court decision. In fact, FDA and at least one court have deemed waivers to be permissible under the Hatch-Waxman Amendments in two other contexts. First, FDA has established that a generic manufacturer qualifying for 180-day exclusivity may waive some or all of its exclusive marketing period in favor of a subsequent ANDA holder. See 64 Fed. Reg. 42873, 42881 (Aug. 6, 1999); Boehringer Ingelheim Corp. v. Shalala, 993 F. Supp. 1, 2 (D.D.C. 1997) ("The statute is simply silent on the point, and certainly does not clearly express a statutory policy precluding waivers"). Second, FDA has established that drug manufacturers may waive the benefit of market exclusivity under the non-patent exclusivity provisions of the Hatch-Waxman Amendments. 59 Fed. Reg. at 50359.

The waiver concept permits FDA and affected firms to maintain the benefits and protections provided by the Hatch-Waxman Amendments, while also facilitating market competition. For the reasons set forth in this letter, Andrx's requested waiver would directly advance both of these goals.

C. Biovail Would Not Be Harmed By Andrx's Waiver Of Finality

Andrx's contemplated waiver of court decision "finality" protection would not harm Biovail in any way. During the pendency of the appeal, Biovail could seek to obtain an injunction to prevent Andrx from marketing its product. Andrx has sufficient assets to cover the full amount of damages that Biovail conceivably could recover if Andrx were to market its product during appeal and the Court of Appeals were to overturn the District Court ruling in Andrx's favor. Should Biovail succeed on appeal, that company's only "injury" would be lost profits due to sales lost to Andrx -- an amount that is easily quantifiable and remediable by monetary payment. Patent courts routinely

21 U.S.C. § 355(j)(5)(B)(iv); 21 C.F.R. § 314.107(c)(2) and (e). While Andrx is at this time unaware of any subsequently filed ANDA, the longer Andrx must wait to begin marketing Taztia XT™, the longer any such subsequent ANDA filers will be delayed in bringing their products to market.

assess and award damages for patent infringement; there is no reason to distinguish this case.⁶

Andrx also points out that, but for the timing of Andrx's filing of ANDA 75-401, Andrx would be entitled to market its product immediately under FDA's new "court decision" regime. Yet, as discussed below, the prospective effect of the guidance was specifically predicated on concerns and factors that have no application to recognition of Andrx's waiver.

D. The Balance Of Interests Clearly Favors Andrx's Waiver

The balance of interests in this case clearly favors recognition of Andrx's waiver. FDA has found that Taztia XT™ are bioequivalent to Tiazac®.

Biovail's pending appeal of the patent non-infringement decision that was rendered in Andrx's favor is the sole reason preventing Andrx from preparing for the immediate marketing of Taztia XT™. If Andrx's District Court judgment of non-infringement is upheld, there will be no mechanism by which Andrx may recoup its lost sales and there will be no means for the public to recoup the higher prices they will have continued to pay for Tiazac®.

Biovail, by contrast, would not face any prospect of unrecompensed injury should Andrx's decision be reversed on appeal. In that unlikely event, Andrx will have sufficient capital to satisfy any damages that might be owed to Biovail.

Moreover, as above stated, two courts and FDA now recognize that "a decision of a court" should be construed to include decisions of United States district courts, regardless of whether a decision is appealed. FDA's guidance on this issue states that it will apply this new interpretation prospectively. This prospective effect is premised on the Court's approach in Mylan, and concerns that giving immediate effect to this new interpretation "may substantially change the value of the 180-day exclusivity" provisions and thereby "lessen the likelihood that ANDA applicants will sue the Agency alleging that they ... relied in good faith on the Agency's regulation." These concerns, which

⁶ The mere existence of competition is not irreparable harm, and should not prevent Andrx from going to market. E.g., WMATC v. Holiday Tours, 559 F.2d 841, 843 n.3 (D.C. 1977).

Andrx agrees with, have no application to FDA's immediate and final marketing approval of Taztia XT™ prior to the expiration of the 30-month period which would otherwise be applicable.

CONCLUSION

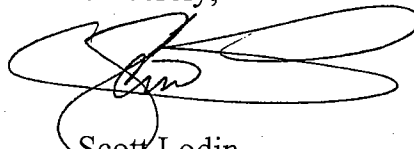
The public interest in Hatch-Waxman-related cases is multi-faceted and in all relevant respects points strongly in favor of permitting Andrx to waive a right created to protect it, for the benefit of consumers. It includes both (1) promoting the prompt availability of generic drug products, and (2) promoting industry incentives for innovation. Pharmachemie slip op. at 36. In many cases, there is tension between these two legislative goals. However, here the goals are simultaneously served by Andrx's proposed waiver arrangement.

As it has done in the past, FDA should interpret the Hatch-Waxman Amendments to permit the waiver of a protection, where waiver will protect the interests of all concerned parties and at the same time promotes competition. Cf. Pharmachemie, slip op. at 26 ("Courts are advised that statutes should not be interpreted so as to create anticompetitive effects").

Andrx respectfully requests that the agency recognize Andrx's waiver of its right to await an appellate court decision in this matter, and grant final approval to ANDA 75-401 for Taztia XT™.

Thank you for your attention to this letter. Please do not hesitate to contact me if Andrx can provide further information.

Sincerely,



Scott Lodin

Vice President and General Counsel

Attachments

EXHIBIT "A"

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF FLORIDA

CASE NO. 98-7096-CIV-DIMITROULEAS

BIOVAIL CORPORATION INTERNATIONAL, et al.,

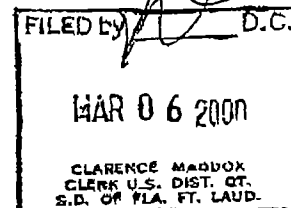
Magistrate Judge Johnson

Plaintiffs,

vs.

ANDRX PHARMACEUTICALS, INC.,

Defendant.



FINAL JUDGMENT

THIS CAUSE is before the Court upon the non-jury trial on January 24, January 31, February 14, February 15 and February 16, all in the year 2000.. For the reasons expressed in this Court's Findings of Fact and Conclusions of Law, separately entered today, it is

ORDERED AND ADJUDGED as follows:

1. Judgment is hereby entered in favor of the defendant, Andrx Pharmaceuticals, Inc., and against the plaintiffs, Biovail Corporation International, Inc., Biovail Laboratories, Inc., and Galephar P.R., Ltd., on Plaintiffs' Complaint, and plaintiffs shall take nothing from this action.
2. All pending motions are denied as moot;
3. The Clerk shall close this case, however, the Court retains jurisdiction to hear any appropriate post-judgment motions.

DONE AND ORDERED in Chambers at Fort Lauderdale, Broward County, Florida,
this 6 day of March, 2000.

WILLIAM P. DIMITROULEAS
United States District Judge

Copies furnished to:

Eric C. Cohen, Esq./Robert B. Breisblatt, Esq./Charles Krikorian, Esq.
Benedict Kuehne, Esq.
James Costigan, Esq./Martin Andres, Esq./ Alan Clement, Esq.
Gerald Houlihan, Esq.

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF FLORIDA

CASE NO. 98-7096-CIV-DIMITROULEAS

BIOVAIL CORPORATION INTERNATIONAL, et al.,

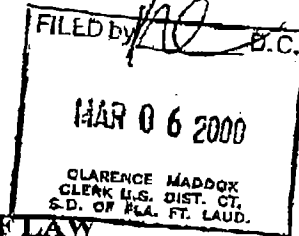
Plaintiffs,

vs.

ANDRX PHARMACEUTICALS, INC.,

Defendant.

Magistrate Judge Johnson



FINDINGS OF FACT AND CONCLUSIONS OF LAW

THIS CAUSE came on for non-jury trial on January 24, January 31, February 14, February 15 and February 16, all in the year 2000. The Court has carefully considered the arguments of counsel, the evidence presented, and the testimony of the witnesses. The Court has also determined the credibility of witnesses and is otherwise fully advised in the premises.

Pursuant to Rule 52(a) of the Federal Rules of Civil Procedure, the Court makes the following Findings of Fact and Conclusions of Law.

1. Plaintiff, Biovail Corporation International, is an Ontario Canada corporation with its principal place of business at 2488 Dunwin Dr., Mississauga, Ontario, Canada L5L 1J9.
2. Plaintiff, Biovail Laboratories, Inc., is a Barbados corporation with its principal place of business at Chelston Park, Building 2, Collymore Rock, St. Michael, BH1, Barbados, West Indies.
3. Plaintiff, Galephar P.R., Inc., is a Puerto Rico corporation with its principal place of business at Carolina, Puerto Rico 00984-33468.
4. Defendant, Andrx Pharmaceuticals, Inc., is a Florida corporation with its principal place of business at 4001 S.W. 47th Avenue, Fort Lauderdale, Florida 33314.

5. Galephar P.R., Inc. is the owner of United States Patent No. 5,529,791 ("the '791 patent").
6. Biovail Corporation International is the exclusive licensee of Galephar P.R. Inc. under the '791 patent.
7. Biovail Laboratories, Inc. is a wholly owned subsidiary of Biovail Corporation Inc.
8. The alleged act of infringement constituted the filing by Defendant (hereinafter "Andrx") of an Abbreviated New Drug Application (hereinafter "ANDA") with the Food and Drug Administration (hereinafter "FDA") for permission to sell a bioequivalent formulation to the brand name drug Tiazac®.
9. Shortly after filing the ANDA on June 22, 1998, Andrx served Biovail with its paragraph IV certification stating that the formulation described in the ANDA did not infringe the '791 patent which Biovail had listed in the FDA Orange Book as covering the Tiazac® product and that the claims of the '791 were invalid.
10. On October 7, 1998, Biovail filed the present action against Andrx alleging infringement of the '791 patent under 35 U.S.C. 271(c)(2)(a).

CLAIM INTERPRETATION

11. The invention claimed by the '791 patent provides for an extended-release composition for the drug diltiazem.
12. Diltiazem is a well known drug compound which itself is no longer the subject of an extant patent.
13. Diltiazem is generally prescribed for its calcium channel blocking properties, and, therefore, is useful in the treatment of angina and/or hypertension; either alone or in combination with other medications.

14. The '791 patent contains four claims. Col. 8, line 59 to col. 10, line 11 of '791 patent (Defendant's Exhibit 1).¹

15. Claim 1 of the '791 patent states:

1. An extended-release galenical composition of one or more pharmaceutically-acceptable salts of Diltiazem which comprises beads containing an effective amount of one or more of said Diltiazem salts as the active ingredient, each bead containing one or more of the Diltiazem salts and an effective amount of wetting agent in admixture with the one or more Diltiazem salts to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein, said beads being coated with a microporous membrane comprising at least a water-soluble or water-dispersible polymer or copolymer, and a water-, acid- and base-insoluble polymer and a pharmaceutically acceptable adjuvant, and wherein the wetting agent is selected from the group consisting of sugars, C₁₂-C₂₀ fatty acid esters of sucrose, or xylose, glycerides of sucrose, fatty acid esters of polyoxyethylene, ethers of fatty alcohols and polyoxyethylene, esters of sorbitan, esters of polyoxyethylene sorbitan, alcohol-polyglycide esters, glyceride-polyglycides, lecithins and a combination thereof.

Col. 8, line 59 to col. 9, line 13 of '791 patent (DX1).

16. In Claim 1, the core of the '791 patent is claimed as containing two components:

(a) an effective amount of the drug diltiazem or salt thereof as the active ingredient;

in admixture with

(b) an effective amount to maintain the solubility of the diltiazem in each bead and to ensure that the solubility of diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions, of one of a number of specifically listed wetting agents, namely, sugars, C₁₂-C₂₀ fatty acid esters of sucrose or xylose, glycerides of sucrose, fatty acid esters of polyoxyethylene, ethers of fatty alcohols and polyoxyethylene, esters of sorbitan, esters of polyoxyethylene sorbitan, alcohol-polyglycide esters, glyceride-polyglycides, lecithins, and combinations thereof.

Col. 8, line 59 to col. 9, line 13 of '791 patent (Def. Exh. 1).

¹ Hereinafter, "DX" or "Def. Exh." will refer to Defendant's Exhibits.

17. All of the four claims of the '791 patent clearly require the two components of the core, i.e., the diltiazem and the wetting agent, to be in admixture. Col. 8, line 67 to col. 10, line 10 of '791 patent (Def. Exh. 1).

The '791 Patent Specification

18. The specification of the '791 patent supports the requirement that the wetting agent be in admixture with the diltiazem in the dry state.
19. The '791 patent specification describes two methods for preparing the diltiazem beads.

The patent states as follows:

A first technique consists in mixing the Diltiazem or salt thereof with the wetting agent(s) in a melted or finely divided form, or in solution, in the presence of a solvent, such as water, so as to obtain an extrudable paste or plastic mass. Col. 4, lines 26-30 of the '791 patent (DX1).

20. The patent specification further states that:

Another conventional technique for obtaining beads consists in spraying and/or dusting cores obtained through agglomeration of the Diltiazem or salt thereof, such as the chlorohydrate, contingently mixed to at least a wetting agent, with a dispersions or solution of at least one wetting agent. Col. 4, lines 39-44 the '791 patent (DX1).

21. Additionally, each of the Examples of the '791 patent specification exemplifies the preparation of the beads specifically describing mixing the bead components during the bead manufacturing stage, such as in a planetary mixer for approximately 15 minutes.

Col. 5, lines 55-67 and col. 6, lines 4-15 of '791 patent (DX1).

22. The '791 patent issued as a continuation of two prior patent applications, one of which issued as a patent, and the other resulted in an abandonment. Cover of '791 patent (Def. Exh. 1); '791 file history (Def. Exh. 3); '505 file history (Def. Exh. 4)

23. The original application was filed on June 26, 1991 and received Serial No. 721,396 ("the

- '396 application"). The '396 application eventually issued as United States Patent No. 5,288,505 on February 22, 1994 ("the '505 patent"). '505 file history (DX4).
24. The '505 patent has not been asserted against Andrx in the present lawsuit, and, in fact, is not listed in the FDA Orange Book as covering Tiazac®. Complaint; FDA Orange Book (DX12).
25. Prior to the issuance of the '505 patent, Biovail filed a continuation of the '396 application on May 28, 1993, which continuation application received Serial No. 68,951 ("the '951 application"). '791 patent file history (DX3).
26. The '951 application did not issue as a patent, but instead was abandoned in favor of another continuation application which was filed on September 23, 1994 and which received Serial No. 311,722 ("the '722 application"). '791 patent file history (DX3).
27. The '722 application eventually issued as the '791 patent on June 25, 1996. '791 file history (DX3).
28. During the prosecution of the '951 application and the '396 application, Biovail consistently referred to the bead as comprising an admixture of the diltiazem and wetting agent during the manufacturing stage in order to avoid the prior art. '505 file history (DX4); '791 file history (DX3).
29. In fact, during the prosecution of the '951 application and the '396 application, Biovail made numerous representations to the USPTO that the claims required the diltiazem and wetting agent needed to be homogeneously admixed during the manufacturing state. '505 file history (DX4); '791 file history (DX3).
30. On pages 8-9 of the May 28, 1993 Preliminary Amendment in the '951 application, Biovail made the following representations regarding the scope of the claims to the

USPTO:

Thus, at the outset, it is noted that the present composition is characterized by the use of beads consisting essentially of in admixture together an effective amount of Diltiazem or one or more salts thereof as an active ingredient and the wetting agent as defined in the claims. The beads are also coated with a microporous membrane as defined in the claims.

In essence, in admixture, the wetting agent appears to control, or strongly influence, the solubility of Diltiazem and does not permit this solubility to be affected by pH or other adverse conditions in the gastrointestinal tract. Further, this control appears to occur within the core of Diltiazem and wetting agent. This control affords a gradual release of Diltiazem in a relatively uniform manner over a period of about 24 hours. Further, the system of the present invention, as noted in the parent application is quite different from that of Debregeas et al. In particular, from column 3, lines 3-31 of Debregeas et al., it is clear that the process thereof results in a compositional form having i) an 'core' of mutual excipient, which is described as a mixture of saccharose or fructose and starch, ii) an outer layer thereon of polyvinylpyrrolidone (PVP) and Diltiazem and iii) a coating thereon. Thus, in Debregeas et al., Diltiazem is in admixture with only PVP, and not with the "core of that composition.

By contrast, the present formulation contains Diltiazem or one or more salts thereof in admixture together with the wetting agent. By combining the wetting agent in admixture with Diltiazem or one or more salts thereof, the solubility of the Diltiazem may be controlled and rendered independent of pH. This is quite important due to the wide variation in pH in the gastrointestinal tract. (emphasis in original).

Pages 8-9 of May 28, 1993 Preliminary Amendment (Def. Exh. 5).

31. The above-paragraph from the Preliminary Amendment was interpreted by Mr. Deboeck, one of the inventors of the '791 patent and the Rule 30(b)(6) designee of Biovail for the topic of the prosecution history of the '791 patent, as referring to a distinction which only exists at the time of manufacture of the products, i.e., in the dry state, and not after placement in an aqueous media. Page 75, line 16 to page 79, line 12 of Deboeck deposition transcript.
32. The prosecuting attorney for Biovail of the '791 patent testified in his deposition that he did not recall why he made the statement. Page 149, line 2 to page 15, line 5 of Beaumont deposition transcript.

33. On page 11 of the May 28, 1993 Preliminary Amendment in the '951 application, Biovail further represented to the USPTO that the admixing was dependent on the manufacturing process:

... in accordance with the present invention, the extrusion-spheronization process leads to homogeneous type beads while the "building-up" process, starting with a sugar core, leads to heterogeneous type beads. Clearly, it is impossible to have a sugar central core in a homogeneous bead as in the present invention. Such a bead is, by nature, heterogeneous. (emphasis in original).

Page 11 of May 28, 1993 Preliminary Amendment (DX5).

34. Additionally, on pages 13-14 of the May 28, 1993 Preliminary Amendment Biovail represented to the USPTO that a sucrose central core cannot constitute a wetting agent within the scope of the claims:

... The saccharose contained in the central core of the bead cannot act as a wetting agent because in order to do so the saccharose must be mixed with the Diltiazem and, therefore, saccharose must be in solution with Diltiazem. Unfortunately, in this system saccharose can only end up in solution after all the layers of Diltiazem are dissolved. In other words, saccharose can only become effective when there is not longer a need therefor. (emphasis in original).
Pages 13-14 of May 28, 1993 Preliminary Amendment (DX5).

35. Accordingly, the prosecution history of the '791 patent supports the interpretation that the claims of the '791 patent require the diltiazem and wetting agent to be in admixture at the time of manufacture and do not cover a formulation where the diltiazem is layered on top of a sugar sphere core. '791 file history (DX3); Banakar testimony.

LITERAL INFRINGEMENT

36. The product for which Andrx has requested approval from the FDA to market as a bioequivalent form of Tiazac® is the subject matter of ANDA 75-401 ("the Andrx product"). DX46.
37. The Andrx product does not include a wetting agent in admixture with diltiazem.

- Manufacture flow chart (DX43); Jan deposition testimony; CMC ANDA Section (DX46).
38. The Andrx product is comprised of beads which are placed in gelatin capsules. The beads themselves are comprised of three components, (i) an inert core, (ii) a drug layer, and (iii) a coating. Manufacture flow chart (DX43); CMC ANDA section (DX46); Jan deposition testimony.
39. The inert core of the Andrx product is comprised of spherical seeds which are referred to as sugar spheres and which are comprised of sucrose and starch. Manufacture flow chart (DX43); CMC ANDA section (DX46); Jan deposition testimony.
40. The drug layer of the Andrx product is comprised of a mixture of three components: (a) diltiazem HCl, (b) ethylcellulose (Ethocel 10cps) and (c) povidone (K-30). Manufacture flow chart (DX43); CMC ANDA section (DX46); Jan deposition testimony.
41. The coating of Andrx product is comprised of five components: (1) Eudragit NE30D, (2) Hydroxypropyl Methylcellulose 2910 (Methocel E5), (3) magnesium stearate, (4) talc, and (5) polysorbate 80. Manufacture flow chart (DX43); CMC ANDA section (DX46); Jan deposition testimony.
42. A diagram of the Andrx product was shown wherein (a) represents the inert sugar sphere core, (b) represents the diltiazem containing layer, and (c) represents the coating. Non-infringement exhibit (DX38); Jan deposition testimony.
43. The manufacturing process for producing the Andrx product may be divided into six basic stages. Manufacture flow chart (DX43); CMC ANDA section (DX46); Jan deposition testimony.
44. In the first stage, Active Drug Layering, the diltiazem HCl is layered onto sugar spheres by suspension layering in a fluidized bed coater to produce active pellets which contain

75% diltiazem by weight. Manufacture flow chart (DX43); CMC ANDA section (DX46); Jan deposition testimony.

45. In the second stage, Extended Release Coating, the active pellets are then coated with a polymeric film in a fluidized bed coater to yield diltiazem HCl extended-release pellets. Manufacture flow chart (DX43); CMC ANDA section (DX46); Jan deposition testimony.
46. In the third stage, Blending, up to three sub-lots of diltiazem HCl extended-release pellets may be manufactured and blended to yield enough diltiazem HCl extended-release pellets for encapsulation of the maximum product batch size. Manufacture flow chart (DX43); CMC ANDA section (DX46); Jan deposition testimony.
47. In the fourth stage, Encapsulation, following testing and release, the diltiazem HCl extended-release pellets are filled into the appropriate size hard gelatin capsules. Manufacture flow chart (DX43); CMC ANDA section (DX46); Jan deposition testimony.
48. In the fifth stage, Check Weighing, during encapsulation, check weighing of the entire batch is performed if any individual capsule fill weight falls beyond $\pm 8\%$ of the target fill weight. Manufacture flow chart (DX43); CMC ANDA section (DX46); Jan deposition testimony.
49. In the sixth stage, Packaging and Labeling, following testing and release, the encapsulated product is packaged, as required, into to packaging sizes - 30's and 1000's. Manufacture flow chart (DX43); CMC ANDA section (DX46); Jan deposition testimony.
50. A flow chart of the manufacturing process is shown in Defendant's Exhibit 43. Manufacture flow chart (DX43); CMC ANDA section (DX46); Jan deposition testimony.

COMPARISON OF ANDRX PRODUCT TO '791 PATENT CLAIMS

51. The Andrx product avoids the literal claim language on a number of grounds. Banakar

testimony; Weiner testimony.

52. The Andrx product does not contain a wetting agent in admixture with diltiazem as required by the claims of the '791 patent.
53. The term "admixture" means two or more items are commingled and interdispersed to obtain a homogeneous product.
54. The term "homogeneous" means that samples of the product taken anywhere throughout the product should have the same compositions.
55. The term "wetting agent" is defined as any of a group of surface active agents which, when added to a liquid, cause the liquid to spread more easily over, or penetrate into, a solid surface. Weiner testimony; Banakar testimony.
56. Ethylcellulose is not a wetting agent within the scope of the '791 patent claims. Biovail Response to Admission Request No. 8 (DX37).
57. Povidone (polyvinylpyrrolidone) is not a wetting agent within the scope of the '791 patent claims. Biovail Response to Admission Request No. 4 (DX37).
58. Neither polyvinylpyrrolidone or ethylcellulose are included in the list of wetting agents recited in claim 1 of the '791 patent. Col. 9, lines 5-13 of '791 patent (DX1); Biovail Response to Admission Request Nos. 6 and 7 (DX37).
59. At the time of manufacture, the diltiazem in the Andrx product is only in admixture with polyvinylpyrrolidone and ethylcellulose.
60. At the time of manufacture, the sugar sphere of the Andrx product cannot be considered to be in admixture with the diltiazem hydrochloride because in manufacturing the Andrx product the drug layer containing the diltiazem hydrochloride is layered onto the sugar sphere producing a heterogeneous or layered structure and not a homogeneous structure

as required by the plain meaning of the term "admixture" in the claims of the '791 patent.

61. Sucrose is only a wetting agent when it is in the dry state.
62. Sucrose is not commonly referred to as a wetting agent because it is not surface active, i.e., it does not reduce the surface tension of water.
63. Instead sucrose is more commonly referred to as a dispersing or wicking agent, which may be classified as a wetting agent only because sucrose may have utility in helping to disperse solids in water. These types of wetting agents are solids which have no surface activity, but have very high water solubility.
64. When a solid has difficulty in wetting, it can be admixed with dispersing or wicking agents which easily wet, thereby increasing the permeability of water to the region of the solid which has difficulty in wetting, thus improving its ability to be dissolved by not allowing it to aggregate together to the extent that it would aggregate if these dispersing agents were not present.
65. For example, when one experiences problems adding an insoluble drug to a vat of liquid that needs to be dispersed in this vat, very often if they add the drug directly to the liquid it will "glomp up" and if they try to stir it faster, the ball of "glomp" will just move faster. So a common technique for solving this problem is to take the drug with solid sugar, mix it intimately with the solid sugar and then add this admixture to the liquid, which improves the ability of the drug to be dispersed. Weiner testimony.
66. While solid sucrose may act as a dispersing or wicking agent, a sucrose solution acts as an anti-wetting agent. Weiner testimony; Banakar testimony.
67. Solid sucrose if it is interdispersed and intimately mixed with another solid will allow more water to come into contact with that solid because the solid sucrose is attracting the

water. However, if sucrose is in solution, the water is already there, and in fact, sucrose and water mix extremely well. Thus, the water now has a choice of whether it will go to the solid or stay with the sucrose, it will always stay with the sucrose and go away from the solid because it is already very happy with its intimate mixture with sucrose. Weiner testimony.

68. There is no physical or chemical basis to support defining a hydrophilic or water-soluble non-surface active agent in water as a wetting agent, and because there is a disincentive for the hydrophilic or water-soluble non-surface active agent in water to act as wetting agent because the water is interacting more strongly with the hydrophilic or water-soluble non-surface active agent than with the solid surface you desire to wet, it is in fact more clearly defined as an anti-wetting agent. Weiner testimony.
69. Furthermore, all wetting agents decrease the surface tension of water. However, once sucrose has been dissolved in water the surface tension of water increases, thereby negating solid sucrose's tendency to wet a substance. Weiner testimony.
70. Biovail has failed to prove that an admixture between the sugar and the diltiazem forms in the body.
71. Biovail has admitted that as manufactured the Andrx product does not contain an admixture of diltiazem and wetting agent.
72. Andrx performs its dissolution testing in a USP Apparatus 2 (paddles) at 75 rpm. Biovail employed a shaker table at 30 rpm.
73. Biovail has provided no evidence that a shaker table provides equivalent results to what goes on in body. Conditions in gastrointestinal tract are not the same as those created in a shaker table.

74. Biovail's tests are not reliable for a number of reasons:

(a) no showing that beads used for weight loss study were equivalent (storage time, conditions, lot number, etc.) to those Andrx used in dissolution testing subtracted from weight loss to determine alleged sugar release,

(b) use of sodium azide (a strong ion that can affect dissolution and destroy the test),

(c) difference in shaker table v. dissolution apparatus,

(d) temperature control,

(e) effect of lyophilization,

(f) flow patterns or hydrodynamics will affect dissolution rate tests.

75. Biovail's own tests, particularly the Electron Scanning Microscope (ESM) slides submitted in evidence, do not show that a homogenous admixture is formed in the Andrx product. Plaintiff's Exhibit 30 (Exhibit 30a et al.).

76. Biovail has not met its burden to show that the Andrx product employs an amount of a wetting agent which maintains the solubility of diltiazem in each bead.

77. In solution, sucrose does not function as a wetting agent and therefore no amount can be effective to maintain the solubility of diltiazem.

78. Biovail has not met its burden to show that the Andrx product employs an amount of a wetting agent which ensures that the solubility of the diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.

79. In solution, sucrose does not function as a wetting agent and therefore it cannot be effective to maintain the solubility of diltiazem.

DOCTRINE OF EQUIVALENTS

THE USE OF A SUGAR CORE IS A SUBSTANTIAL DIFFERENCE

80. Use of a solid sugar core as opposed to a sugar or another wetting agent in admixture with the diltiazem is a substantial difference.
81. The sugar core functions substantially differently because it is inert and does not function as a wetting agent.
82. The sugar core acts in a substantially different way because it does not provide any wetting to the diltiazem but merely provides a means for which to build up the diltiazem.
83. The sugar core provides a substantially different result because once solubilized it functions as an anti-wetting agent.

SUCROSE STEARATE IS NOT EQUIVALENT TO SUCROSE

84. Regarding claim 4, sucrose stearate does not function in an equivalent manner to a solution of sucrose.
85. A solution of sucrose functions as an anti-wetting agent, while sucrose stearate functions as a wetting agent.
86. A sucrose core surrounded by a layer of diltiazem acts in a substantially different way from a mixture of diltiazem and sucrose stearate because it does not provide any wetting to the diltiazem.
87. Sucrose in solution does not form the same type of structure with diltiazem that sucrose stearate does.

PRIOR ART ESTOPPEL

88. A product having a sugar sphere on top of which is built up a layer of diltiazem and polyvinylpyrrolidone having an outer coating thereon is within the prior art. '240 patent

(DX7); '619 patent (DX8); '596 patent (DX9); '083 patent (DX10); '097 patent (DX11).

89. This was specifically admitted by Plaintiff in the prosecution history of the '791 patent May 28, 1993 Preliminary Amendment (DX5).

90. Specifically, on page 9 of the May 28, 1993 Preliminary Amendment, Plaintiff stated as follows with regard to the Debregeas patent:

In particular, from column 3, lines 3-31, of Debregeas et al, it is clear that the process thereof resulted in a compositional form having i) [a] 'core' of mutual excipient, which is described as a mixture of saccharose or fructose and starch [i.e. sugar], ii) an outer layer thereon of polyvinylpyrrolidone (PVP) and Diltiazem, and iii) a coating thereon. (emphasis in original)
May 28, 1993 Preliminary Amendment (DX5).

91. This is an exact description of the composition of the Andrx formulation which is alleged to infringe the claims of the '791 patent (except that the Andrx formulation also contains ethyl cellulose in the layer built up on top of the sugar core). Jan deposition testimony; Banakar testimony.

92. Other prior art references also employ the same inert sugar core; diltiazem layer; coating structure which is employed by Andrx and taught in the '596 patent. For example, see, Panoz et al., United States Patent No. 4,721,619 ("the '619 patent"); Valducci, European Patent No. 0 263 083 ("the '083 patent"); Geogheghan et al., European Patent No. 0 320 097 ("the '097 patent"); Geogheghan et al., United States Patent No. 4,894,240 ("the '240 patent"); and the '596 patent '240 patent (DX7); '619 patent (DX8); '596 patent (DX9); '083 patent (DX10); '097 patent (DX11); Banakar testimony.

93. To the extent any of these Findings of Fact constitute Conclusions of Law, they are hereby adopted as both.

CONCLUSIONS OF LAW

1. The present action was brought by Plaintiffs (hereinafter "Biovail") for the alleged infringement of United States Patent No. 5,529,791 (hereinafter "the '791 patent") under 35 U.S.C. § 271(e)(2)(a) which defines a narrow act of infringement.
2. This narrow act of infringement derives from a statutory scheme which was enacted by Congress in the Drug Price and Patent Term Restoration Act, 98 Stat. 1585 (hereinafter "Patent Term Act"). The Patent Term Act sought to facilitate entry of lower priced bioequivalent drugs into the marketplace while also providing incentives for promoting the development of new drug products.
3. Accordingly, the Patent Term Act defined a new form of infringement, which was codified at 35 U.S.C. § 271(e)(2)(a), which covers the narrow situation wherein an ANDA is filed to obtain FDA approval for a drug product which is bioequivalent to a drug claimed in a patent listed in the FDA Orange Book, and which infringes the claims of the listed patent. 1984 U.S.C.C.A.N. 2678-79; 35 U.S.C. § 271(3)(2).
4. Upon the filing of an ANDA for a drug for which a patent is listed in the FDA Orange Book, the ANDA applicant is required to make one of four certifications regarding the patent. If the ANDA applicant makes what is known as a paragraph IV certification, i.e., that the ANDA applicant believes that the drug formulation described in the ANDA does not infringe the claims of the patent(s) listed in the FDA Orange Book, or that the claims of the listed patent are invalid, then the patent owner may file a lawsuit under 35 U.S.C. § 271(e)(2)(a) within forty-five days of the notice. 21 U.S.C. § 355(j)(5)(iii).
5. Upon the filing of such a lawsuit, the ANDA statute forbids the FDA from approving the ANDA until either there is a final decision of no infringement or invalidity by a United

States court, or thirty months expires, whichever occurs first. 21 U.S.C. § 355(j)(5)(iii).

6. Plaintiffs filed the instant complaint on October 7, 1998, seeking: 1) a declaratory judgment that Defendant's submission of an ANDA for commercial production of its proposed generic equivalent of Tiazac® before the expiration of the '791 Patent constitutes infringement of the '791 patent; 2) an order under 35 U.S.C. § 271(e)(4)(A) directing the effective date of any approval of Defendant's proposed generic equivalent to be a date which is not earlier than the expiration of the '791 patent; 3) injunctive relief prohibiting Defendant from further infringing on the '791 patent; and 4) attorney fees and costs.
7. Defendant, in response, filed an answer and counterclaim seeking declaratory judgment and alleging the following claims: 1) Defendant has not infringed the '791 patent (Count I); 2) the '791 patent is invalid due to prior art, previous full public disclosure of the alleged invention prior to the application for the '791 patent, and various other reasons for invalidity (Count II); 3) the '791 patent is invalid due to fraud by Plaintiff Galephar in submitting fees and a verified statement based upon Galephar's small entity status, when Galephar had already licensed its patent to a large entity (Count III); and 4) the '791 patent is invalid due to misuse by Plaintiffs in commencing "the present action in an unlawful attempt to impermissibly broaden the scope of the '791 patent with the anticompetitive effect of delaying and/or keeping the accused Andrx product from being marketed" (Count IV) (Count IV was previously dismissed by this Court).

Claim Construction of the '791 Patent

8. It is the Court's role to construe the claims of the disputed patent. Markman v. Westview Instruments, Inc., 116 S.Ct. 1384, 1387 (1996).

9. The Court principally looks to the claims made in the patent, the specifications, and the prosecution history. Vitronics Corp. v. Conceptionic, Inc., 90 F.3d 1576, 1582 (Fed. Cir. 1996).
10. Only if these are ambiguous, does the Court look to extrinsic evidence, such as expert affidavits or declarations. Id.
11. The claims herein appear specific enough to allow the Court to construe the claims without the need for extrinsic evidence for purposes of the motions for summary judgment.
12. Based on the '791 patent claim language, the specification of the '791 patent and the prosecution history which led to the issuance of the '791 patent, it is clear that the claims of the '791 patent require that the wetting agent and diltiazem be in admixture in the dry state. Southwall Tech., Inc. v. Cardinal IG Co., 54 F.3d 1570 (Fed. Cir. 1995).

LITERAL INFRINGEMENT

13. In order for a composition to literally infringe a claim, each and every element must be found in the accused product exactly. Southwall Techs., Inc. v. Cardinal IG Co., 54 F.3d 1570, 1575 (Fed. Cir. 1995).
14. The burden to show literal infringement is on the patentee by a preponderance of evidence. Braun Inc. v. Dynamics Corp., 975 F.2d 815 (Fed. Cir. 1992).
15. In this case, Biovail has failed to meet its burden that Andrx's product infringed the '791 patent.

DOCTRINE OF EQUIVALENTS

16. The doctrine of equivalents is sometimes applied in patent cases to enable the claims of a patent to cover products not within the literal scope of the claim if the product only

differs insubstantially from the claim language. Hilton Davis Chem. Co. v. Warner Jenkinson Co., 35 USPQ 2d 1641 (Fed. Cir. 1996).

17. One way to show an insubstantial difference is to shown that the substituted element provides substantially the same functions in substantially the same way to achieve substantially the same result. Warner-Jenkinson Co. v. Hilton Davis Chem. Co., 520 U.S. 35 (1997).
18. The burden to show infringement under the doctrine of equivalents is on the patentee by a preponderance of evidence. Braun Inc. v. Dynamics Corp., 975 F.2d 815 (Fed. Cir.1992).
19. In reviewing the scientific evidence, the Court is mindful to follow the teachings of the Federal Circuit:

As we have repeatedly said, it is error for a court to compare in its infringement analysis the accused product or process with the patentee's commercial embodiment of other version of the product or process; the only proper comparison is with the claims of the patent.

Zenith Laboratories, Inc. v. Bristol-Myers Squibb, 19 F.3d 1418, 1423 (Fed. Cir. 1994);
Glaxo, Inc. v. Torpharm, Inc., 153 F.3d 1266, 1373 (Fed. Cir. 1998).

20. In this case, Biovail has failed to prove infringement by Andrx's diltiazem product.
21. In making a doctrine of equivalents analysis, the scope of equivalents to which a claim may be allowed is limited by the doctrine of prosecution history estoppel. Athletic Alternatives, Inc. v. Prince Mfg. Inc., 73 F.3d 1537, 1582 (Fed. Cir. 1996).
22. Under the doctrine of prosecution history estoppel, actions taken by a patentee during the prosecution history act as legal limits on the application of the doctrine of equivalents by excluding from the range of equivalents subject matter surrendered during prosecution of the application for patent. The estoppel may arise from matter surrendered as a result of

amendments to overcome patentability rejections, or as a result of argument to secure allowance of a claim. Sextant Avionique S.A. v. Analog Devices, Inc., 49 USPQ 2d 1865, 1870 (Fed. Cir. 1999).

23. A patentee is simply not entitled to greater rights under the doctrine of equivalents that he would be under the language of the claims of the patent. White v. Dunbar, 119 U.S. 47, 51-52, 7 S.Ct. 72, 74-75 (1886).
24. Unequivocal assertions or arguments made during the prosecution of a patent create an estoppel which bars application of the doctrine of equivalents. Desper Prods. Inc. v. QSound Labs. Inc., 48 USPQ 2d 1088, 1098 (Fed. Cir. 1998); Haynes Int'l. Inc. v. Jessop Steel Co., 8 F.3d 1573, 1579 (Fed. Cir. 1993).
25. A patentee who has limited claims of patents for controlled release drug formulation primarily in consideration of obviousness rejection, is estopped from asserting relinquished claim scope against a defendant under theory of infringement by equivalents. Merck & Co. v. Mylan Pharms. Inc., 51 USPQ 2d 1954 (Fed. Cir. 1999).
26. Statements made during the prosecution of a patent bar plaintiff from asserting the doctrine of equivalents infringement against accused products, regardless of whether the statements were required to distinguish prior art, where a reasonable competitor could conclude from the statements that the plaintiff disclaimed the subject matter at issue in order to obtain the issuance of the patent.
27. The Federal Circuit has stated that: "For an estoppel to apply, such assertions in favor of patentability must evince a clear and unmistakable surrender of subject matter."
Pharmacia & Upjohn Company v. Mylan Pharmaceuticals, Inc., 170 F.3d 1373, 1377 (Fed. Cir. 1999) (internal quotation omitted).

28. The Court hereby concludes that Biovail did clearly and unmistakably surrender the building up process of using an inert sugar core in an extended release diltiazem product.
29. The Federal Circuit has also held that the relevant inquiry is whether a competitor would reasonably believe that the applicant had surrendered the relevant subject matter. Cybor Corporation v. Fas Technologies, Inc., 138 F.3d 1448, 1457 (Fed. Cir. 1998) (en banc).
30. In this case, a competitor would reasonably believe that Biovail had disclaimed the inert sugar core products in favor of their admixture form.
31. As an alternative conclusion to the above conclusion that Biovail has failed to meet its burden that Andrx infringed its patent, the Court concludes that because Biovail amended its claims to exclude a sugar core not in admixture with the diltiazem from the scope of the claims in response to a prior art rejection, Biovail is estopped from asserting that the inert sugar core of the Andrx formulation is a "wetting agent" within the scope of the claims of the '791 patent. Ekschian v. Home Depot, Inc., 104 F.3d 1299, 1304 (Fed. Cir. 1997).
32. Such an amendment in response to a prior art rejection constitutes the essence of prosecution history estoppel and operates as a complete bar to infringement by doctrine of equivalents. Sextant Avionique S.A. v. Analog Devices, Inc., 49 USPQ 2d 1865, 1874-75 (Fed. Cir. 1999).
33. Additionally, because Biovail continuously argued on numerous occasions that the use of a sugar core surrounded by a diltiazem layer to form a heterogeneous structure, as prepared by a "building up" process was not within the scope of the claims of the '791 patent, Biovail is estopped from asserting that the inert sugar core of the Andrx formulation is a "wetting agent" within the scope of the claims of the '791 patent. Desper

Prods. Inc. v. OSound Labs. Inc., 48 USPQ 2d 1088, 1098 (Fed. Cir. 1998); Haynes Int'l Inc. v. Jessop Steel Co., 8 F.3d 1573, 1579 (Fed. Cir. 1993).

34. It is only reasonable that explicit arguments made during the prosecution of a patent in order to overcome the prior art lead to a narrowing of the interpretation of the claims. As the Federal Circuit has held that "the public has a right to rely on such definitive statements made during prosecution." Digital Biometrics, 149 F.3d 1335, 1347 (Fed. Cir. 1998) (pointing to "[n]otice [as] an important feature of patent prosecution, as reflected by the [patent] statute itself).
35. The public's reliance on statements made during prosecution of a patent is entirely justified because "[b]y distinguishing the claimed invention over the prior art, an applicant is indicating what the claims do not cover." Ekschian, Home Depot, Inc., 104 F.3d 1299, 1304 (Fed. Cir. 1997).

PRIOR ART ESTOPPEL

36. The doctrine of prior art estoppel provides a legal limitation on the application of the doctrine of equivalents by mandating that the asserted range of equivalents may not encompass the prior art at the very point at which the claims distinguish from that art.
37. The doctrine of prior art estoppel prevents the doctrine of equivalents from expanding the scope of the claims to protect subject matter in, or obvious in light of, the prior art. Athletic Alternatives, Inc. v. Prince Mfg. Inc., 73 F.3d 1573, 1582 (Fed. Cir. 1996).
38. Thus, because the Andrx formulation was admitted by Plaintiff to be within the scope of the prior art, the doctrine of equivalents cannot be asserted by Plaintiffs to bring the Andrx formulation within the scope of the '791 patent claims. Stewart-Warner, 767 F.2d at 1572; Athletic Alternatives, 73 F.3d at 1582.

39. The Court declines to reach the counterclaims for invalidity brought by Andrx against the Biovail patent given the Court's conclusions that Biovail has not proven that the Andrx product infringes the patent. Thus, resolution of the counterclaims is not necessary to provide Andrx with the full relief it requested, namely, that its product does not infringe the Biovail patent
40. To the extent any of these Conclusions of Law constitute Findings of Fact, they are hereby adopted as both.
41. A separate Final Judgment will be entered herein consistent with the Court's Findings of Fact & Conclusions of Law.

DONE AND ORDERED in Chambers at Fort Lauderdale, Broward County, Florida,
this 7 day of March, 2000.


WILLIAM P. DIMITROULEAS
United States District Judge

Copies furnished to:

Eric C. Cohen, Esq./Robert B. Breisblatt, Esq./Charles Krikorian, Esq.
Benedict Kuehne, Esq.
James Costigan, Esq./Martin Andres, Esq./ Alan Clement, Esq.
Gerald Houlihan, Esq.



AC noted, dup
forward to Bio for review
Decision regarding
major/minor classification.
JMS 5/5/00
OK Label
AC

April 28, 2000

Gary Buehler, Acting Director
Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: ANDA 75-401; Taztia™ XT Capsules (Diltiazem HCl Extended-Release Capsules USP), 120 mg, 180 mg, 240 mg, 300 mg and 360 mg

MAJOR AMENDMENT – BIOEQUIVALENCY AND LABELING AMENDMENT
and
REQUEST FOR RECLASSIFICATION TO MINOR AMENDMENT

Dear Mr. Buehler:

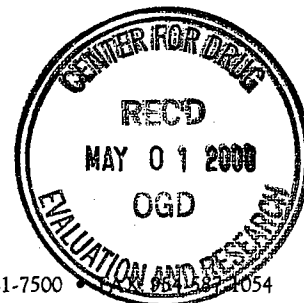
We refer to your facsimile dated April 13, 2000 (copy attached) providing *Bioequivalence* and *Labeling* comments regarding our abbreviated new drug application submitted on June 22, 1998. We also refer to an additional facsimile from Adolf Vezza of your Labeling Review Branch, dated April 19, 2000 and a telephone communication with Mr. Vezza on April 26, 2000. Pursuant to 21 CFR 314.120, Andrx Pharmaceuticals, Inc. ("Andrx") is herewith submitting an amendment responding to the comments included in your facsimile. We are also requesting that this amendment be reclassified as a minor amendment.

I. Bioequivalence response:

FDA Comment:

The reference listed drug labeling has been amended to incorporate dosage administration by sprinkling the contents of a capsule on applesauce. The Division of Bioequivalence current practice is to request an additional sprinkling bioequivalence study when the dosage and administration section of the labeling describes administration of the product sprinkled on food.

A single dose, two-way crossover sprinkling study on the 360 mg ER capsules should be conducted comparing your 360mg ER capsule to the 360mg ER Tiazac capsule by sprinkling both on applesauce.



Response:

We are aware of the agency's general policy concerning "sprinkle" BE studies, however, Andrx is requesting a waiver of the *in-vivo* bioequivalence study requested in your April 13, 2000 letter, based on the following scientific rationales:

1. Based on a determination of the f_2 values for the test and reference products, intact capsules vs. — sprinkled on applesauce have similar dissolution profiles in various media.

We have generated in-vitro dissolution data under the following conditions:

Dissolution Conditions	Andrx Product (360 mg, lot #700R001A – ANDA biobatch)		Tiazac Product (360 mg, lot #990905)	
	Intact capsule shells	No shell/- applesauce ¹	Intact capsule shells	No shell/- applesauce ¹
_____	X	X	X	X
_____	X	X	X	X
_____	X		X	

The Similarity Factor, f_2 values, have been calculated for the following comparisons:

- Andrx product (360 mg, lot #700R001): intact capsules vs. — on applesauce in —
 $f_2 =$ —
- Andrx product (360 mg, lot #700R001): intact capsules vs. — on applesauce in —
 $f_2 =$ —
- Tiazac product (360 mg, lot #990905): intact capsules vs. — on applesauce in —
 $f_2 =$ —
- Tiazac product (360 mg, lot #990905): intact capsules vs. — on applesauce in —
 $f_2 =$ —
- Andrx product (360 mg, lot #700R001) vs. Tiazac product (360 mg, lot #990905): intact capsules in water: $f_2 =$ —

The dissolution data described above are included as *Exhibit 1*. The data are presented in graphs, as well as tables providing the individual values and statistics for the twelve dosage units tested under each condition. A copy of the protocol for this testing is also included, describing the procedures used to generate the data. The data included in Exhibit 1 demonstrate that the dissolution profiles for this product, in various media, remain unchanged whether the testing is conducted on intact capsules or — sprinkled on applesauce.

¹ The — were removed from the capsule shell and sprinkled on 9 grams of applesauce just prior to introduction into the dissolution media

2. The test product does not have a different food effect than the reference product.

A Food Effect study was conducted as a part of our ANDA submission for this product. The summary results of this study are shown in *Exhibit 2*. The study results clearly show that there is no statistical difference in food effect between the test and reference products. In all cases, the AUC and Cmax parameters were well within the 20% range permitted by the agency for this type of study. It should be noted that the high-fat breakfast used in the food challenge study, which included an 8-ounce of orange juice, provides a much greater "worst case scenario" than the applesauce treatment.

3. The release-controlling polymer (_____) used in the test product is exactly the same as that used in the reference product.

As shown in *Exhibit 3*, _____ is a neutral, pH-independent, _____. Since the test product uses the same _____ as the reference product, it further supports the above finding that there is no change in dissolution profile after treatment with applesauce.

4. The dissolution profiles are similar with or without applesauce, demonstrating that applesauce does not have an effect on the release-controlling polymer used in the formulation.

5. There are no safety and efficacy concerns of medical significance when the test product and reference products are administered as a "sprinkle".

We refer you to the agency's response to our citizen petition (Docket No. 98P-0145/CP1 & SUP1, Oct. 22, 1999 and 98P-0145/PRC1 on Feb 29, 2000) regarding the plasma profile (one-peak vs. two-peak) issue related to another of our Diltiazem HCl ER Capsules (ANDA 74-752). One of the reasons FDA denied our petition was related to "medical significance". FDA asserted that there was no medical significance in approving a generic product with a one-peak plasma profile, while the reference product has a two-peak profile.

We believe there is no medical significance in administering this product as intact capsules vs. sprinkling the _____ on applesauce. The applesauce treatment is much less abrasive than the high-fat food challenge study to which this product was already subjected. It is reasonable to believe there are no safety and efficacy concerns when the product is administered with applesauce.

The rationales discussed in items (1) through (5) above provide an adequate basis for the agency to approve our request to waive the "sprinkle" BE study. The requirement for this type of study has no merit for a generic extended-release _____ product.

II. Labeling response:

We have enclosed four draft copies of our revised insert, incorporating the revisions requested in your April 13, 2000 facsimile, as well as the additional revisions requested by Adolph Vezza in an April 19, 2000 facsimile and an April 26, 2000 telephone communication. We have also included an annotated side-by-side comparison of the revisions made. (See *Exhibit 4*).

III. Request for Reclassification:

Your April 13, 2000 letter requesting that Andrx conduct a new bioequivalence study, and then revised our labeling for this product, was the result of a recent voluntary change in the labeling of the Reference Listed Drug (RLD), Tiazac®. The primary objective of that change, which allows the sprinkling of extended-release pellets over applesauce, was to further delay the marketing of Andrx's bioequivalent product. By classifying Andrx's required response to that change as a major amendment, rather than a minor amendment, FDA has effectively delayed the public's access to the first and only generic for Tiazac by imposing a six-month review cycle. By reclassifying its letter as a minor amendment, FDA will expedite its internal review and approval of our ANDA, and thereby better achieve the objective of the Hatch-Waxman Amendments of making bioequivalent products available to the public. Biovail Corporation International, the NDA holder for Tiazac, should not be rewarded for its pattern of tactics intended to delay the introduction of the Andrx product.

We cite the following as further grounds for this request:

1. Andrx had already satisfied the previously established bioequivalence requirements for this product in January 2000, and had been repeatedly advised by OGD that it would receive tentative approval of its ANDA in February 2000.
2. On March 6, 2000, the United States District Court for the Southern District of Florida entered an Order that the Andrx product does not infringe the patent Biovail listed in the Orange Book for Tiazac.
3. On March 7, 2000, one day following that Order, Biovail filed a notice of appeal of that Court decision. The filing of a notice of appeal may be done within 45 days of the entry of a lower court decision, and the filing one day after a court decision (and before Andrx was even aware of that decision), is unprecedented.
4. On March 14, 2000, Biovail commenced a lawsuit against FDA the United States District Court for the District of Maryland, seeking to prevent FDA from granting final approval of the Andrx ANDA until the expiration of 30 months after Biovail received Andrx's Paragraph IV Certification for this product or the Court decision in the patent action initiated by Biovail became final and nonappealable.
5. On March 16, 2000, Biovail filed a Citizen Petition seeking to prevent FDA's approval of the Andrx ANDA without additional testing which is not required by the applicable guidance, is not justified by any scientific rationale, would be impossible (or very

impracticable) to perform on products, such as the Andrx product, comprised of a blend of beads and, though ostensibly for the purpose of ensuring better uniformity, is sought to be performed on a product that has exhibited — through other test methods — better uniformity than Tiazac.

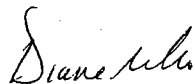
6. From the timing of each of these events, it is readily apparent that Biovail's new administration for Tiazac was timed in a manner that would preclude Andrx and others from performing, beforehand, the tests that FDA might require as a result of such new administration. Indeed, Andrx believes its sole purpose was to delay approval of Andrx's ANDA.
7. At the time of our submission, the labeling for Tiazac did not contain a provision for the administration of the  on applesauce. It is therefore unjust and unwarranted for the Agency to now impose an additional six-month review cycle, when the cause of the major amendment was an obvious attempt by the NDA holder to delay generic competition.

We would like to point out that both before and after we received the favorable court decision in our patent infringement suit with Biovail, we were in contact with FDA in an effort to market our product prior to the appellate court's final determination. Indeed, shortly following the current FDA policy regarding court decisions (which does not apply to ANDAs submitted before March 2000), our general counsel met with FDA counsel to discuss the possibility of "waiving" the benefit established by that guidance for this particular ANDA. While this waiver imposes certain risks on Andrx, we are in the process of obtaining insurance to cover that and thereby be able to market our product as soon as we obtain a final approval.

Accordingly, we respectfully request that FDA accept our scientific rationales for not performing the requested bioequivalence study and/or reclassification of this matter as a minor amendment. Acceptance of these requests would be beneficial to American consumers and would be in better keeping with the Hatch-Waxman Amendments objective of making bioequivalent products available to the public.

Should you have any questions concerning this submission, please contact the undersigned at (954) 327-4412 (telephone) or (954) 587-1054 (fax).

Sincerely,



Diane Servello
Director of Regulatory Affairs



Gary Buehler, Acting Director
Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

NEW CONCEPT

FACSIMILE AMENDMENT
(Hard copy to follow by Federal Express)

Dear Mr. Buehler:

As a follow-up to a telephone call from Mr. Timothy Ames on March 29, 2000, we are herewith amending this application to withdraw references to _____ is a

outside firm. Their intended function was to serve as an alternate [REDACTED] performed by our primary [REDACTED] We are requesting that [REDACTED] be withdrawn from our application as an outside firm.

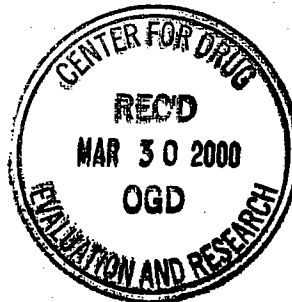
Andrx Pharmaceuticals, Inc. certifies that a true copy of this amendment was sent to the Florida District Office as a Field Copy.

Please direct any questions concerning this submission to the undersigned at (954) 327-4412 (telephone) or (954) 587-1054 (fax).

Sincerely,

Diane Loh

Diane Servello
Director, Regulatory Affairs



*labeling review
drafted 1/28/00
A. Vezza*

January 19, 2000

Douglas L. Sporn, Director
Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

ANDA 075 AMENDMENT

AF

**RE: ANDA 75-401; Diltiazem Extended-Release Capsules USP (Once-a-Day Dosage)
120 mg, 180 mg, 240 mg, 300 mg and 360 mg**

TELEPHONE AMENDMENT

Dear Mr. Sporn:

In response to a telephone call from Mr. Adolph Vezza on January 19, 2000, we are providing enlarged copies of the insert labeling for Diltiazem Extended-Release Capsules USP (Once-a-Day Dosage submitted on January 14, 1999.

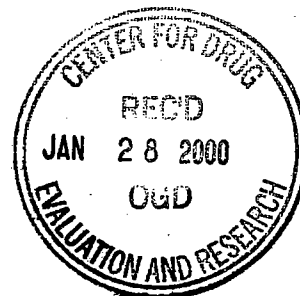
This submission contains 4 enlarged copies of the package insert in both the archival and review copies.

Please direct any questions concerning this submission to Jacqueline Davis at (954) 321-5229 (telephone) or (954) 587-1054 (fax).

Sincerely,

Diane Servello

Diane Servello
Director, Regulatory Affairs





Sent via fax to 301-827-4337 – Hard copy by mail

November 1, 1999

NEW CORRESP

Douglas L. Sporn, Director
Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: ANDA 75-401; Diltiazem Extended-Release Capsules USP
120 mg, 180 mg, 240 mg, 300 mg and 360 mg

FOLLOW-UP TO FAX AMENDMENT
DATED OCTOBER 29, 1999

Dear Mr. Sporn:

We refer to our fax amendment dated October 29, 1999, submitted in response to your facsimile dated October 25, 1999 providing chemistry and labeling comments on the above referenced ANDA. This submission provides additional information concerning the chemistry comment in your October 25, 1999 facsimile.

Please see the attachments for additional information concerning your comments.

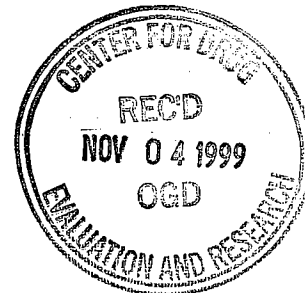
Andrx Pharmaceuticals, Inc. certifies that a true copy of this amendment was sent to the Florida District Office as a Field Copy.

Should you have any questions concerning this submission, please contact the undersigned at (954) 327-4412 (telephone) or (954) 587-1054 (fax).

Sincerely,

A handwritten signature in cursive script, appearing to read "Diane Servello".

Diane Servello
Director of Regulatory Affairs





May 4, 1999

Douglas L. Sporn, Director
Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

*Labeling review
drafted 5/13/99
A. Sporn*

ORIG AMENDMENT

AC

**RE: ANDA 75-401; Diltiazem Extended-Release Capsules USP
120 mg, 180 mg, 240 mg, 300 mg and 360 mg**

MAJOR AMENDMENT

Dear Mr. Sporn:

We refer to your facsimile dated March 11, 1999 (copy attached) providing chemistry, labeling and bioequivalence comments on our abbreviated new drug application submitted on June 22, 1998. Pursuant to 21 CFR 314.120, we are herewith submitting a MAJOR amendment responding to all the listed comments.

Please see the attachments for item-by-item responses to your comments.

Andrx Pharmaceuticals, Inc. certifies that a true copy of this amendment was sent to the Florida District Office as a Field Copy.

Should you have any questions concerning this submission, please contact the undersigned at (954) 327-4412 (telephone) or (954) 587-1054 (fax).

Sincerely,

Diane Servello
Director of Regulatory Affairs

RECEIVED

MAY 13 1999

GENERIC DRUGS



ANDA 75-401

October 16, 1998

Douglas Sporn, Director
Office of Generic Drugs (HFD-600)
CDER, FDA
Metro Park North II
7500 Standish Place, Rm. 150
Rockville, MD 20855-2773

NEW CORRESP

RE: Patent Amendment – Documentation of Receipt of Notice and Documentation of Litigation

Dear Mr. Sporn:

Andrx Pharmaceuticals, Inc. ("Andrx Pharmaceuticals") is hereby amending its Abbreviated New Drug Application, ANDA 75-401, for Diltiazem Hydrochloride Extended-release Capsules to provide documentation of receipt of notice and documentation of litigation as follows:

1) Documentation of Notification & Receipt of Notice

In accordance with 21 CFR 314.95(b), Andrx Pharmaceuticals, Inc. certifies that:

- (i) the required notices of certification of noninfringement of a patent have been provided to Biovail Corporation International, Galephar P.R. Inc. Ltd. and Bank of Nova Scotia, the persons identified under section 314.95(a), on two separate occasions, each time by both U.S. registered mail, return receipt requested, and by next day courier;
- (ii) the notices met the content requirements under section 314.95(c). The first set of notices were sent by James Costigan, patent counsel for Andrx Pharmaceuticals, on July 30, 1998 (the "First Notification"), and the second set of notices were sent by Martin Endres, also patent counsel for Andrx Pharmaceuticals, on August 25, 1998 (the "Second Notification");
- (iii) the return receipt postcards for the First Notification are attached (attachment A) and reflect receipt by Galephar P.R. Inc. Ltd. on August 4, 1998 and by Biovail Corporation International and Bank of Nova Scotia, on August 10, 1998;
- (iv) the return receipt postcard for the Second Notification is attached (attachment B) (except as hereafter set forth) and reflects receipt by Galephar P.R. Inc. Ltd. on August 28, 1998 and by Bank of Nova Scotia on September 4, 1998;
- (v) the return receipt postcard for the Second Certification sent to Biovail Corporation International has not been returned to Andrx Pharmaceuticals and a "tracer" has been filed with the postal authorities. In accordance with section 314.95(e), we are providing a copy of the Complaint filed by Biovail Corporation International (and others) as evidence of the date

OCT 20 1998

that notification was received (attachment C). However, although Paragraph 9 of the Complaint states that Andrx Pharmaceuticals' notice of certification was received "Biovail" (which is defined as including both Biovail Corporation International and Biovail Laboratories Inc.) on August 25, 1998, Andrx Pharmaceuticals notes that the Second Notification was not sent until August 25, 1998 (making August 26, 1998 the actual date of receipt via the overnight courier), and that no certification was sent to Biovail Laboratories Inc., which is not a person identified under section 314.95 (a).

2) **Documentation of Untimely Litigation**

This certifies that an action for patent infringement (**Case No. 98-7096, CIV-DIMITROULEAS**) has been filed by Biovail Corporation International, Biovail Laboratories Inc., and Galephar P.R. Inc. Ltd. against Andrx Pharmaceuticals alleging infringement of United States patent No. 5,529,791 ("the '791 patent"). Andrx Pharmaceuticals is hereby providing notification of the legal action filed against it. However, that Complaint was filed in the United States District Court for the Southern District of Florida on October 7, 1998, after the expiration of the 45-day period that began by August 10, 1998, the last date on which the First Notification was received by all of the persons identified under section 314.95(a).

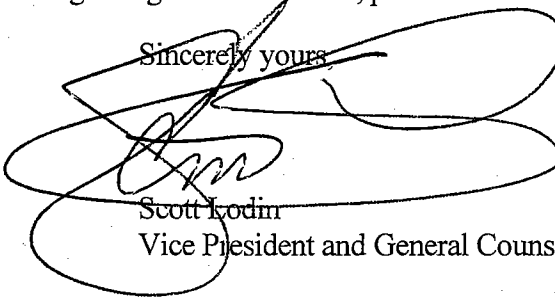
ANDA No.: **75-401**

Name of Applicant: **Andrx Pharmaceuticals, Inc.**

Established name of Drug Product: **Diltiazem Hydrochloride Extended-release Capsules, 120 mg, 180 mg, 240 mg, 300 mg, 360 mg**

Should you have any questions regarding this submission, please contact the undersigned.

Sincerely yours



Scott Kodin

Vice President and General Counsel



January 14, 2000

Douglas L. Sporn, Director
Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

ANDA ORIG AMENDMENT
N/AF

**RE: ANDA 75-401; Diltiazem Extended-Release Capsules USP (Once-a-Day Dosage)
120 mg, 180 mg, 240 mg, 300 mg and 360 mg**

LABELING AMENDMENT

Dear Mr. Sporn:

Andrx Pharmaceuticals is amending its application to respond to the November 18, 1999 facsimile from the OGD's Labeling Review Branch (copy attached). We have revised our package insert and container labels to address all deficiencies listed. In addition the labeling has been revised to reflect the proprietary name for this drug product – Taztia XT™ – and to correct minor typographical errors.

We note that the labeling for the reference listed drug was revised (revised August 1998, approved October 16, 1998) and we will monitor the Labeling Review Branch's website for any approved changes.

1. INSERT

In addition to the General Comments, revisions were made to the PRECAUTIONS, ADVERSE REACTIONS, OVERDOSAGE, and DOSAGE AND ADMINISTRATION sections as detailed in the OGD's facsimile. The proprietary name was also added to the TITLE and HOW SUPPLIED sections.

2. CONTAINER

The container labels have been revised to include the proprietary name.

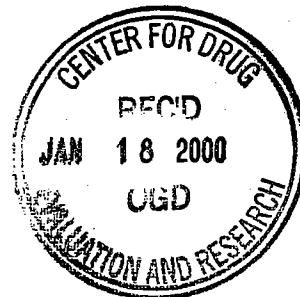
This amendment contains:

- (i) a side-by side comparison of the current labeling versus the last submission with all differences annotated and explained
- (ii) 4 draft copies of the container labels (10 labels total) and the package insert.

Please direct any questions concerning this submission to Jacqueline Davis at (954) 321-5229 (telephone) or (954) 587-1054 (fax).

Sincerely,

Diane Servello
Director, Regulatory Affairs





Sent via fax to 301-827-4337 – Hard copy by Federal Express

December 3, 1999

Douglas L. Sporn, Director
Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

NEW CORRESP

NC to
FAX

RE: **ANDA 75-401; Diltiazem Extended-Release Capsules USP**
120 mg, 180 mg, 240 mg, 300 mg and 360 mg

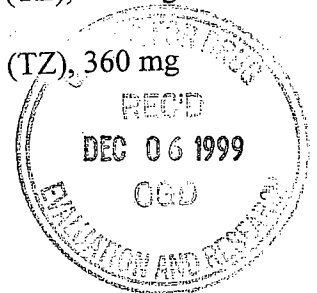
TELEPHONE AMENDMENT

Dear Mr. Sporn:

We refer to a telephone communication on December 2, 1999 between Tim Ames of the Office of Generic Drugs and Diane Servello of Andrx Pharmaceuticals, Inc. ("Andrx") concerning the above referenced ANDA. In that communication, Mr. Ames requested that Andrx revise our dissolution specifications for the 4 hour time interval from "_____ to _____". The revisions were requested for testing for finished product release and stability. It was requested that revised specifications be prepared and submitted as a telephone amendment to this application.

Accordingly, we have enclosed the following revised specifications:

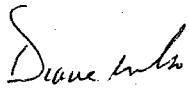
1. In-process Specification: Diltiazem HCl Extended-release — (TZ2) (Code #151)
2. Release/Stability Specification: Diltiazem HCl Extended-release Capsules (TZ), 120 mg (Code #696)
3. Release/Stability Specification: Diltiazem HCl Extended-release Capsules (TZ), 180 mg (Code #697)
4. Release/Stability Specification: Diltiazem HCl Extended-release Capsules (TZ), 240 mg (Code #698)
5. Release/Stability Specification: Diltiazem HCl Extended-release Capsules (TZ), 300 mg (Code #699)
6. Release/Stability Specification: Diltiazem HCl Extended-release Capsules (TZ), 360 mg (Code #700).



Andrx Pharmaceuticals, Inc. certifies that a true copy of this amendment was sent to the Florida District Office as a Field Copy.

Should you have any questions concerning this submission, please contact the undersigned at (954) 327-4412 (telephone) or (954) 587-1054 (fax).

Sincerely,

A handwritten signature in cursive script, appearing to read "Diane Servello".

Diane Servello
Director of Regulatory Affairs

**APPEARS THIS WAY
ON ORIGINAL**



ANDA 75-401
ANDA AMENDMENT

NEW CORRESP

August 10, 1998

Douglas Sporn
Director, Office of Generic Drugs (HFD-600)
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Mr Sporn:

Please refer to Andrx's ANDA 75-401, for Diltiazem Hydrochloride Extended-release Capsules, and to Andrx's citizen's petition, No. 98P-0429/CP1, which requested that the FDA permit the filing of an ANDA citing Tiazac™ (diltiazem hydrochloride) Extended-release Capsules as the reference listed drug. Andrx's citizen's petition was approved on July 31, 1998. A copy of the approval letter is enclosed.

Should you have any questions or comments regarding this amendment please contact Ms. Jacqueline Davis, Regulatory Affairs Manager, Tel. (954) 321-5229/ Fax. (954) 587-1054.

Sincerely yours,

A handwritten signature in dark ink, reading "David A. Gardner". The signature is fluid and cursive, with the first name "David" and last name "Gardner" clearly legible.

David A. Gardner
Vice President, Regulatory Affairs/QA/QC

RECEIVED

AUG 11 1998

GENERIC DRUGS



BIOAVAILABILITY
Sept Bio

VIA AIRBORNE EXPRESS

July 29, 1998

Douglas L. Sporn
Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW URGESP

NC

RE: ANDA 75-401: Diltiazem HCl Extended-release Capsules ('TZ'), 360 mg

Dear Sir:

Please refer to Andrx's Abbreviated New Drug Application for Diltiazem Hydrochloride Extended-release Capsules ('TZ'), 360 mg, which was submitted on June 22, 1998.

In accordance with 21 CFR 314.96, we are amending this application to include four additional strengths of the ANDA product (i.e. 120 mg, 180 mg, 240 mg and 300 mg). Please note that the five strengths have a common formulation. A bioequivalence waiver request, *in vitro* dissolution data, and manufacturing and controls information for the 120, 180, 240, and 300 mg strengths are included in this amendment.

This amendment consists of 2 volumes. Please note that the sections provided in the amendment retain the same section numbers as the original submission. Two copies are provided — an archival copy and a review copy separated into two parts containing the bioequivalence data and the chemistry, manufacturing and controls information. **NOTE: THIS APPLICATION CONTAINS AN ELECTRONIC SUBMISSION OF LABELING DATA** — the revised draft package insert is provided in WordPerfect v.6.1 format on two 3.5" diskettes. The data contained in the electronic submission is the same as in the hardcopy submission.

Andrx Pharmaceuticals, Inc. certifies that in accordance with 21 CFR 314.94(d)(5), a field copy of this amendment has been submitted to the Florida District Office concurrently with this submission. That field copy is a true copy of the chemistry, manufacturing, and controls technical sections contained in the archival and review copies of the application.

Please direct any questions regarding this submission to Jacqueline Davis, Regulatory Affairs Manager, at 954-321-5229 (Tel.) or 954-587-1054 (Fax.).

Sincerely,

David A. Gardner

RECEIVED

David A. Gardner
Vice President, Regulatory Affairs/QA/QC

JUL 30 1998

GENERIC DRUGS



VIA AIRBORNE EXPRESS

June 22, 1998

Douglas L. Sporn
Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

505(j) OK
8/13/98
Gregory S. Davis

RE: ABBREVIATED NEW DRUG APPLICATION
Diltiazem HCl Extended-release Capsules ('TZ'), 360 mg

Dear Sir:

Pursuant to the requirements of Section 505(j) of the FD&C Act and 21 CFR 314.94, Andrx Pharmaceuticals, Inc. submits an original Abbreviated New Drug Application for approval to market its formulation of Diltiazem Hydrochloride Extended-release Capsules ('TZ') which are bioequivalent to Tiazac™ (diltiazem hydrochloride) Extended-release Capsules, manufactured by Biovail Laboratories, Inc.

This application consists of 18 volumes containing the required information to demonstrate that Andrx's Diltiazem Hydrochloride Extended-release Capsules ('TZ') are both pharmaceutically equivalent and bioequivalent to the reference listed drug. Two copies are provided — an archival copy and a review copy separated into the bioequivalence review section and the chemistry review section. **NOTE: THIS APPLICATION CONTAINS AN ELECTRONIC SUBMISSION OF LABELING DATA** — the proposed package insert is provided in WordPerfect v.6.1 format on 3.5 inch diskettes. The data contained in the electronic submission is the same as in the hardcopy submission.

Andrx Pharmaceuticals, Inc. certifies that in accordance with 21 CFR 314.94(d)(5), a field copy has been submitted to the Florida District Office concurrently with this submission. That field copy is a true copy of the chemistry, manufacturing, and controls technical sections contained in the archival and review copies of the application.

Please note that Andrx is the holder of two other ANDAs for diltiazem HCl extended-release capsules: ANDA #74-752 for Diltiazem HCl Extended-release Capsules, 120, 180, 240, and 300 mg, which are bioequivalent to Cardizem CD®; and ANDA #74-852 for Diltiazem HCl Extended-

Card
Hofmann
Davis

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JUN 23 1998

GENERIC DRUGS

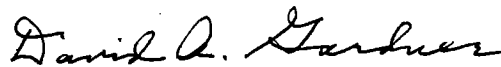
June 22, 1998

Page 2

release Capsules USP (Once-A-Day-Dosage), 120, 180, and 240 mg, which are bioequivalent to Dilacor XR®. We recognize that these three formulations are not considered to be therapeutically equivalent and will make appropriate distinctions to ensure dispensing of the correct product.

Please direct any questions regarding this submission to Jacqueline Davis, Regulatory Affairs Manager, at 954-321-5229 (Tel.) or 954-587-1054 (Fax).

Sincerely,

A handwritten signature in cursive script that reads "David A. Gardner".

David A. Gardner

Vice President, Regulatory Affairs/QA/QC

**APPEARS THIS WAY
ON ORIGINAL**

Andrx Pharmaceuticals, Inc.
Attention: David A. Gardner
4001 S.W. 47th Avenue
Fort Lauderdale, FL 33314
|||||

Dear Sir:

Reference is made to your amendment dated August 10, 1998, that provided a copy of FDA's correspondence approving your Citizen Petition which designated different reference listed drugs. To be in compliance with 21 CFR 314.94(a)(3)(iii), and establish a basis for your abbreviated new drug application submission, your August 10, 1998 amendment will be the date acceptable for filing.

DATE OF APPLICATION: June 22, 1998

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(I)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:
 - 1) Each owner of the patent or the representative designated by the owner to receive the notice;
 - 2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.
 - 3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).
- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.
- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.
- You must submit a copy of a final order or judgement from which no appeal may be taken (which might not be the one from the District Court), or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Peter Rickman, Chief, Regulatory Support Branch, at (301)827-5862.

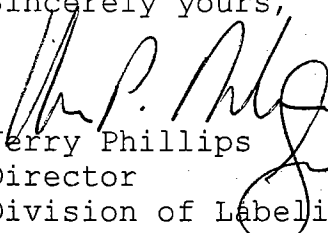
We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Tim Ames
Project Manager
(301) 827-5849

Sincerely yours,

 8/15/88
Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research



VIA FACSIMILE TO (301) 594-0183

ANDA 75-401

Taztia XT (Diltiazem HCl Extended-release Capsules USP)

March 1, 2001

Gary Buehler, Acting Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: General Correspondence - Study

Dear Mr. Buehler:

Please refer to our abbreviated new drug application for Diltiazem Hydrochloride Extended-release Capsules, ANDA #75-401. Reference is also made to my March 1, 2001 telephone conversation with Frank Holcombe, Office of Generic Drugs. Mr. Holcombe indicated that the agency is requesting that Andrx perform a study to examine the _____ of the extended-release _____ during the _____ process.

Andrx commits to developing a protocol and conducting the requested study. We understand that the results of the completed study can be submitted either prior to or after the final approval of the ANDA.

Should you have any questions concerning this submission, please contact the undersigned at (954) 585-1412 (telephone) or (954) 585-1848 (fax).

Sincerely,

Diane Servello
Director, Regulatory Affairs



Consider this study
a Phase 4 commitment.
(Post Approval).
B. McNeal
3/12/01