74-752

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 74752

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74752

APPROVAL LETTER

ANDA 74-752

JUL 9 1998

Andrx Pharmaceuticals, Inc.
Attention: David A. Gardner
4001 S.W. 47th Avenue, #201
Fort Lauderdale, FL 33314

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated September 22, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for CARTIA XT (Diltiazem Hydrochloride Extended-release Capsules, USP); 120 mg, 180 mg, 240 mg and 300 mg.

Reference is also made to your amendments dated February 18 and 26, May 8, June 2 and 25, 1998.

The listed drug product referenced in your application is subject to a period of patent protection as follows:

Patent No. 5,470,584 - Expires May 20, 2011
Patent No. 5,439,689 - Expires August 8, 2012
Patent No. 5,364,620 - Expires November 14, 2011
Patent No. 5,286,497 - Expires May 20, 2011
Patent No. 5,002,776 - Expires March 26, 2008
Patent No. 4,894,240 - Expires January 16, 2007

Your application contains a patent certification under section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, or sale of Diltiazem Hydrochloride Extended-release Capsules will not infringe on the patent or that the patent is otherwise invalid. You also included in your application notice to each patent holder as required under section 505(j)(2)(B)(I). You further informed the Agency that Hoechst Marion Roussel Inc. initiated a patent infringement suit (Patent No. 5,470,584) against you in United States District Court for the Southern District of Florida(Hoechst Marion Roussel, Inc. and Carderm Capital L.P. v. Andrx Pharmaceuticals, Inc., Civil Action No. 96-06121-CIV-Roettger) within the 45 day period described in section 505(j)(5)(B)(iii), thereby triggering the 30 month period identified in that section. The 30-month period identified in section 505(j)(5)(B)(iii) has now expired.

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 CARTIA XT (Diltiazem Hydrochloride Extended-release Capsules USP) 120 mg, 180 mg, 240 mg and 300 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Cardizem CD Capsules, 120 mg, 180 mg, 240 mg and 300 mg of Hoechst Marion Roussel Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Andrx was the first applicant to submit a substantially complete ANDA with a section 505(j)(2)(A)(vii)(IV) ("paragraph IV") certification and thus is eligible for 180 days of market exclusivity. Such exclusivity will begin to run either from the date Andrx begins commercial marketing, or from the date of a decision of a court finding the patent invalid or not infringed, whichever is earlier (Section 505(j)(5)(B)(iv) of the Act). Please note that you are required to inform the Office of Generic Drugs of a relevant court order and judgement under 21 CFR 314.107(e)(2)(iv) and of the date that you commence commercial marketing of this drug product under 21 CFR 314.107(c)(4).

Under 21 CFR 314.70, 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 proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-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 FD-2253 at the time of their initial use.

Sincerely yours,

1/9/98

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74752

TENTATIVE APPROVAL LETTER

ANDA 74-752

SEP 15 1997

Andrx Pharmaceuticals, Inc.
Attention: David A. Gardner
4001 S. W. 47th Avenue, Suite 201
Fort Lauderdale, FL 33314

Dear Sir:

This is in reference to your abbreviated new drug application dated September 22, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Diltiazem Hydrochloride Extended-release Capsules USP, 120 mg, 180 mg, 240 mg and 300 mg.

Reference is also made to your amendments dated March 25, May 2, August 22, October 8, 1996; February 27, March 10, March 19, May 28 and June 20, 1997.

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 your application is **tentatively approved.** This determination is contingent 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)(4)(B)(iv) of the Act.

The listed drug product referenced in your application is subject to a period of patent protection which expires on May 20, 2011 [Patent No. 5,470,584]. However, litigation is underway in the United States District Court for the Southern District of Florida-Miami, involving a challenge to the patent (Hoechst Marion Roussel, Inc. and Carderm Capital L.P., v. Andrx Pharmaceuticals, Inc., Civil Action No. CIV 96-06121). Therefore, final approval cannot be granted until:

1. a. the expiration of the 30-month period provided for in section 505(j)(4)(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)(4)(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 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.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74752

FINAL PRINTED LABELING

JUL -9- 1998

APPROVED

7001 (05/98)

LOT:

EXP:

N 3 62037-597-30 5

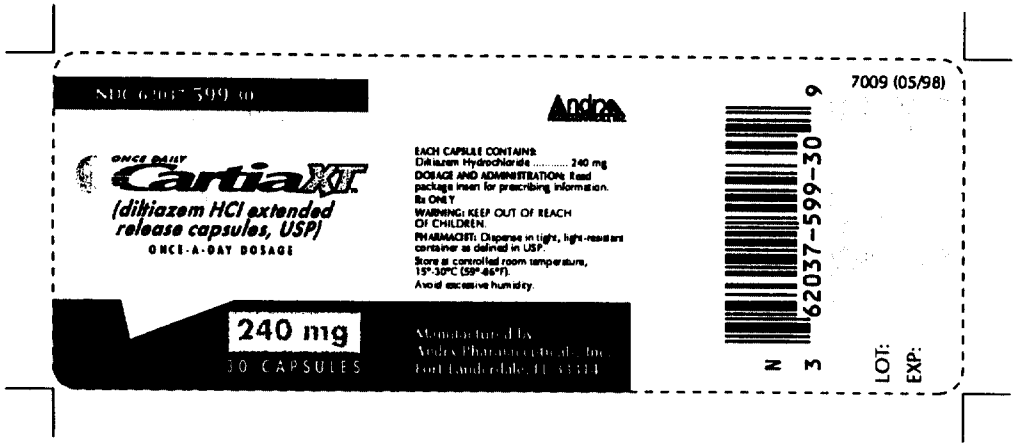
Andrx

EACH CAPSULE CONTAINS:
Diltiazem Hydrochloride ..... 120 mg
DOSAGE AND ADMINISTRATION: Read package insert for prescribing information
Rx ONLY
WARNING: KEEP OUT OF REACH OF CHILDREN.
PHARMACIST: Dispense in tight, light-resistant container as defined in USP.
Store at controlled room temperature, 15-30°C (59-86°F).
Avoid excessive humidity.

ONCE DAILY
Cartia XT
(diltiazem HCl extended release capsules, USP)
ONCE-A-DAY DOSAGE

120 mg
30 CAPSULES

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


NDC 62037-599-30
ONCE DAILY
Cartia XT
(diltiazem HCl extended release capsules, USP)
ONCE-A-DAY DOSAGE
EACH CAPSULE CONTAINS:
Diltiazem Hydrochloride ..... 240 mg
DOSAGE AND ADMINISTRATION: Read package insert for prescribing information.
Rx ONLY
WARNING: KEEP OUT OF REACH OF CHILDREN.
PHARMACIST: Dispense in tight, light-resistant container as defined in USP.
Store at controlled room temperature, 15°-30°C (59°-86°F).
Avoid excessive humidity.
240 mg
30 CAPSULES
Manufactured By
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314
7009 (05/98)
N 3 62037-599-30 9
LOT:
EXP:

JUL 9 1998

NDC 62037-599-05

7011 (05/98)

ONCE DAILY

CartiaXT™

(diltiazem HCl extended release capsules, USP)

ONCE-A-DAY DOSAGE

Andrx PHARMACEUTICALS, INC.

EACH CAPSULE CONTAINS:
Diltiazem Hydrochloride ..... 240 mg

DOSAGE AND ADMINISTRATION: Read package insert for prescribing information.

℞ ONLY

WARNING: KEEP OUT OF REACH OF CHILDREN.

PHARMACIST: Dispense in tight, light-resistant container as defined in USP.

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

Avoid excessive humidity.

240 mg

500 CAPSULES

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

JUL 9 1998

N 3 62037-599-05 7

LOT:

EXP:

Cardizem CD
(diltiazem HCl extended release capsules, USP)
300 mg
30 CAPSULES
Andrx
N 62037-600-30 2
LOT:
EXP:
7013 (05/98)

JUL -9 1998

NDC 62037-600-05

7015 (05/98)

Andrx PHARMACEUTICALS, INC.

ONCE DAILY

CartiaXT™

(diltiazem HCl extended release capsules, USP)

ONCE-A-DAY DOSAGE

EACH CAPSULE CONTAINS:
Diltiazem Hydrochloride ..... 300 mg

DOSAGE AND ADMINISTRATION: Read package insert for prescribing information.

Rx ONLY

WARNING: KEEP OUT OF REACH OF CHILDREN.

PHARMACIST: Dispense in tight, light-resistant container as defined in USP.

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

Avoid excessive humidity.

300 mg

500 CAPSULES

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

N 3 62037-600-05 0

LOT:

EXP:

JUL 9 1998

NDC 62037-597-05

ONCE DAILY

CartiaXT™

(diltiazem HCl extended release capsules, USP)

ONCE-A-DAY DOSAGE

EACH CAPSULE CONTAINS:
Diltiazem Hydrochloride ..... 120 mg

DOSAGE AND ADMINISTRATION: Read package insert for prescribing information.

Rx ONLY

WARNING: KEEP OUT OF REACH OF CHILDREN.

PHARMACIST: Dispense in tight, light-resistant container as defined in USP.

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

Avoid excessive humidity.

120 mg

500 CAPSULES

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

Andrx PHARMACEUTICALS, INC.

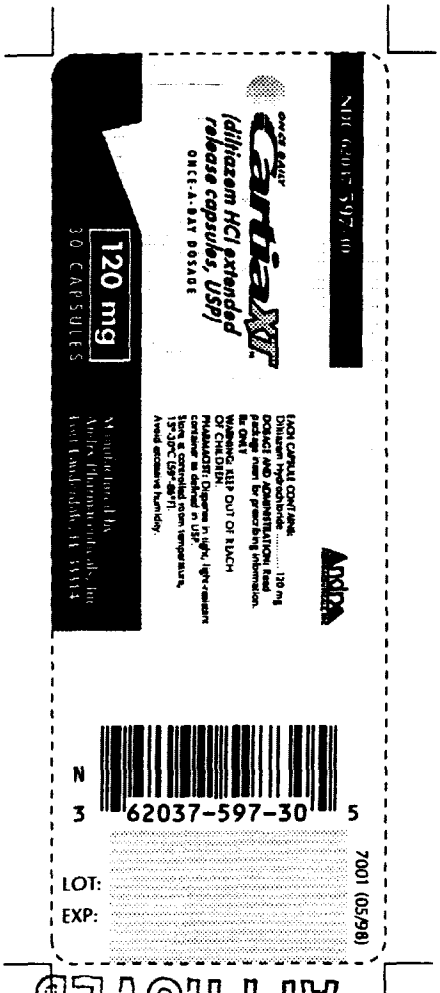
7003 (05/98)

JUL 9 1998

N 3 62037-597-05 3

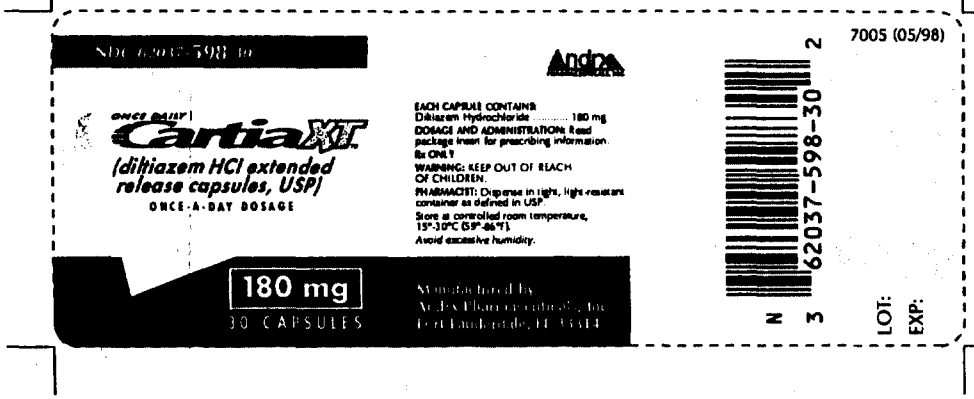
LOT:

EXP:



APPROVED

JUL 9 1998


NDC 62037-598-30
ONCE DAILY
Cartia XT
(diltiazem HCl extended release capsules, USP)
ONCE-A-DAY DOSAGE
EACH CAPSULE CONTAINS:
Diltiazem Hydrochloride ..... 180 mg
DOSAGE AND ADMINISTRATION: Read package insert for prescribing information.
Rx ONLY
WARNING: KEEP OUT OF REACH OF CHILDREN.
PHARMACIST: Dispense in tight, light-resistant container as defined in USP.
Store at controlled room temperature, 15°-30°C (59°-86°F).
Avoid excessive humidity.
180 mg
30 CAPSULES
Manufactured By
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314
7005 (05/98)
N 3 62037-598-30 2
LOT:
EXP:

JUL 9 1998

NDC 62037-598-05

ONCE DAILY

CartiaXT™

(diltiazem HCl extended release capsules, USP)

ONCE-A-DAY DOSAGE

Andrx PHARMACEUTICALS, INC.

7007 (05/98)

EACH CAPSULE CONTAINS:
Diltiazem Hydrochloride ..... 180 mg

DOSAGE AND ADMINISTRATION: Read package insert for prescribing information.

Rx ONLY

WARNING: KEEP OUT OF REACH OF CHILDREN.

PHARMACIST: Dispense in tight, light-resistant container as defined in USP.

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

Avoid excessive humidity.

180 mg

500 CAPSULES

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

N 3 62037-598-05 0

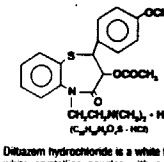
LOT:

EXP:

DILTIAZEM HYDROCHLORIDE EXTENDED-RELEASE CAPSULES USP (ONCE-A-DAY DOSAGE)

DESCRIPTION

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



$CH_2CH_2N(CH_3)_2 \cdot HCl$

($C_{22}H_{26}N_2O_4S \cdot HCl$)

Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.99. Each diltiazem hydrochloride extended-release capsule (once daily dosage), for oral administration, is formulated as a once-a-day extended release capsule containing either 120 mg, 180 mg, 240 mg, or 300 mg diltiazem hydrochloride.

In addition, each capsule contains the following inactive ingredients:

acetyltributyl citrate, D & C Red #28, D & C Yellow #10, D & C Yellow #10 Aluminum Lake, ethylcellulose, ammonio methacrylate copolymer-NF, FD & C Blue #1 Aluminum Lake, FD & C Blue #2 Aluminum Lake, methacrylic acid copolymer-NF, FD & C Red #40, FD & C Red #40 Aluminum Lake, gelatin-NF, propylene glycol, polysorbate 80-NF, starch, sucrose, talc USP, and titanium dioxide. The 180 mg and 240 mg capsules contain yellow iron oxide. In addition, the 240 mg capsule also contains black iron oxide and red iron oxide.

USP Drug release test pending.

CLINICAL PHARMACOLOGY

The therapeutic effects of Diltiazem Hydrochloride Extended-release Capsules USP (once-a-day dosage) are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action

Hypertension. Diltiazem Hydrochloride Extended-release Capsules USP (once-a-day dosage) 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 Extended-release Capsules USP (once-a-day dosage) 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 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.

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 workload. 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 have 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.

In hypertensive patients, Diltiazem Hydrochloride Extended-release Capsules USP (once-a-day dosage) produces antihypertensive effects both in the supine and standing positions. In a double-blind, parallel, dose-response study utilizing doses ranging from 90 to 540 mg once daily, diltiazem hydrochloride extended-release capsule (once-a-day dosage) lowered supine diastolic blood pressure in an apparent linear manner over the entire dosage range studied. The changes in diastolic blood pressure, measured at trough, for placebo, 90 mg, 180 mg, 360 mg, and 540 mg were -2.9, -4.5, -6.1, -9.5, and -10.5 mm Hg, respectively. Postural hypotension is infrequently noted upon suddenly assuming an upright position. No reflex tachycardia is associated with the chronic antihypertensive effects. Diltiazem Hydrochloride Extended-release Capsules USP (once-a-day dosage) 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 Extended-release Capsules USP (once-a-day dosage) produces no change or an increase in plasma catecholamines. No increased activity of the renin-angiotensin-aldosterone axis has been observed. Diltiazem Hydrochloride Extended-release Capsules USP (once-a-day dosage) 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 [illegible] sodium/potassium.

In a double-blind study of doses once daily di extended-release dosage) increased exercise in a line entire dose range s ment in time to ten utilizing a Bruce exer sured at trough, for p mg, 240 mg, 360 mg, 29, 40, 56, 51, 69 respectively. As dose hydrochloride extend sule (once-a-day dos creased, overall angina decreased. Diltiazem extended-release capsule dosage) 180 mg once dail was administered in a double to patients receiving concor ment with long-acting nitra beta-blockers. A significant time to termination of exercise nificant decrease in overall ar quency was observed. In this overall frequency of adverse ev the diltiazem hydrochloride ext release capsule (once-a-day dc treatment group was the same a placebo group.

Intravenous diltiazem in doses of 2(prolongs AH conduction time and node functional and effective refract periods by approximately 20%. In study involving single oral doses of 3(mg of diltiazem hydrochloride in six no mal volunteers, the average maximun PR prolongation was 14% with no instances of greater than first-degree AV block. 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). Chronic oral administration of diltiazem hydrochloride to patients in doses of up to 540 mg/day has resulted in small increases in PR interval, and on occasion produces abnormal prolongation. (See WARNINGS).

Pharmacokinetics and Metabolism

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

Total radioactivity measurement following short IV administration in healthy volunteers suggests the presence of other unidentified metabolites, which attain higher concentrations than those of diltiazem and are more slowly eliminated; half-life of total radioactivity is about 20 hours compared to 2 to 5 hours for 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. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 to 4.5 hours. Deacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent as a coronary vasodilator as diltiazem. Minimum therapeutic plasma diltiazem concentrations appear to be in the range of 50 to 200 ng/mL. There is a departure from linearity when dose strengths are increased; the half-life is slightly increased with dose. A study that compared patients with normal hepatic function to patients with cirrhosis found an increase in half-life and a 69% increase in bioavailability in the hepatically impaired patients. A single study in patients with severely impaired renal function showed no difference in the pharmacokinetic profile of diltiazem compared to patients with normal renal function.

When compared to a regimen of diltiazem tablets at steady-state, more than 95% of drug is absorbed from the diltiazem hydrochloride extended-release capsules (once-a-day dosage) formulation. A single 360-mg dose of the capsule results in detectable plasma levels within 2 hours and peak plasma levels between 10 and 14 hours; absorption occurs throughout the dosing interval. When diltiazem hydrochloride extended-release capsule (once-a-day dosage) was coadministered with a high fat content breakfast, the extent of diltiazem absorption was not affected. Dose-dumping does not occur. The apparent elimination half-life after single or multiple dosing is 5 to 8 hours. A departure from linearity similar to that seen with diltiazem tablets and diltiazem hydrochloride capsules (twice daily) is observed. As the dose of diltiazem hydrochloride extended-release capsules (once-a-day dosage) is increased from a daily dose of 120 mg to 240 mg, there is an increase in the area-under-the curve of 2.7 times. When the dose is increased from 240 mg, to 360 mg there is an increase in the area-under-the-curve of 1.6 times.

INDICATIONS AND USAGE

Diltiazem Hydrochloride Extended-release Capsules USP (once-a-day dosage) is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive medications.

Diltiazem Hydrochloride Extended-release Capsules USP (once-a-day dosage) is indicated for the management of chronic stable angina and angina due to coronary artery spasm.

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 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 3290 patients or 0.40%). 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. (See ADVERSE REACTIONS.)
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% ±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 hydrochloride 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, 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.)

PRECAUTIONS

General

Diltiazem hydrochloride 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 reversible with continued dosing. 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 beta-blockers or digitalis concomitantly with diltiazem. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. Diltiazem undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of diltiazem with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Especially in patients with renal and/or hepatic impairment, dosages of similarly metabolized drugs, particularly those of low therapeutic ratio, may require adjustment when starting or stopping concomitantly administered diltiazem 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 hydrochloride 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 at 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.

Digitalis. 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.

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

Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies there was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

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 is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The following table presents the most common adverse reactions reported in placebo-controlled angina and hypertension trials in patients receiving diltiazem hydrochloride extended-release capsule (once-a-day dosing) product up to 360 mg with rates in placebo patients shown for comparison.

Diltiazem Hydrochloride Extended-release Capsule (once-a-day) Placebo-controlled Angina and Hypertension Trials*Combined

Adverse Reactions	Diltiazem Extended-release Capsule (once-a-day) n=887	Placebo n=491
Headache	5.4%	5.9%
Dizziness	3.8%	2.9%
Bradycardia	3.3%	1.3%
AV Block First-Degree	3.2%	0.8%
Edema	2.8%	1.3%
ECG Abnormality	1.8%	2.3%
Asthenia	1.2%	1.7%

In clinical trials of Diltiazem hydrochloride Extended-release Capsules (Once A Day Dosage), diltiazem hydrochloride tablets and diltiazem hydrochloride extended-release capsules involving over 3200 patients, the most common events (i.e., greater than 1%) were edema (4.6%), headache (4.6%), dizziness (3.5%), asthenia (2.8%), first-degree AV block (2.4%), bradycardia (1.7%), flushing (1.4%), nausea (1.4%) and rash (1.2%).

In addition, the following events were reported infrequently (less than 1%) in angina or hypertension trials:

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, dysgeusia, dyspepsia, mild elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see hepatic warnings), thirst, vomiting, weight increase.

Dermatological:

Petechiae, photosensitivity, pruritus, urticaria.

Other:

Ambliopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties.

The following postmarketing events have been reported infrequently in patients receiving diltiazem: allergic reactions, alopecia, angioedema (including facial or periorbital edema), asystole, erythema multiforme (including Stevens-Johnson syndrome, toxic epidermal necrolysis), exfoliative dermatitis, 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, some 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 LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 680 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 36 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 280 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 twofold, limiting the usefulness of blood levels in overdose cases.

There have been 29 reports of diltiazem overdose in doses ranging from less than 1 g to 10.8 g. Sixteen of these reports involved multiple drug ingestions.

Twenty-two reports indicated patients had recovered from diltiazem overdose ranging from less than 1 g to 10.8 g. 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, gastric lavage, 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. Limited data suggest that plasmapheresis or charcoal hemoperfusion may hasten diltiazem elimination following overdose. 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 blockade, 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.

DOSAGE AND ADMINISTRATION

Patients controlled on diltiazem alone or in combination with other medications may be switched to Diltiazem Hydrochloride Extended-release Capsules USP (once-a-day dosage) at the nearest equivalent total daily dose. Higher doses of Diltiazem Hydrochloride Extended-release Capsules USP (once-a-day dosage) may be needed in some patients. Patients should be closely monitored. Subsequent titration to higher or lower doses may be necessary and should be initiated as clinically warranted. There is limited general clinical experience with doses above 360 mg, but doses to 540 mg have been studied in clinical trials. The incidence of side effects increases as the dose increases with first-degree AV block, dizziness, and sinus bradycardia bearing the strongest relationship to dose.

Hypertension. Dosage needs to be adjusted by titration to individual patient needs. When used as monotherapy reasonable starting doses are 180 to 240 mg once daily, although some patients may respond to lower doses. 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 240 to 360 mg once daily. Individual patients may respond to higher doses of up to 480 mg once daily.

Angina. Dosages for the treatment of angina should be adjusted to each patient's needs, starting with a dose of 120 or 180 mg once daily. Individual patients may respond to higher doses of up to 480 mg once daily. When necessary, titration may be carried out over a 7- to 14-day period.

Concomitant Use With Other Cardiovascular Agents.

1. **Sublingual nitrovasodilators.** May be taken as required to abort acute anginal attacks during Diltiazem Hydrochloride Extended-release Capsules. (Once A Day Dosage) therapy.
2. **Prophylactic Nitrate Therapy.** Diltiazem Hydrochloride Extended-release Capsules, (Once A Day Dosage) may be safely coadministered with short- and long-acting nitrates.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)
4. **Antihypertensives.** Diltiazem hydrochloride extended-release capsules (Once A Day Dosage) have an additive antihypertensive effect when used with other antihypertensive agents. Therefore, the dosage of Diltiazem Hydrochloride Extended-release Capsules USP (once-a-day dosage) or the concomitant antihypertensives may need to be adjusted when adding one to the other.

HOW SUPPLIED

Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day dosage)

Strength	Qty.	NDC#	Description
120 mg	30 bot 500 bot	62037-687-30 62037-687-05	White/orange opaque capsule imprinted with "Andrx 687" on one end and "120 mg" on the other
180 mg	30 bot 500 bot	62037-688-30 62037-688-05	Yellow/orange opaque capsule imprinted with "Andrx 688" on one end and "180 mg" on the other
240 mg	30 bot 500 bot	62037-689-30 62037-689-05	Light brown/orange opaque capsule imprinted with "Andrx 689" on one end and "240 mg" on the other
300 mg	30 bot 500 bot	62037-690-30 62037-690-05	Orange/orange opaque capsule imprinted with "Andrx 690" on one end and "300 mg" on the other

Storage Conditions: Store at controlled room temperature 15-30°C (59-86°F). Avoid excessive humidity.

R, only

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

Dispense in tight, light resistant container as defined in USP.

Rev. date: 04/98 7000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74752

CHEMISTRY REVIEW(S)

ADDENDUM

1. CHEMIST'S REVIEW NO. 4

2. ANDA #74-752

3. NAME AND ADDRESS OF APPLICANT
Andrx Pharmaceuticals, Inc.
4001 S. W. 47th Avenue, Suite 201
Fort Lauderdale, FL 33314

4. LEGAL BASIS FOR ANDA SUBMISSION
Innovator Drug: Cardizem SR Capsules, Marion Labs.
NDA 19-471; Product Exclusivity - 1.23.92
NCE Exclusivity - 11.5.92
The firm includes the following patents and their expiration dating for this drug product.

U.S. 5,286497 - 5/20/2011
U.S. 5,439689 - 8/20/2012
U.S. 5,470584 - 5/20/2011
U.S. 4,894240 - 1/6/2007
U.S. 5,002776 - 3/26/2008
U.S. 5,364620 - 11/24/2011

Andrx also includes reasons for which these patents will not be infringed on a case-by-case basis.

NOTE: Prior to the filing of this amendment, Hoechst Marion Roussel, Inc. and Cardem Capital L.P. filed legal action against Andrx for patent infringement (U.S. Patent no.5,470,584). Hence Andrx has amended an in-process dissolution specification.

5. SUPPLEMENT(s) N/A

6. ESTABLISHED NAME
Diltiazem Hydrochloride
Extended Release Capsules USP

7. PROPRIETARY NAME **N/A**

8. SUPPLEMENT(s) PROVIDE(s) FOR **Original ANDA**

9. AMENDMENTS AND OTHER DATES

Firm

9/22/95	Orig. Submission
11/22/95	Amendment
1/17/96	New correspondence
2/5/96	New correspondence re: law suits for patent infringement
3/25/96	New correspondence for bio study
4/21/96	Amendment includes notice to Marion and owners of other patents involved
4/4/96	Amendment includes a new dissolution specification for in-process testing
5/2/96	Amendment
8/22/96	Amendment (Major - response to deficiency letter)
10/8/96	Amendment (Minor - dissolution results with modifications recommended by the Division of Bioequivalance)
2/27/97	Amendment (response to deficiency letter from FDA)
3/10/97	Amendment (Facsimile - for chemistry upon request from chemist)
3/19/97	Amendment (Facsimile - finished product specification)
5/28/97	Amendment (labeling)
6/20/97	Amendment (Telephone for labeling)
7/28/97	New correspondence
9/10/97	New correspondence
9/15/97	New correspondence
10/6/97	New correspondence
1/14/98	New correspondence
2/6/98	Amendment (container/closure info)
2/18/98	Amendment (labeling)
2/26/98	Amendment (labeling)
5/8/98	Amendment (minor - labeling)
6/2/98	Amendment (minor - labeling)
6/10/98	New correspondence
6/23/98	New correspondence
6/25/98	Amendment (facsimile - labeling)

FDA

11/17~~/95~~	Refu~~sal~~ to file
12/29/95	Acceptable for filing as 11/24/95
7/11/96	Deficiency letter
10/31/96	Bio recommendation for dissolution
1/6/97	Bio recommended 75 RPM for dissolution
1/30/97	Deficiency letter (chemistry and labeling)
3/10/97	Telephone request for in-process testing data
3/19/97	Telephone request for finished product and stability testing data
5/7/97	Telephone conversation with Mr. David Gardner regarding withdrawing labeling for Firm has accepted it.
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2/26/98	Tentatively approved summary (labeling)
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10. PHARMACOLOGICAL CATEGORY
Antihypertensive (antianginal)
(Ca antagonist)

11. Rx or OTC
℞

12. RELATED IND/NDA/DMF(s)
See #37 for list of DMFs

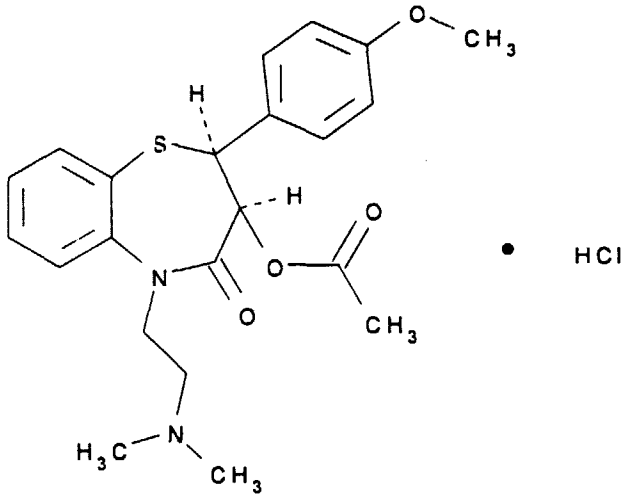
13. DOSAGE FORM
SR Capsules (Oral)

14. STRENGTH(S)
120 mg, 180 mg, 240 mg and 300 mg

15. CHEMICAL NAME AND STRUCTURE

Diltiazem Hydrochloride USP

Formula: $C_{22}H_{26}N_2O_4S.HCl$; Molecular Weight: 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]

Drug substance and drug product are official USP 23 items.

16. RECORDS AND REPORTS None

17. COMMENTS

a. CMC deficiencies are all addressed
b. EER acceptable, 6/18/97
c. Methods validation not required - Compendial
d. Bio review **SATISFACTORY**
e. Labeling review **SATISFACTORY**
f. DMFs **SATISFACTORY** for all referred

18. CONCLUSIONS AND RECOMMENDATIONS

Applicant stated in the May 8, 1998 amendment "there have been no changes in the chemistry, manufacturing and control data or any other conditions that were outlined in the abbreviated new drug application since the date of tentative approval on September 15, 1997."

APPROVE

19. REVIEWER:
Raymond Brown for
Radhika Rajagopalan

DATE COMPLETED:
June 29, 1998

1. CHEMIST'S REVIEW NO. 3

ANDA # : 74-752

3. NAME AND ADDRESS OF APPLICANT

Andrx Pharmaceuticals, Inc.
Attention: Mr. David A. Gardner
4001 S. W. 47th Avenue, Suite 201
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Note: Prior to the filing of this amendment, Hoechst Marion Roussel, Inc. and Cardem Capital L.P. filed legal action against Andrx for patent infringement (U.S. Patent no. 5, 470,584). Hence Andrx has amended an in-process dissolution specification.

5. SUPPLEMENT(s) None

6. PROPRIETARY NAME

None

7. NONPROPRIETARY NAME

Diltiazem Hydrochloride
Extended Release Capsules USP

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

9. AMENDMENTS AND OTHER DATES:

Firm:

9/22/1995- Original Application
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3/25/1996 - New Correspondence for biostudy
4/2/1996 - Amendment to ANDA including notice to Marion and owners of

JAN 30 1997

38. Chemistry Comments to be Provided to the Applicant

ANDA: 74-752 FIRM: ANDRX Pharmaceuticals

DRUG PRODUCT: Diltiazem Hydrochloride Extended-Release Capsules

The deficiencies presented below represent FACSIMILE deficiencies.

Chemistry Deficiencies

1. Please refer to the new dissolution specification recommendation from the Division of Bioequivalence to test the product at 75 RPM paddle speed and justify your in-process testing for blend uniformity at 100 RPM. Please provide any available dissolution data at 75 RPM paddle speed for the SR1 and SR2 beads.

2. Please provide moisture permeation data (<USP 671>) for the packaging configuration bags inside drum).

3. The tentative limits proposed for alcohol given on pages 58 and 62 are different. The tentative upper limit given on page 58 for the beads is On page 62, is given as a tentative limit (w/w). Please clarify this discrepancy. We prefer the lower limit of

Sincerely yours,

/S/

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

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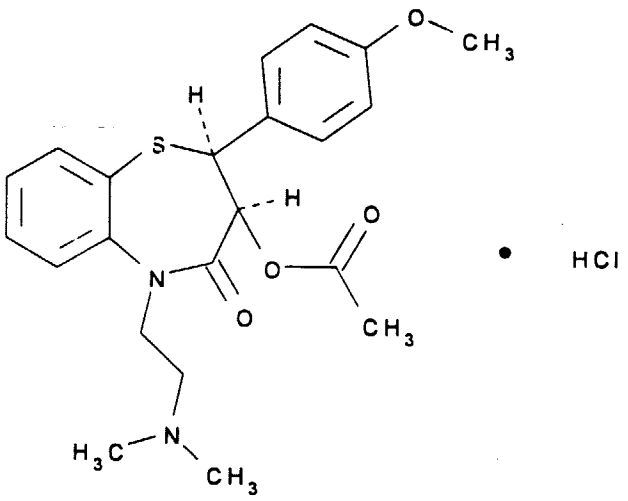

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Extended Release Capsules USP

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

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Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74752

BIOEQUIVALENCE REVIEW(S)

DIV

Diltiazem Hydrochloride ER Capsules
120 mg, 180 mg, 240 mg & 300 mg
ANDA # 74-752 / SC 4
Reviewer: Sikta Pradhan
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Andrx Pharmaceuticals, Inc.
Fort Lauderdale, Florida
Submission Date:
September 11, 1998
December 22, 1998

Review of An In Vivo Bioequivalence Study In Vitro Dissolution Data and Waiver Requests

Background:

Diltiazem is a calcium ion influx inhibitor (slow-channel blocker or calcium antagonist).

The firm had previously conducted acceptable bioequivalence studies and got approval on its Diltiazem Hydrochloride ER Capsules,120 mg,180 mg, 240 mg and 300 mg strengths. Diltiazem HCl Extended-release Capsules, USP (Once-A- day Dosage) contain two type of pellets: Diltiazem HCl Extended-release pellets, SR1 (SR1 pellets) and Diltiazem HCl Extended-release pellets, SR2 (SR2 pellets).

In this supplement Andrx Pharmaceuticals, Inc. informed the Agency that the firm wants to change the component and composition of SR2 pellets by replacing a small amount of talc, with a different , magnesium stearate (see 1. Formulations). In addition, the firm is also requesting a change (tightened specification) in the dissolution specification in for the new **SR2 pellets** from to . (see II. Dissolution Specifications). However, there is no change to the dissolution specifications in The firm has further stated that there will be no change to the dissolution specifications for, a) the **SR1 pellets** and, b) the **Finished Product**. To support these proposed changes, the firm has provided the following:

1. The results of a bioequivalence study conducted on the reformulated 300 mg diltiazem test capsules under fasting conditions.
2. The dissolution testing including the F2 calculations on the 300 mg capsules of the test (reformulated) and reference products.
3. The dissolution testing on the 120 mg, 180 mg & 240 mg strengths of the reformulated test capsules and requested for waiver in vivo bioequivalence study on them.

1. FORMULATIONS.

The firm has previously got approval on Diltiazem HCl Extended-release Capsules, USP (Once-A- Day Dosage), 120, 180, 240 and 300 mg. All lower strengths were dose proportional to 300 mg strength on which the bioequivalence study was conducted. Each dose contains 40% of diltiazem from the SR1 pellets and 60% of diltizem from the SR2 pellets.

Composition of the Diltiazem HCl Extended-release (Once-A- Day Dosage)300 mg Capsule:

Ingredient	Diltiazen,%LC	Diltiazem %w/w (Theoretical)	Amount (mg)
PelletOrange opaque hard gelatin capsule	0	0	120 mg
SRI Pellets	40% (120mg)	62.7%	191 mg
SR2 Pellets*	60% (180 mg)	47.6%	379 mg
Total			690 mg

*SR2 Pellets

In order to enhance the quality of the product, the firm has proposed a small change in the compositions of SR2 pellets.

Proposed Change in SR2 Pellets:

	ANDA Biobatch (%)	Validation Batches* (%)	Proposed Change (%)
Eudragit			
Talc,			
Mg Stearate			
Acetyl tributyl citrate			
Polysorbate			
Subtotal Polymer coating level			
Diltiazem Active Pellets			
Total	100.0	100.0	100.0

*Coating level

(Validation Batch).

The proposed change replaces talc from the Validation Batch with magnesium stearate in the SR2 formulation. There is no change to the SR1 pellets.

II. DISSOLUTION SPECIFICATIONS

Current Dissolution Specifications of Once-A-Day Capsules are presented below:

- * pH 7.5 phosphate buffer

Proposed Dissolution Specification:

The proposed dissolution specification for the new SR2 pellets in

There is no change to the dissolution specifications in uffer.
There is also no change to the dissolution specifications for the SR1 pellets or the finished product.

Firm's Rationales in Support of Proposed Specification Change for SR2 Pellets and Proposed Component and Composition Change for SR2 Pellets:

1. As the gastric emptying time for the pellets is relatively short, i.e. 0.5 hr. (fast) to 2 hr. (fed), most of the time the pellets are in the intestinal region. Therefore, the dissolution in (gastric condition) is only relevent up to the 2 hr. time point, and consequently, the specification for SR2 pellets in has no physiological meaning. After gastric emptying, the dissolution in the buffer becomes more relevant. Hence, the proposed

dissolution specification, , for the new SR2 pellets would be justifiable, if the in vivo bioavailability and in vitro dissolution of the **finished reformulated capsule** remain comparable to the RLD and previously approved product, respectively.

2. Both talc and magnesium stearate serve as during the and are therefore, To support the change from talc to magnesium stearate in the compositions of the proposed test product (SUPAC-MR level 3 change), the firm has conducted an in vivo bioequivalence study under fasting conditions and the dissolution testing, including F2 calculations, on the proposed reformulated test product.

III. SINGLE DOSE STUDY UNDER FASTING CONDITIONS

Study Information:
Sponsor: Andrx Pharmaceuticals, Inc.
Clinical Facility:
& Analytical Facilities:
Clinical Director:
Analytical Director:
Project No.: 98090 (approved by IRB)
Pharmacokinetic and statistical Analysis:

Study Design: Andrx's Diltiazem (reformulated) 300 mg Capsules to the reference drug product, Cardizem CD^{R} 300 mg Capsules under fasting conditions

This was a randomized, single dose, two-way crossover design study comparing the test product, Andrx's Diltiazem (reformulated) 300 mg Capsules with the reference product, Cardizem CD^{R} 300 mg Capsules in twenty-eight (28) healthy male volunteers under fasting conditions.

Subject Selection

Subjects selected for the study met the following acceptance criteria:

1. Age range: 18 to 43 years.
2. Healthy as determined by physical examination, medical history, and clinical laboratory diagnostic tests: blood chemistry, hematology, urinalysis and HIV.
3. Absence of any exclusion criteria observed during the physical or laboratory evaluations.

4. Body weight within 10% of their ideal body weight according to Table of "Desirable Weights of Adults", Metropolitan Life Insurance Company, 1983.

Thirty volunteers met all eligibility requirements and successfully passed the exclusion criteria. In each study period, subjects were confined to the Clinical Research Center from the evening before drug administration until after the 24-hour post-dose blood draw.

Subject Restrictions:

1. No antacids and no alcohol-, grapefruit- or xanthine-containing beverages and foods for the 24 hours before dosing and throughout the period of sample collection.
2. No medication (including over-the-counter products) for the 7 days preceding the study.
3. Water intake was prohibited from one hour pre-dose until one hour post-dose.
4. Subjects remained ambulatory or seated upright and were prohibited from smoking during the first four hours following drug administration in each period.
5. No strenuous activity was permitted at any time during the housing period.

Clinical Study Dates: May 9, 1998 - May 18, 1998

Treatments:

A. 1x300 mg capsule of diltiazem HCl extended release capsule (test product) of Andrx Pham. Inc., Lot #600R003A, Lot size . apsules, Potency 100.8%

B. 1x300 mg capsule of Cardizem CD^{R} (Reference product) manufactured by Marion Roussel, Lot #P70395; Potency 100.2%, Exp. Date: June, 1998.

Dose Administrations:

A single oral dose of 300 mg diltiazem HCl extended release capsule (test or reference) was administered with of water following a 10 hour fast.

Drug Washout Period: One week

Meal and Food Restrictions:

All volunteers fasted for 10 hours prior to and 4 hours after drug administration. No fluid except that given with drug administration was allowed from 1 hour prior to dose administration until 1 hours after dosing. Standard meal was served during the in-house confinement period. No caffeine-containing food or beverages were served during the study. All subjects were confined from 12 hours pre-dose to 36 hours post-dose.

Blood Samples Collection

Blood samples were collected in vacutainers containing heparin (anticoagulant) at 0 (pre-dose), and at 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 30, 36, and 48 hours post dose. The plasma samples were separated and kept frozen at -70°C until shipment to the analytical facility.

Safety Evaluations: Vital signs were obtained at 0 (pre-dose), and at 6, 10, 14, 24, and 36 hours post dose

Analytical Study Dates: May 26, 1998 – June 12, 1998

Assay Methodology

Method: The plasma samples were analyzed for diltiazem, desacetyldiltiazem and desmethyldiltiazem by a validated

The during study assay validation is presented in Table 1 below:

Table 1

Parameter	Quality Control Samples
QC Samples[] Conc. (ng/mL)	Diltiazem: Desmethyldiltiazem: same as above Desacetyldiltiazem: same as above
Precision (CV%) of Calibration Curve Standard Conc. (ng/mL)	Diltiazem Desmethyldiltiazem: Desacetyldiltiazem:
Accuracy (%) of Calibration Curve Standard	Diltiazem: Desmethyldiltiazem: Desacetyldiltiazem:
Intra day Precision (CV%) of QC	Diltiazem: Desmethyldiltiazem: Desacetyldiltiazem:
Inter day Precision (CV%) of QC	Diltiazem: Desmethyldiltiazem: Desacetyldiltiazem:
Inter day Accuracy (%) of QC	Diltiazem: Desmethyldiltiazem: Desacetyldiltiazem:
Linearity	
Sensitivity/LOQ (ng/mL)	
Stability in Plasma: ((all 3 omponents) a) At room temp. b) Freeze-Thaw Cycles c)Long-Term Frozen	a) Stable for 4 hrs. @ 20 C (prior extraction) and extracted samples Stable at-5 C for at least 48 hours prior to injection days b) Stable after 3 freeze-thaw cycles c) Stable at-20 C for at least 56 days

Specificity: No interference was observed at the retention times for all three components and the corresponding standards.

Results:

Thirty (30) volunteers were selected for the study. However, 28 subjects entered into the study and all 28 subjects completed the study. Therefore, the statistical analyses were performed on data obtained from 28 subjects.

There was no serious adverse event or any event which required terminating any subject from the study. Mean plasma diltiazem and its two metabolites, desmethyldiltiazem and desacetyldiltiazem levels are presented in Tables 2 (and in Fig.1 attached), 3 (and in Fig.2 attached) 4, (and in Fig.3 attached), respectively, below:

The pharmacokinetic parameters derived from diltiazem and its two metabolites, desmethyldiltiazem and desacetyldiltiazem levels are presented in Tables 5, 6, and 7, respectively, below:

Table 2. Mean Plasma Diltiazem Levels (ng/mL) of 28 Subjects:

TIME(HR)	TEST TREATMENT A		REF. TREATMENT B		
0	0	(---)*	0	(---)	
2	1.27	(199)	0.07	(529)	
4	46.81	(136)	13.72	(108)	
6	106.32	(48)	118.67	(45)	
8	100.64	(44)	95.75	(37)	
10	80.72	(46)	81.85	(48)	
12	100.87	(46)	95.51	(50)	
14	120.91	(48)	105.59	(43)	
16	127.03	(41)	111.19	(36)	
18	114.65	(46)	104.87	(39)	
20	91.36	(47)	88.60	(41)	
24	67.88	(44)	67.49	(42)	
30	44.64	(54)	47.93	(56)	
36	23.82	(75)	25.80	(74)	
48	6.10	(106)	7.07	(100)	

* Coefficient of Variation (CV%)

Table 3. Mean Plasma Desmethyldiltiazem Levels (ng/mL) of 28 Subjects:

TIME(HR)	TEST TREATMENT A		REF. TREATMENT B		
0	0	(---)*	0	(---)	
2	0.0	(---)	0.0	(--)	
4	7.51	(132)	2.15	(125)	
6	21.92	(42)	23.56	(33)	
8	25.12	(26)	24.24	(21)	
10	23.75	(27)	23.75	(22)	
12	27.71	(27)	27.19	(26)	
14	32.26	(28)	30.71	(25)	
16	35.38	(25)	32.62	(22)	
18	34.59	(25)	32.83	(23)	
20	30.46	(28)	30.28	(25)	
24	25.08	(26)	24.49	(25)	
30	20.24	(33)	20.94	(32)	
36	13.11	(45)	13.80	(44)	
48	4.50	(68)	4.80	(70)	

* Coefficient of Variation (CV%)

Table 4. Mean Plasma Desacetyldiltiazem Levels (ng/mL) of 28 Subjects:

TIME(HR)	TEST TREATMENT A		REF. TREATMENT B		
0	0	(---)*	0	(---)	
2	0.0	(---)	0.0	(---)	
4	1.26	(191)	0.0	(---)	
6	6.33	(79)	6.00	(69)	
8	9.69	(67)	8.98	(62)	
10	10.86	(62)	10.61	(63)	
12	12.96	(73)	12.57	(80)	
14	16.66	(73)	15.64	(81)	
16	20.03	(77)	18.04	(84)	
18	22.72	(82)	20.21	(83)	
20	22.20	(84)	21.49	(86)	
24	23.24	(95)	21.02	(89)	
30	22.38	(114)	21.42	(100)	
36	15.30	(122)	15.19	(116)	
48	7.60	(172)	6.97	(165)	

- Coefficient of Variation (CV%)

Table 5. Mean Pharmacokinetic Parameters for Diltiazem and Summary of Statistical Analysis of Log-transformed Data

PK PARAMETER	TEST TREATMENT A LS Mean	REFERENCE TREATMENT B LS Mean	RATIO (A/B)x100	90% C.I.
AUCT [ng.hr/mL]	2712.38	2606.81	104	
AUCI [ng.hr/mL]	2798.71	2704.32	103	
Cmax [ng/mL]	145.17	136.24	107	
Tmax [hr]	12.79	10.07	127	
K_{el} [1/hr]	0.1142	0.1087	105	
T1/2 [hr]	6.327	6.713	94.3	
LnAUCT	2477.40 *	2417.11*	102	96; 109
LnAUCI	2557.73*	2503.68*	102	96; 109
LnCMAX	133.31*	128.46*	104	94; 115

* For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported.

Table 6. Mean Pharmacokinetic Parameters for Desmethyldiltiazem and Summary of Statistical Analysis of Log-transformed Data

PK PARAMETER	TEST TREATMENT A LS Mean	REFERENCE TREATMENT B LS Mean	RATIO (A/B)x100	90% C.I.
AUCT [ng.hr/mL]	891.75	880.38	101	
AUCI [ng.hr/mL]	967.90	960.45	101	
Cmax [ng/mL]	37.34	35.02	107	
Tmax [hr]	15.71	15.36	102	
K_{el} [1/hr]	0.0803	0.0794	101	
T1/2 [hr]	8.9073	9.0264	98.7	
LnAUCT	857.40*	852.84	101	97; 104
LnAUCI	931.52*	929.02*	100	97; 104
LnCMAX	36.32*	34.26*	106	101; 111

* For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported.

Table 7. Mean Pharmacokinetic Parameters for Desacetyldiltiazem and Summary of Statistical Analysis of Log-transformed Data

PK PARAMETER	TEST TREATMENT A LS Mean	REFERENCE TREATMENT B LS Mean	RATIO (A/B)x100	90% C.I.
AUCT [ng.hr/mL]	689.79	649.07	106	
AUCI [ng.hr/mL]	940.46	879.69	107	
Cmax [ng/mL]	26.05	24.82	105	
Tmax [hr]	20.57	21.57	95.4	
K_{el} [1/hr]	0.0705	0.0672	105	
T1/2 [hr]	10.8274	11.3595	95.3	

LnAUCT	454.68	441.04	103	98; 109
LnAUCI	571.84	569.42	100	95; 106
LnCMAX	18.73	17.65	106	99; 113

For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported.

Comments on the fasting study:

Both test and reference drugs produced two peak concentrations within six to twenty hours of their administrations. The larger peak (produced by both the test and reference products) was used in pharmacokinetic and statistical analysis. There were no nonzero predose concentrations for diltiazem or its metabolites, and there were no cases where the first nonzero concentration was the CMAX for diltiazem.or its metabolites. Analysis of variance (ANOVA) was done using the GLM procedure of SAS. The 90% confidence intervals for $LnAUC_{0-T}$, $LnAUC_{0-inf}$ and LnC_{MAX} of the test product (both parent compound and metabolites) remained within the acceptable range of

IV. Dissolution Comparison:

The firm has conducted the dissolution testing on Diltiazem Capsules of different strengths. The dissolution testing data are presented in Table 8 below:

Table 8. In Vitro Dissolution Testing

Drug (Generic Name): Diltiazem
ANDA #74-752 / SC 4
Firm: Andrx
Submission Date: September 11, 1998

I. Conditions for Dissolution Testing:

USP XXIII Basket: Paddle: X RPM: 75
No. Units Tested: 12
Medium#1: Vol.: 900mL;
Medium#2:.Buffer vol.: 900 mL
Reference Drug: Cardizem
Assay Methodology:
Specifications:

II. Results of In Vitro Dissolution Testing in (

Sampling Times (hr.)	Proposed Changed Formulation Lot #600R003B; 300 mg Capsules			Approved ANDA Formulation Lot #600H001; 300 mg Capsules.		
	Mean %	Range	%CV	Meam %	Range	%CV
2	2		11.5	2		11.5
12	20		2.5	20		2.5
18	66		3.0	66		3.0
24	84		1.4	84		1.4

III. Results of In Vitro Dissolution Testing in Buffer pH 7.5 (SIF):

Sampling Times (hr.)	Proposed Changed Formulation Lot #600R003B; 300 mg Capsules			Approved ANDA Formulation Lot #600H001; 300 mg Capsules		
	Mean %	Range	%CV	Mean %	Range	%CV
2	41		3.0	41		3.0
12	44		1.7	44		1.7
18	87		1.3	87		1.3
24	94		1.6	94		1.6

IV. Results of In Vitro Dissolution Testing in						
Sampling Times (hr.)	Proposed Changed Formulation Lot #599R002; 240 mg Capsules			Approved ANDA Formulation Lot #599H001; 240 mg Capsules		
	Mean %	Range %	% CV	Mean %	Range %	% CV
2	3		13.6	3		11.3
12						
18						
24						
V. Results of In Vitro Dissolution Testing in Buffer						
Sampling Times (hr.)	Proposed Changed Formulation Lot #599R002; 240 mg Capsules			Approved ANDA Formulation Lot #599H001; 240 mg Capsules		
	Mean %	Range %	% CV	Mean %	Range %	% CV
2	38		5.6	38		2.1
12	42		2.9	43		2.0
18	83		2.3	85		2.1
24	92		2.0	94		1.5
VI. Results of In Vitro Dissolution Testing						
Sampling Times (hr.)	Proposed Changed Formulation Lot #598R002; 180 mg Capsules			Approved ANDA Formulation Lot #598H001; 180 mg Capsules		
	Mean %	Range %	% CV	Mean %	Range %	% CV
2	3		12.8	3		16.5
12						
18						
24						
VII. Results of In Vitro Dissolution Testing in Buffer (SIF):						
Sampling Times (hr.)	Proposed Changed Formulation Lot #598R002; 180 mg Capsules			Approved ANDA Formulation Lot #598H001; 180 mg Capsules		
	Mean %	Range %	% CV	Mean %	Range %	% CV
2	41		2.2	40		1.8
12	44		1.9	43		3.0
18	85		2.4	85		2.2
24	97		1.5	92		2.3

VIII. Results of In Vitro Dissolution Testing in						
Sampling Times (hr.)	Proposed Changed Formulation Lot #597R005; 120 mg Capsules			Approved ANDA Formulation Lot #597H001; 120 mg Capsules		
	Mean %	Range %	% CV	Mean %	Range %	% CV
2	4		19.6	3		13.9
12						
18						
24						
IX. Results of In Vitro Dissolution Testing in Buffer						
Sampling Times (hr.)	Proposed Changed Formulation Lot #597R005; 120 mg Capsules			Approved ANDA Formulation Lot #597H001; 120 mg Capsules		
	Mean %	Range %	% CV	Mean %	Range %	% CV
2	38		2.3	41		2.6
12	46		1.8	44		3.7
18	90		2.4	84		3.1
24	99		2.8	93		2.7

V. Compositions of Lower Strengths:

The compositions of 120 mg, 180 mg, 240 mg and 300 mg capsules are presented in Tables 9 and 10 (attached).
The compositions of the lower strengths are proportional to that of the highest strength and the capsules contain identical pellets.

Comments:

1. The in vivo bioequivalence study under fasting conditions and the dissolution testing, including F2 calculations (F2=87, see Table 11, attached) on the proposed reformulated test product, 300 mg Diltiazem CD Capsules are acceptable.

2. The firm's rationale for Proposed Specification Change for SR2 Pellets is justifiable.

3. The firm's rationale for Proposed Component and Composition Change for SR2 Pellets is justifiable.

4. The in vitro dissolution testing including F2 calculations (F2 values are 90, 78, and 71 for 240, 180, & 120 mg capsules, respectively; see Table 12, 13 & 14, attached) conducted on 120 mg, 180 mg and 240 mg capsules (reformulated) are also acceptable. The formulation of the 120 mg, 180 mg and 240 mg capsules are proportionally similar to that of the 300 mg strength of the test product.

5. Therefore, the proposed changes in the formulation of the test product of all strengths are acceptable, and the supplement is approvable.

RECOMMENDATIONS:

1. The in vivo Bioequivalence study conducted under fasted conditions by Andrx Pharmaceuticals on its 300 mg Diltiazem CD reformulated capsules, Lot # 600R003B versus the listed reference product, Cardizem CD^{R} Capsules, 300 mg, manufactured by Marion Merrell Dow has been found acceptable by the Division of Bioequivalence. This study demonstrates that under fasting conditions, 300 mg reformulated diltiazem CD capsule of Andrx is bioequivalent to the reference product, Cardizem CD^{R} Capsule, 300 mg, manufactured by Marion Merrell Dow.

2. The comparative in vitro dissolution testing conducted by Andrx on the test product, 300 mg Diltiazem CD reformulated capsules, Lot # 600R003B and the reference product, Cardizem CD^{R} Capsules, 300 mg, manufactured by Marion Merrell Dow has been found acceptable. The in vitro dissolution testing conducted by Andrx on its reformulated Diltiazem CD Capsules, 120 mg, 180 mg and 240 mg are also acceptable. The formulation of the 120 mg, 180 mg and 240 mg capsules are proportionally similar to that of the 300 mg strength of the test product which underwent bioequivalency testing. Hence, the waivers of in vivo bioequivalence study requirements for 120 mg, 180 mg and 240 mg capsules of the test product are granted. The 120 mg, 180 mg and 240 mg capsules of the test product are therefore deemed bioequivalent to the Cardizem CD^{R}, 120 mg, 180 mg and 240 mg Capsules, respectively, manufactured by Marion Merrell Dow.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in for 2 hours at 37°C using

USP XXIII apparatus II (paddle) at 75 rpm. The testing should also be conducted simultaneously at 75 rpm in SIF for 24 hours.The test drug should meet the following specifications:

Time	Time	SIF
2 hr	2 hr	
	12 hr	
	18 hr	
	24 hr	

4. Hence, the current supplement is acceptable.

/S/

Sikta Pradhan, Ph. D.
Division of Bioequivalence
Review Branch I

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Concur.---------- Date: 1/11/99

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

Figure 1 Linear Plot of Mean Plasma Diltiazem Concentrations vs Time

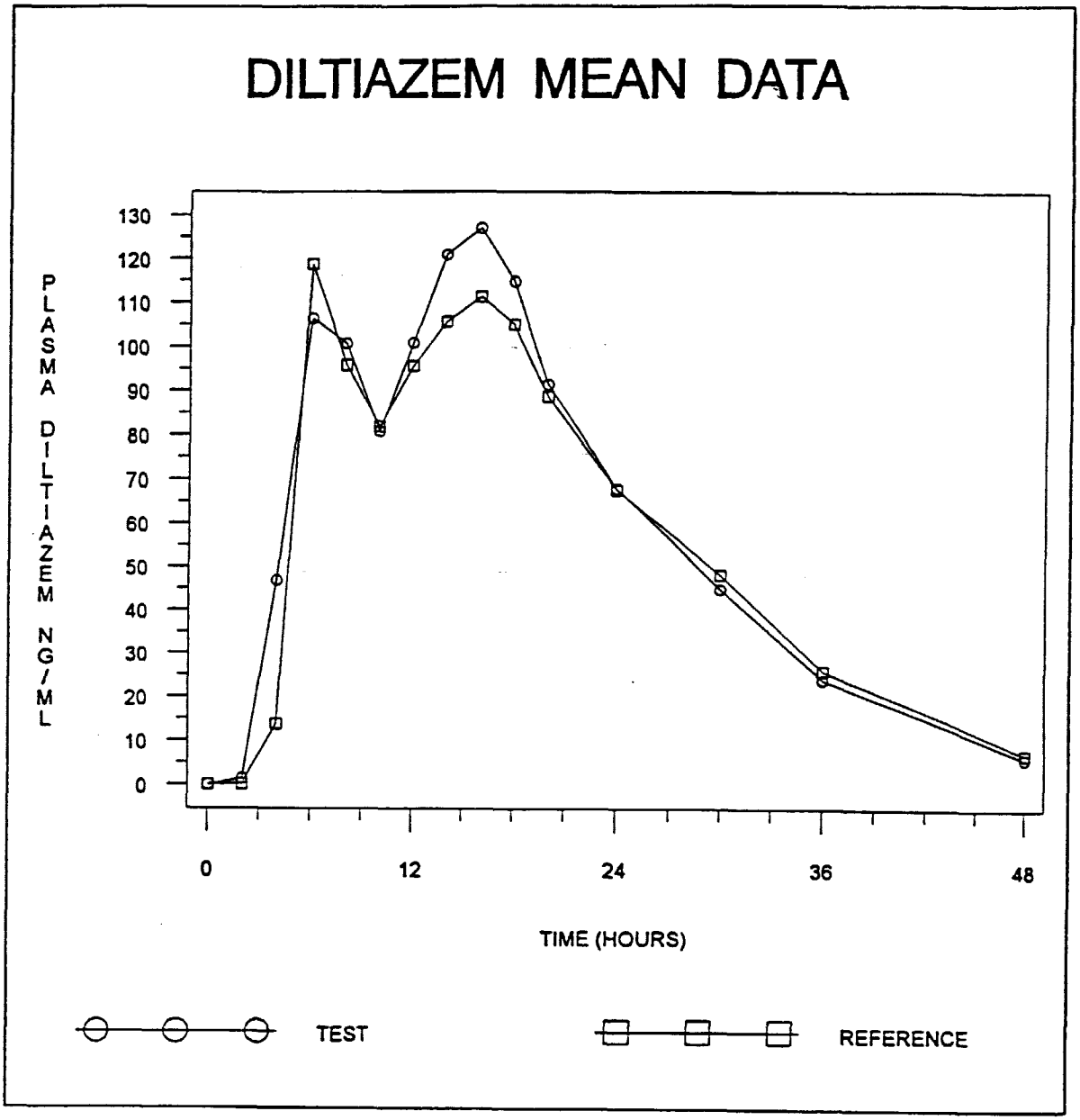

Figure 2 Linear Plot of Mean Plasma Desmethyldiltiazem Concentrations vs Time

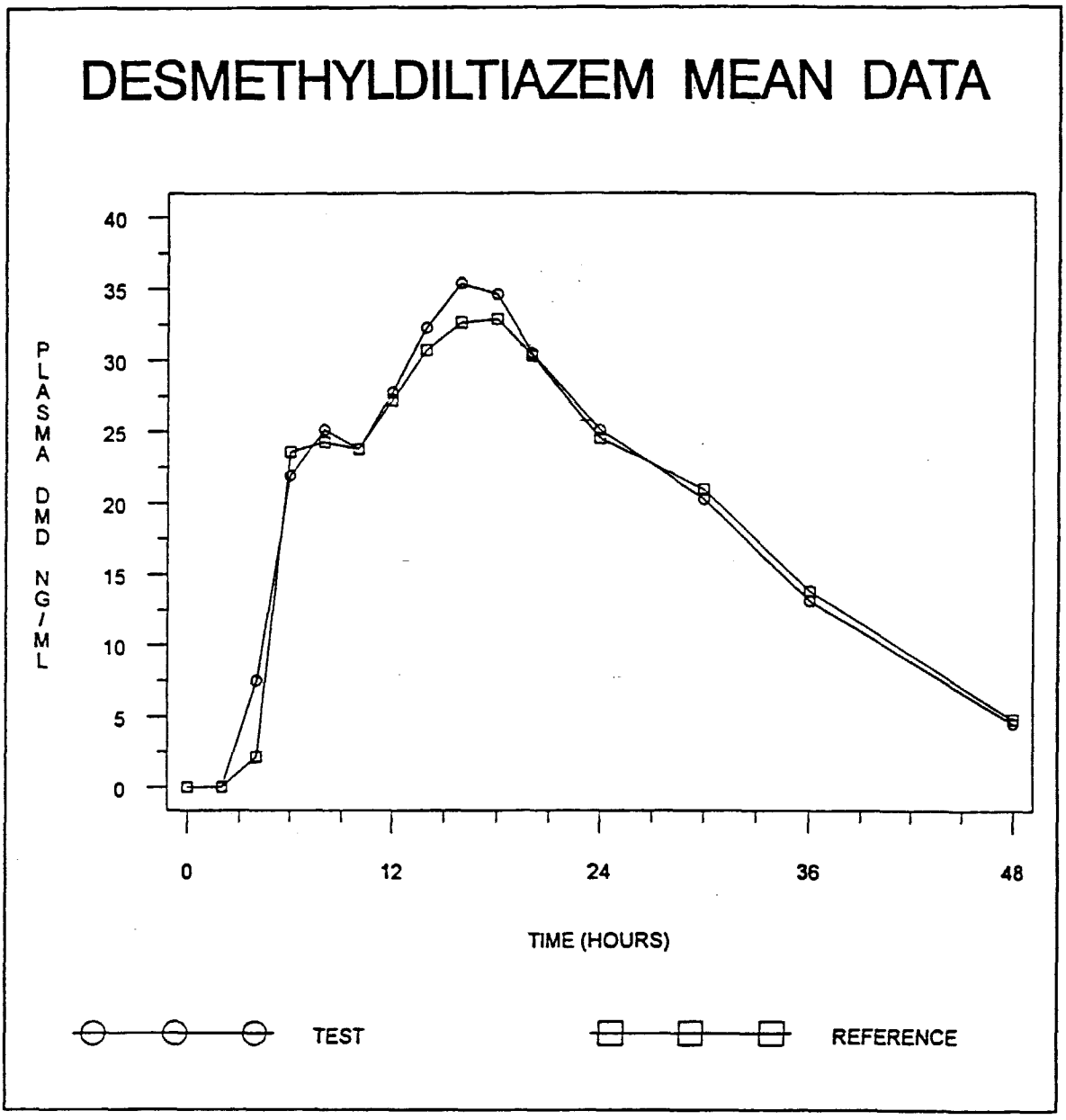

Figure 3 Linear Plot of Mean Plasma Desacetyldiltiazem Concentrations *vs.* Time

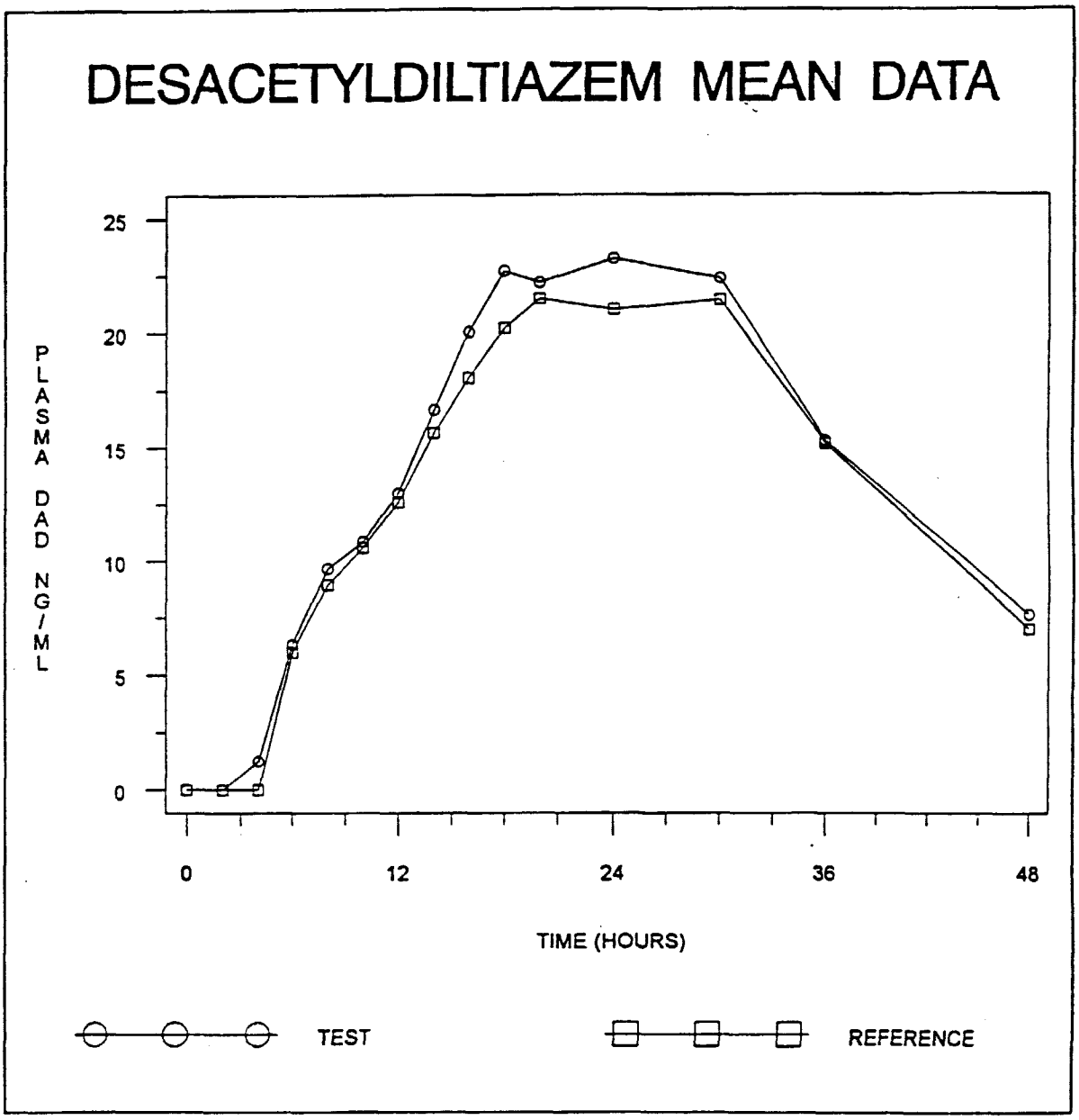

Table 9

Unit Dose Composition (Original vs. Revised Formulation)

Composition of Diltiazem HCl E-R Capsules, 300 mg

Component	ANDA mg/capsule	ANDA wt.%	Validation Batches* mg/capsule	Validation Batches* wt.%	Proposed Change mg/capsule	Proposed Change wt.%
Diltiazem HCl,USP	299.99	52.64	300.00	54.52	300.00	54.52
Sugar						
Eudragit						
Talc,						
Ethylcellulose						
Acetyl tributyl citrate						
Eudragit						
Polysorbate						
Magnesium stearate, USP						
Isopropyl alcohol, USP	**		**		**	
Purified water, USP	**		**		**	
Total filled weight without capsule						
Orange opaque capsule size 00						
Total capsule weight	689.90		670.28		670.28	

Composition of Diltiazem HCl E-R Capsules, 240 mg

Component	ANDA mg/capsule	ANDA wt.%	Validation Batches* mg/capsule	Validation Batches* wt.%	Proposed Change mg/capsule	Proposed Change wt.%
Diltiazem HCl,USP	239.99	52.64	240.00	54.52	240.00	54.52
Sugar						
Eudragit						
Talc,						
Ethylcellulose,						
Acetyl tributyl citrate						
Eudragit						
Polysorbate						
Magnesium stearate, USP						
Isopropyl alcohol, USP	**		**		**	
Purified water, USP	**		**		**	
Total filled weight without capsule						
Lt brown/orange opaque cap. size 0L						
Total capsule weight	560.92		545.22		545.22	

Table 10

Unit Dose Composition (Original vs. Revised Formulation)

Composition of Diltiazem HCl E-R Capsules, 180 mg

Component	ANDA mg/capsule	ANDA wt.%	Validation Batches* mg/capsule	Validation Batches* wt.%	Proposed Change mg/capsule	Proposed Change wt.%
Diltiazem HCl,USP	180.00	52.64	180.00	54.52	180.00	54.52
Sugar						
Eudragit RS30D						
Talc,						
Ethylcellulose,						
Acetyl tributyl citrate						
Eudragit						
Polysorbate						
Magnesium stearate, USP	-	-	-	-		
Isopropyl alcohol, USP	**		**			
Purified water, USP	**		**		**	
Total filled weight without capsule						
Rich yellow/orange opaque cap. size 0						
Total capsule weight	436.95		425.17		425.17	

Composition of Diltiazem HCl E-R Capsules, 120 mg

Component	ANDA mg/capsule	ANDA wt.%	Validation Batches* mg/capsule	Validation Batches* wt.%	Proposed Change mg/capsule	Proposed Change wt.%
Diltiazem HCl,USP (I	120.00	52.64	120.00	54.52	120.00	54.52
Sugar						
Eudragit						
Talc,						
Ethylcellulose,						
Acetyl tributyl citrate						
Eudragit						
Polysorbate						
Magnesium stearate, USP						
Isopropyl alcohol, USP	**		**			
Purified water, USP	**		**		**	
Total filled weight without capsule						
White/orange opaque cap. size 2						
Total capsule weight	287.96		280.11		280.11	

Table 11

Spreadsheet of Calculation for the F2 Matrix	Diltiazem HCl ER Capsules 300 mg											
Dissolution Data :	Percent Dissolved					HYPOTHETICAL DATA						
Biobatch	600R003B	Reformult	TEST					Approved	REF.	600H001		
Unit #	2hr	12hr	18hr	24hr				2hr	12hr	18hr	24hr	
Average	39.08333	43.91667	85.83333	96.5				40.5	44	86.75	93.58333	
Minimum												
Maximum												
STDEV	1.240112	0.900337	1.527525	1.445998				1.243163	0.738549	1.13818	1.505042	
%CV	3.172996	2.050102	1.779641	1.498443				3.069539	1.67852	1.312023	1.608237	
F2 formula : 50*log{[1+(1/n)(sum from t=1 to n of (Rt-Tt)**2]**-0.5*100}												
Sample n	1	2	3	4								
Rn-Tn	1.416667	0.083333	0.916667	-2.91667								
(Rn-Tn)**2	2.006944	0.006944	0.840278	8.506944								
SUMOD	11.36111											
1/n	0.2											
1/n*sumod	2.272222											
(1+above)	3.272222											
(a30)**-0.	0.552813											
a31*100	55.28135											
log(a32)	1.742579											
f2=50(a33	87.12893											
passlimit	50											
Conclusio	Passes											

Table 12

Spreadsheet of Calculation for the F2 Matrix	Diltiazem HCl ER Ca	240 mg								
Dissolution Data :	Percent Dissolved				HYPOTHETICAL DATA					
Biobatch	599R002	Reformult	TEST				Approved	REF.	599H001	
Unit #	2hr	12hr	18hr	24hr			2hr	12hr	18hr	24hr
Average	37.66667	42	83.25	91.91667			38.16667	42.5	84.91667	94.08333
Minimum										
Maximum										
STDEV	2.059715	1.193416	2.005674	1.831955			0.717741	0.904534	1.831955	1.505042
%CV	5.468269	2.841467	2.409218	1.993061			1.880543	2.128315	2.157357	1.59969
F2 formula : 50*log{[1+(1/n)(sum from t=1 to n of (Rt-Tt)**2]**-0.5*100}										
Sample n	1	2	3	4						
Rn-Tn	0.5	0.5	1.666667	2.166667						
(Rn-Tn)**2	0.25	0.25	2.777778	4.694444						
SUMOD	7.972222									
1/n	0.2									
1/n*sumod	1.594444									
(1+above)	2.594444									
(a30)**-0.	0.620837									
a31*100	62.08373									
log(a32)	1.792978									
f2=50(a33	89.64889									
passlimit	50									
Conclusio	Passes									

Table 13

Spreadsheet of Calculation for the F2 Matrix	Diltiazem HCl ER Ca	180 mg								
Dissolution Data :	Percent Dissolved				HYPOTHETICAL DATA					
Biobatch		Reformult	TEST	598R002			Approved	REF.	598F001	
Unit #	2hr	12hr	18hr	24hr			2hr	12hr	18hr	24hr
	42						41			
Average	40.58333	44	84.66667	97.33333			40.5	43.16667	85.41667	91.75
Minimum										
Maximum										
STDEV	1.083625	0.852803	2.015095	1.61433			0.797724	1.466804	2.020726	2.22077
%CV	2.670122	1.938188	2.380033	1.658558			1.969689	3.398002	2.365728	2.420457
F2 formula : 50*log{[1+(1/n)(sum from t=1 to n of (Rt-Tt)**2]**-0.5*100}										
Sample n	1	2	3	4						
Rn-Tn	-0.08333	-0.83333	0.75	-5.58333						
(Rn-Tn)**2	0.006944	0.694444	0.5625	31.17361						
SUMOD	32.4375									
1/n	0.2									
1/n*sumod	6.4875									
(1+above)	7.4875									
(a30)**-0.	0.365453									
a31*100	36.5453									
log(a32)	1.562832									
f2=50(a33	78.14158									
passlimit	50									
Conclusio	Passes									

Table 14

Spreadsheet of Calculation for the F2 Matrix		Diltiazem HCl ER Ca		120 mg							
Dissolution Data :		Percent Dissolved				HYPOTHETICAL DATA					
Biobatch		Reformult	TEST	597R005				Approved	REF.	597H001	
Unit #	2hr	12hr	18hr	24hr				2hr	12hr	18hr	24hr
											1
Average	39.41667	46	89.41667	98.66667				41.33333	44	83.75	93.25
Minimum											
Maximum											
STDEV	0.996205	1.044466	2.234373	2.674232				0.984732	1.658312	2.527126	2.632835
%CV	2.52737	2.270578	2.498833	2.71037				2.382416	3.768892	3.017463	2.823415
F2 formula : 50*log{[1+(1/n)(sum from t=1 to n of (Rt-Tt)**2]**-0.5*100}											
Sample n	1	2	3	4				1	2	3	4
Rn-Tn	1.916667	-2	-5.66667	-5.41667							
(Rn-Tn)**2	3.673611	4	32.11111	29.34028							
SUMOD	69.125										
1/n	0.2										
1/n*sumod	13.825										
(1+above)	14.825										
(a30)**-0.	0.259718										
a31*100	25.97184										
log(a32)	1.414503										
f2=50(a33	70.72513										
passlimit	50										
Conclusio	Passes										

OCT 7 1996

Diltiazem
300 mg CD Capsule
240 mg CD Capsule
180 mg CD Capsule
120 mg CD Capsule
ANDA# 74752
Reviewer: Andre J. Jackson
WP #74752SDW.995

Andrx Pharmaceuticals
Fort Lauderdale, Florida
Submission Dated:
September 22, 1995
November 24, 1995(accep.)
March 25, 1996
May 2, 1996

REVIEW OF SINGLE DOSE FASTING, MULTIPLE DOSE STEADY-STATE, POST-PRANDIAL SINGLE DOSE BIOEQUIVALENCE STUDIES FOR 300 MG CD CAPSULE AND DISSOLUTION DATA AND WAIVER REQUESTS FOR 240 MG, 180 MG and 120 MG CAPSULES

Background

Diltiazem is a calcium ion influx inhibitor(slow-channel blocker or calcium antagonist). The therapeutic effects of diltiazem are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle. The marketed sustained-release diltiazem formulation is indicated for angina and hypertension in the approved labeling. It produces its antihypertensive effect primarily by relaxing arteriolar vascular resistance. The magnitude of blood pressure reduction is related to the degree of hypertension; thus, hypertensive individuals experinece an antihypertensive effect, whereas there is only a modest fall in blood pressure in normotensives.

Diltiazem is well absorbed from the gastrointestinal tract and is subject to an extensive first-pass effect, giving an absolute bioavailability of about 40%. Desacetyldiltiazem, a major metabolite, possesses 25% to 50% of diltiazem's pharmacologic activity as diltiazem. Whereas N-monodemethyldiltiazem, the major metabolite, is less active. The apparent biological half-life following multiple-dose administration is 5 to 7 hours. The therapeutic dose for sustained release diltiazem starts at 120 mg to 180 mg once daily, and is titrated to adjust to each patient's needs.

STUDY I
SINGLE-DOSE FASTING STUDY

Objective:

The aim of this study is to compare the oral bioavailability of a 300 mg test capsule formulation of diltiazem HCL to an equivalent oral dose of the reference product, Cardizem^{R} CD capsule manufactured by Marion Merrell Dow following a single 300 mg dose under fasting conditions.

Methods:

The study was conducted at _____ under the direction of _____ The samples were analyzed by _____ under the direction of _____ The study was conducted over the period of April 1 through April 10, 1995. Sample analysis began on April 24, 1995, and ended on May 1, 1995.

I. Characterization of Study Group:

A. Inclusion criteria

1. All volunteers selected for this study were male volunteers between the ages of 18 and 45 years. Weight range of the volunteers was within ±10% of normal body weight for height and frame with a minimum weight of 140 lbs.

2. Each volunteer was given a general physical examination within 21 days of initiation of the study. Each examination included blood pressure, general observations, history, complete hemogram (hemoglobin, hematocrit, WBC, differential), urinalysis (including microscopic), biochemistry (blood urea nitrogen, serum bilirubin [total], BUN, total protein and alkaline phosphatase), HIV antibody screen, hepatitis B surface antigen screens. Volunteers selected for the study had no laboratory values greater than ± 20% of the normal range.

3. Normal electrocardiogram at time of screening.

4. Have provided written informed consent.

B. Exclusion Criteria

1. Volunteers with a history of alcohol or drug addiction during the past two years, gastrointestinal, renal, hepatic or cardiovascular diseases, tuberculosis, epilepsy, asthma or any other medical disorder requiring medication.

2. Any noted EKG abnormality.

3. History of allergic response to diltiazem.

4. Participation in a previous clinical trial or the donation of one pint or more of blood within the past 4 weeks.

5. Use of any prescription drug during the four week period prior to study initiation, or any OTC drug during the two week period prior to study initiation.

6. Positive screen for drugs of abuse.

7. Positive HBsAg or HIV screen.

8. Subjects that smoke.

C. Informed Consent

All prospective volunteers had the study explained by a member of the research team or a member of their staff. The nature of the drug substance to be evaluated was explained together with the potential hazards involving drug allergies and possible adverse reactions. An acknowledgement of the receipt of this information and the participant's freely-tendered offer to volunteer was obtained in writing from each participant in the study.

II. Study Conduct

The study was conducted as a two-treatment two-period crossover study. 30 subjects were screened and accepted into the study. Subject 3 did not return for his 48 hour sample but was included in the data analysis since only one sample was missing.

A. Subjects fasted 10 hours before dosing and until 4.0 hrs after their scheduled dosing times. All subjects were given of water at the time of drug administration. Water

was not allowed from 1 hour before until 1 hour following drug administration and then provided ad libitum.

Subjects were instructed not to lie down for 4 hours following study drug administration, and not to engage in any strenuous physical activity.

Standard meals were provided at 4 and approximately 10 hours after dosing.

B. The products employed in the study were:

1. Test: Andrx Pharmaceuticals 300 mg diltiazem HCL sustained-release capsule, Lot # 600R001A, potency-SR1 beads- SR2 beads- expiration date 3/97, lot size expiration date March 1997.

2. Reference product: Cardizem^{R} 300 mg capsule, Lot # P70056, potency-SR1 beads 101.2%; SR2 beads 101.6%, expiration date December 1995.

There was a 7 day washout between doses.

C. A 300 mg dose (1 x 300 mg) of each product (test and reference) was administered at time zero with of water. The randomization scheme is presented in Table 1.

Table 1. Random Assignment of 30 subjects

Sequence	SUBJECT
A,B	1,4,5,9,12,15,16,17,19,22,23,25,27,29,30
B,A	2,3,6,7,8,10,11,13,14,18,20,21,24,26,28

Treatment A: Andrx diltiazem CD 1 X 300 mg capsule
Treatment B: Marion Merrel Dow Cardizem^{R} 1 x 300 mg capsule

The composition based upon type of pellets for the 300 mg capsule is given in Table 2.

Table 2. Composition based upon type of pellet.

Ingredients	Active Drug	
	mg	%
SR1 Pellets	120.0	40
SR2 Pellets	180.0	60
Total	300.0	100

Table 3. Final composition of the diltiazem extended-release (CD) capsule, 300 mg.

Ingredient	Amount/Tablet(mg)
Sugar	
Diltiazem HCL,	308.2
Ethylcellulose,	
Polysorbate	
Eudragit	
Eudragit	
Talc,	
Acetyl tributyl citrate	
Orange opaque capsule	
Total	696.9

D. Blood was collected pre-dose and at the following times post-dose: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 30, 36 and 48 hours after dosing.

E. During the study subjects were monitored for adverse reactions. Within 60 minutes prior to dosing, a baseline ECG was obtained to determine drug-free PR interval. Additional ECG determinations were done at post-dosing hours 4, 6, 8, 14, 16 and 18 within 30 minutes of the blood sample in order to determine drug effect on PR interval prolongation.

III. Analytical

Plasma concentrations of diltiazem, desacetyldiltiazem and desmethyldiltiazem were analyzed by with ultraviolet detection using as an internal standard. Total storage time for samples was approximately 30 days.

DILTIAZEM

Assay sensitivity:
The assay was linear over the range of . The limit of sensitivity of the assay was defined as with values less than this reported as zero.

Precision and Reproducibility:
Reproducibility was assessed by comparing the results of standard samples assayed on different days. The coefficient of variation was 3.47% at a concentration of and 6.48% at

Inter-day accuracy was assessed by comparing the results of quality control samples analyzed on different days. The accuracy was 95.0% at 5 ng/ml and 96% at 300 ng/ml.

Absolute Recovery
The overall recovery for diltiazem was 68% and the data is appended in Table 4.

Absolute Recovery-Internal Standard
The overall recovery for following extraction was 82%. The data is appended in Table 5.

Stability-Long Term
The stability data for diltiazem for a set of quality control samples prepared on September 22, 1994, and analyzed May 10, 1995, is presented in appended Table 6. The long term stability data are acceptable.

Freeze-Thaw Stability
Three control concentrations at 5, 75 and 300 ng/ml were studied for 3 freeze-thaw cycles. The results are appended in Table 7. The freeze-thaw stability data are acceptable.

Room Temperature Stability
Three control concentrations at 5, 75 and 300 ng/ml were allowed to sit for 4 hours at room temperature prior to processing. The results are appended in Table 8. The room

temperature stability data are acceptable.

DESACETYLDILTIAZEM

Assay sensitivity:
The assay was linear over the range of 2.0 to 400 ng/ml. The limit of sensitivity of the assay was defined as with values less than this reported as zero.

Precision and Reproducibility:
Reproducibility was assessed by comparing the results of standard samples assayed on different days. The coefficient of variation was 3.24% at a concentration of and 1.58% at

Inter-day accuracy was assessed by comparing the results of quality control samples analyzed on different days. The accuracy was 103.0% at 5 ng/ml and 104% at 300 ng/ml.

Absolute Recovery
The overall recovery for desacetyldiltiazem following extraction was 67.6%. The data is appended in Table 9.

Stability-Long Term
The stability data for desacetyldiltiazem for a set of quality control samples prepared on September 22, 1994 and analyzed May 10, 1995, are presented in appended Table 10. The long term stability data are acceptable.

Freeze-Thaw Stability
Three control concentrations at 5, 75 and 300 ng/ml were studied for 3 freeze-thaw cycles. The results are appended in Table 11. The freeze-thaw stability data are acceptable.

Room Temperature Stability
Three control concentrations at 5, 75 and 300 ng/ml were allowed to sit for 4 hours at room temperature prior to processing. The results are appended in Table 12. The room temperature stability data are acceptable.

DESMETHYLDILTIAZEM

Assay sensitivity:
The assay was linear over the range of ml. The

limit of sensitivity of the assay was defined as [illegible], with values less than this reported as zero.

Precision and Reproducibility:
Reproducibility was assessed by comparing the results of standard samples assayed on different days. The coefficient of variation was 5.27% at a concentration of and 1.63% at

Inter-day accuracy was assessed by comparing the results of quality control samples analyzed on different days. The accuracy was 107.0% at and 108% at

Absolute Recovery
The overall recovery for desmethyldiltiazem following extraction was 61.6%. The data is appended in Table 13.

Stability-Long Term
The stability data for desmethyldiltiazem for a set of quality control samples prepared on September 22, 1994 and analyzed May 10, 1995, are presented in appended Table 14. The long term stability data are acceptable.

Freeze-Thaw Stability
Three control concentrations at were studied for 3 freeze-thaw cycles. The results are appended in Table 15. The freeze-thaw stability data are acceptable.

Room Temperature Stability
Three control concentrations at were allowed to sit for 4 hours at room temperature prior to processing. The results are appended in Table 16. The room temperature stability data are acceptable.

24 Hour Stability
Samples extracted with run 15BBB were injected on Run 16BBB to demonstrate 24 hour extract stability. The results for diltiazem, desacetyldiltiazem and desmethyldiltiazem are presented in Tables 17-19 respectively. The samples exhibit acceptable 24 hour extract stability.

IV. Pharmacokinetic Methodology

Area under the curve(0-t) and AUC(0-inf) were calculated as well as elimination parameters for each subject and dosing group. Observed values for Tmax and Cmax were also reported.

V. Statistical Evaluation

ANOVA was performed at an alpha=0.05 using the GLM procedure of SAS. The model contained the effects of subject within sequence, period and treatment. Sequence effects were tested against the mean square term for subjects within sequence. All other main effects were tested against the mean square error term. The 90% confidence intervals for the difference between formulations and the power to detect a 20% difference between formulations were calculated for each parameter based upon its ANOVA.

Log-transformed data were submitted for analysis.

RESULTS

Diltiazem

Table 20

Diltiazem Plasma Concentrations (ng/mL)
Following a Single Oral 300 mg Capsule Dose
Following an Overnight Fast, n=30
Values are Mean ± (% CV).

Sampling Time (Hours)	Test Drug Andrx	Reference Drug Cardizem® CD Marion Merrell Dow
0	0	0
2	1.93(260.36)	1.18(165.74)
4	50.99(103.86)	33.83(100.70)
6	101.13 (51.03)	106.87 (36.21)
8	81.80 (45.04)	73.40 (34.60)
10	64.96 (41.84)	54.45 (40.68)
12	70.72 (41.05)	62.82 (49.07)
14	88.95 (40.15)	82.65 (48.69)
16	98.86 (34.84)	97.15 (41.00)
18	94.15 (32.78)	93.07 (34.66)
20	82.18 (34.04)	81.90 (35.68)
24	64.55 (35.41)	67.13 (37.23)
30	39.67 (44.68)	43.25 (48.10)
36	17.80 (54.41)	20.34 (56.10)
48	4.61 (82.33)*	5.65 (78.68)

*n=29; Subject #03 failed to return for blood sample

Table 21

Summary of Diltiazem Plasma Concentration PK Parameters
Following a Single Oral 300 mg Capsule Dose
Under Fasting Conditions, n=30
Values are Mean ± (% CV).

Parameter	Test Drug Andrx	Reference Drug Cardizem® CD Marion Merrell Dow	T/R Ratio
Cmax (ng/ml)	121.42(34.74)	117.92 (34.34)	1.03
Ln Cmax (ng/ml)[1]	4.73 (8.38)	4.710 (7.62)	1.02
AUC(0-t) (ng.h/ml)[2]	2287.9 (36.00)	2259.7 (34.50)	1.01
Ln AUC (0-t) (ng.h/ml)[1]	7.66 (5.14)	7.66 (4.62)	1.00
AUC(0-inf) (ng.h/ml)[3]	2348.8 (35.9)	2329.3 (34.60)	1.00
Ln AUC (0-inf) (ng.h/ml)[1]	7.69 (5.05)	7.69 (4.60)	1.00
Tmax (h)	10.8 (50.2)	10.5 (47.80)	1.00
K_{EL} (1/h)	0.11 (18.19)	0.11 (17.62)	
$T_{1/2}$ (h)	6.24(18.86)	6.43 (17.24)	

[1]Log Transformed (LNAUC (0-t), LNAUC (0-inf), Ln Cmax
Ratio is based upon least squares geometric means
[2]AUC(0-t)=AUC (0 to last measurable concentration)
Ratio is based upon the arithmetic means
[3]AUC(0-inf)=AUC (0 to infinity)

Table 22. 90% Confidence Intervals for diltiazem based on Ln transformed data (N=30).

Ln AUC(0-t)	(89.4 112.4)
Ln AUC(0-INF)	(89.3 112.0)
Ln Cmax	(92.6 112.6)

Sample Reassays-
Only 12 samples were reassayed out of a total of 899(1.3%).

Adverse Effects-
Adverse effects are appended in Table 23. Reported effects were mainly headache and some nausea. Most effects were seen for the reference product.

Protocol Deviations in Sample Draw Times
Deviations in planned sample draw times are presented in Table 24.

Desacetyldiltiazem

Table 25

Desacetyldiltiazem Plasma Concentrations (ng/mL)
Following a Single Oral 300 mg Capsule Dose
Following an Overnight Fast, n=30
Values are Mean ± (% CV).

Sampling Time (Hours)	Test Drug Andrx	Reference Drug Cardizem® CD Marion Merrell Dow
0	0	0
2	bql	bql
4	1.81 (146.66)	0.66 (210.07)
6	6.58 (60.32)	0.65 (25.27)
8	8.56 (53.03)	8.08 (36.88)
10	9.42 (55.77)	8.32 (43.17)
12	9.95 (73.32)	9.16 (65.16)
14	12.78 (90.58)	11.64 (77.15)
16	15.16 (99.66)	14.24 (85.93)
18	16.96 (105.22)	16.00 (89.15)
20	17.96 (103.84)	17.17 (97.91)
24	18.17 (103.39)	18.51 (102.88)
30	16.44 (126.24)	17.31 (127.85)
36	10.38 (138.30)	12.05 (140.12)
48	3.31 (167.50)*	4.84 (160.13)

*n=29; Subject #03 failed to return for blood sample

Table 26

Summary of Desacetyldiltiazem Plasma Concentrations PK Parameters
Following a Single Oral 300 mg
Capsule Dose Under Fasting Conditions
N=30
Values are Mean ± (% CV).

Parameter	Test Drug Andrx	Reference Drug Cardizem® CD Marion Merrell Dow	T/R Ratio
Cmax (ng/ml)	19.68 (106.17)	20.28 (104.12)	0.97
Ln Cmax (ng/ml)[1]	2.68 (25.26)	2.719 (24.76)	0.96
AUC(0-t) (ng.h/ml)[2]	499.3 (105.80)	527.0 (108.20)	0.95
Ln AUC (0-t) (ng.h/ml)[1]	5.89 (12.74)	5.95 (11.72)	0.94
AUC(0-inf) (ng.h/ml)[3]	597.5 (107.00)	626.4 (109.30)	0.96
Ln AUC (0-inf) (ng.h/ml)[1]	6.08 (11.36)	6.12 (11.33)	0.96
T_{MAX} (h)	22.1 (22.00)	23.0 (19.90)	
K_{EL} (1/h)	0.07 (26.12)	0.07 (31.28)	
$T_{1/2}$ (h)	10.14 (42.12)	10.34 (25.71)	

[1]Log Transformed (LNAUC (0-t), LNAUC (0-inf), Ln Cmax
Ratio is based upon least squares geometric means
[2]AUC(0-t)=AUC (0 to last measurable concentration)
Ratio is based upon the arithmetic means
[3]AUC(0-inf)=AUC (0 to infinity)

Table 27. 90% Confidence Intervals for desacetyldiltiazem based on Ln-transformed data (N=30).

Ln AUC(0-t)	(82.3 107.8)
Ln AUC(0-INF)	(88.7 105.1)
Ln Cmax	(87.3 107.9)

Desmethyldiltiazem

Table 28
Desmethyldiltiazem Plasma Concentrations (ng/mL)
Following a Single Oral 300 mg Capsule Dose
Following an Overnight Fast
Values are Mean ± (% CV)

Sampling Time (Hours)	Test Drug Andrx	Reference Drug Cardizem® CD Marion Merrell Dow
0	0	0
2	0.29 (388.23)	bql
4	9.76 (102.09)	6.95 (82.22)
6	22.89 (45.32)	26.29 (22.39)
8	24.37 (32.43)	25.04 (19.69)
10	22.97 (28.97)	21.74 (23.39)
12	23.73 (28.29)	23.08 (30.42)
14	27.73 (31.20)	26.48 (34.38)
16	31.06 (27.84)	31.32 (29.55)
18	31.09 (26.64)	31.14 (24.42)
20	29.23 (25.81)	29.39 (23.91)
24	25.42 (25.35)	26.31 (25.32)
30	20.29 (30.95)	21.49 (28.77)
36	12.36 (36.35)	13.38 (33.62)
48	4.61 (48.03)*	5.13 (45.62)

*n=29; Subject #03 failed to return for blood sample

Table 29

Summary Desmethyldiltiazem Plasma Concentration PK Parameters Following a Single Oral 300 mgCapsule Dose Under Fasting Conditions, N=30

Values are Mean ± Mean (% CV)

Parameter	Test Drug Andrx	Reference Drug Cardizem® CD Marion Merrell Dow	T/R Ratio
Cmax (ng/ml)	33.05 (25.23)	33.71 (23.51)	0.98
Ln Cmax (ng/ml)[1]	3.46 (8.49)	3.48 (7.12)	0.97
AUC(0-t) (ng.h/ml)[2]	857.9 (26.30)	882.9 (22.20)	0.97
Ln AUC (0-t) (ng.h/ml)[1]	6.71 (4.59)	6.75 (3.34)	0.95
AUC(0-inf) (ng.h/ml)[3]	924.7 (26.00)	953.0 (23.20)	0.97
Ln AUC(0-inf) (ng.h/ml)[1]	6.97 (4.43)	6.83 (3.34)	1.15
Tmax (h)	15.1 (29.40)	15.2 (36.70)	
K_{EL} (1/h)	0.08 (14.78)	0.08 (16.40)	
$T_{1/2}$ (h)	8.66 (16.52)	8.73 (15.71)	

[1]Log Transformed (LNAUC (0-t), LNAUC (0-inf), Ln Cmax
Ratio is based upon least squares geometric means
[2]AUC(0-t)=AUC (0 to last measurable concentration)
Ratio is based upon the arithmetic means
[3]AUC(0-inf)=AUC (0 to infinity)

Table 30. 90% Confidence Intervals for desmethyldiltiazem based on Ln transformed data (N=30).

Ln AUC(0-t)	(87.3 104.7)
Ln AUC(0-INF)	(87.4 104.9)
Ln Cmax	(90.3 104.6)

All confidence intervals for the parent drug and metabolites were verified by the reviewer

STUDY II

MULTIPLE DOSE STUDY

Objective:

The aim of this study is to compare the oral bioavailability at stead-state of a 300 mg test capsule formulation of diltiazem HCL to an equivalent oral dose of the reference product, Cardizem^{R} CD capsule manufactured by Marion Merrell Dow.

Methods:

The study was conducted at , under the direction of . The samples were analyzed by under the direction of . Study period I was initiated on July 10, 1995; Study period II began on July 24, 1995.

I. Characterization of Study Group:

A. Inclusion criteria

1. All volunteers selected for this study were male volunteers between the ages of 18 and 44 years. Weight range of the volunteers was within ±10% of their desirable height/weight ratio according to the 1983 Metropolitan Insurance Table.

2. All other inclusion criteria were similar to those for the single dose study.

B. Exclusion criteria

1. Same as those for the single dose study

C. Informed Consent

All prospective volunteers had the study explained by a member of the research team or a member of their staff. The nature of the drug substance to be evaluated was explained together with the potential hazards involving drug allergies and possible adverse reactions. An acknowledgement of the receipt of this information and the participant's freely-tendered offer to volunteer was obtained in writing from each participant in the study.

II. Study Conduct

The study was conducted as a two-treatment two-period steady-state crossover study. 26 subjects were screened and accepted into the study. 24 subjects were evaluated while subject 12 was dropped (explanation of probably drug related) and 13 was dropped for personal reasons.

A. Subjects fasted 10 hours before dosing which was scheduled as:

Study Day 1	Dose I
Study Day 2	Dose II
Study Day 3	Dose III
Study Day 4	Dose IV
Study Day 5	Dose V

On the evening of study day 5, subjects checked into the clinic 10 hours prior to dosing on study day 6 to begin an overnight fast. All subjects were sequestered until 24 hours following their last dose.

B. The products employed in the study were:

1. Test: Andrx Pharmaceuticals 300 mg diltiazem HCL sustained-release capsule, Lot # 600R001A, potency-SR1 beads-97.6%, SR2 beads-100.7%, expiration date 3/97, lot size expiration date March 1997.

2. Reference product: Cardizem® 300 mg capsule, Lot # P70056, potency-SR1 beads 101.2%; SR2 beads 101.6%, expiration date December 1995.

There was a 14 day washout between dosing periods.

C. A 300 mg dose (1 x 300 mg) of each product (test and reference) was administered at time zero on each study day with of water. The randomization scheme is presented in Table 31.

Table 31. Random Assignment of 26 subjects

Sequence	SUBJECT
A,B	2,4,6,9,10,15,16,17,19,23,24,25
B,A	1,3,5,7,8,11,12,13,14,18,20,21,22,26

Treatment A:Andrx diltiazem 1 X 300 mg CD capsule
Treatment B: Marion Merrel Dow Cardizem® 1 x 300 mg capsule

D. Blood was collected at hour 0 on study days 1-6. On day 6 additional samples were collected post-dose at 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 and 24 hours.

E. During the study subjects were monitored for adverse reactions. An ECG was obtained prior to the first dose each period to establish a reference value for PR interval evaluation. Additional ECGs were obtained at baseline prior to the 6th dose, and at post-dose hours 4, 6, 8, 14, 16 and 18 in order to determine drug effect on PR interval prolongation.

III. Analytical

Plasma concentrations of diltiazem, desacetyldiltiazem and desmethyldiltiazem were analyzed by with detection using as an internal standard. Analysis of samples began on August 2, 1995, and ended on August 10, 1995.

DILTIAZEM

Assay sensitivity:
The assay was linear over the range of . The limit of sensitivity of the assay was defined as /ml, with values less than this reported as zero.

Precision and Reproducibility:
Reproducibility was assessed by comparing the results of standard samples assayed on different days. The coefficient of variation was 3.32% at a concentration of and 2.55%

Inter-day accuracy was assessed by comparing the results of quality control samples analyzed on different days. The accuracy was 96.8% at and 98% at

DESACETYLDILTIAZEM

Assay sensitivity:
The assay was linear over the range of . The limit of sensitivity of the assay was defined as with values less than this reported as zero.

Precision and Reproducibility:
Reproducibility was assessed by comparing the results of standard samples assayed on different days. The coefficient of variation was 3.44% at a concentration of and 2.48% at

Inter-day accuracy was assessed by comparing the results of quality control samples analyzed on different days. The accuracy was 98.0% at and 99% at

DESMETHYLDILTIAZEM

Assay sensitivity:
The assay was linear over the range of . The limit of sensitivity of the assay was defined as l, with values less than this reported as zero.

Precision and Reproducibility:
Reproducibility was assessed by comparing the results of

standard samples assayed on different days. The coefficient of variation was 3.91% at a concentration of and 2.54% at

Inter-day accuracy was assessed by comparing the results of quality control samples analyzed on different days. The accuracy was 103.0% at and 105% at

IV. Pharmacokinetic Methodology

Area under the curve(0-τ)(ie 24 hrs) at steady-state and per cent fluctuation [(Cmax-Cmin)/Cmin] was calculated. Observed values for Tmax, Cmax and Cmin were also reported.

V. Statistical Evaluation

ANOVA was performed at an alpha=0.05 using the GLM procedure of SAS. The model contained the effects of subject within sequence, period and treatment. Sequence effects were tested against the mean square term for subjects within sequence. All other main effects were tested against the mean square error term. The 90% confidence intervals for the difference between formulations and the power to detect a 20% difference between formulations were calculated for each parameter based upon its ANOVA.

Log-transformed data were submitted for analysis.

RESULTS

Table 32
Diltiazem Plasma Concentrations (ng/ml)
Following Multiple Dosing of an Oral 300 mg Capsule n=24
Values are Mean ± (% CV)

[1]Sampling Time (Days)	Sampling Time (Hours)	Test Drug Andrx Pharmaceuticals	Reference Drug Cardizem® CD Marion Merrell Dow
1	0	0	0
2	0	63.11 (45.78)	66.27 (56.78)
3	0	77.29 (40.97)	78.89 (50.78)
4	0	75.94 (49.76)	79.18 (45.49)
5	0	74.34 (45.57)	76.23 (49.73)
6	0	68.99 (50.33)	79.73 (41.23)
6	2	67.94 (59.54)	78.18 (47.39)
6	4	97.64 (69.30)	110.52 (61.92)
6	6	142.29 (41.39)	187.57 (34.14)
6	8	136.81 (40.32)	143.96 (38.69)
6	10	115.05 (44.34)	111.66 (40.55)
6	12	107.63 (45.54)	106.85 (38.74)
6	14	115.52 (48.83)	115.26 (37.56)
6	16	119.57 (48.41)	119.33 (34.43)
6	18	108.77 (50.45)	112.70 (34.94)
6	20	94.40 (51.72)	98.54 (35.83)
6	24	75.07 (51.26)	79.97 (42.36)

[1]Samples on days 1-6 at time 0 are Cmin values

Table 33

Summary Diltiazem Plasma PK Parameters
Following Multiple Dosing of an Oral 300 mg Capsule, n=24
Values are Mean ± (% CV)

Parameter	Test Drug Andrx Pharmaceuticals	Reference Drug Cardizem® CD Marion Merrell Dow	T/R Ratio
AUC (0-τ) (ng.h/ml)[1]	2524.9 (43)	2707.5 (36.4)	0.93
Ln AUC (0-τ) (ng.h/ml)[2]	7.72 (6.55)	7.82 (5.95)	0.96
Cmax (ng/ml)	168.8 (38)	187.6 (34.1)	0.90
Ln Cmax (ng/ml)	5.05 (8.21)	5.17 (7.24)	0.88
Cmin (ng/ml)	69 (50.34)	79.73 (41.24)	0.86
T_{MAX} (h)	8 (43)	6 (0)	
% Fluctuation	184.52 (73.93)	155.36 (45.56)	-

[1]AUC(0-t)= AUC(0-τ)- AUC for a dosing interval at steady-state
Ratio is based upon the arithmetic means
[2]Log Transformed (LNAUC(0-τ), Ln Cmax)
Ratio is based upon least squares geometric means

Table 34. 90% Confidence Intervals for diltiazem based on Ln transformed data(N=24).

Ln AUC(0-τ)	(84.4 98.6)
Ln Cmax	(81.7 96.4)

Sample Reassays-
Only 18 samples were reassayed out of a total of 816(2.2%).

Adverse Effects-
Adverse effects are appended in Table 35. Reported effects were mainly headache and some nausea. Effects were equally distributed between test and reference products.

Protocol Deviations in Sample Draw Times
Deviations in planned sample draw times are presented in Table 36.

Table 37
Desacetyldiltiazem Plasma Concentrations (ng/mL)
Following Multiple Dosing of an Oral 300 mg Capsule, n=23
Values are Mean ± (% CV)

[1]Sampling Time (Days)	Sampling Time(Hours)	Test Drug Andrx Pharmaceuticals	Reference Drug Cardizem® CD Marion Merrell Dow
1	0	0	0
2	0	13.67 (100.41)	14.59 (120.46)
3	0	21.48 (137.39)	26.06 (151.37)
4	0	23.41 (161.15)	24.50 (149.37)
5	0	23.54 (152.19)	20.95 (149.88)
6	0	22.91 (165.81)	23.44 (139.68)
6	2	22.28 (154.95)	23.97 (152.74)
6	4	23.78 (171.33)	24.22 (148.06)
6	6	26.07 (156.34)	28.91 (140.89)
6	8	24.70 (124.55)	27.71 (141.33)
6	10	24.44 (126.26)	26.38 (136.83)
6	12	22.92 (130.04)	24.64 (147.02)
6	14	24.42 (141.27)	24.70 (140.06)
6	16	23.48 (129.82)	24.26 (131.24)
6	18	22.83 (128.84)	24.69 (133.44)
6	20	23.54 (150.04)	24.52 (142.12)
6	24	22.43 (140.74)	24.57 (147.67)

*Subject #17 omitted due to interference peaks.
[1]Samples on days 1-6 at time 0 are Cmin values.

Table 38
Summary Desacetyldiltiazem Plasma
PK Parameters Following Multiple Dosing of an
Oral 300 mg Capsule, n=23
Values are Mean + (% CV)

Parameter	Test Drug Andrx Pharmaceuticals	Reference Drug Cardizem® CD Marion Merrell Dow	T/R Ratio
AUC (0-τ) (ng.h/ml)[1]	568.4 (142.3)	605.2 (141.6)	0.94
Ln AUC (0-τ) (ng.h/ml)[2]	6.00 (11.16)	6.08 (10.48)	0.92
Cmax (ng/ml)	28.7 (140.7)	29.8 (135.6)	0.96
Ln Cmax (ng/ml)	3.03 (21.35)	3.09 (20.41)	0.95
Cmin (ng/ml)	22.91 (165.81)	23.44 (139.69)	0.98
Tmax (h)	11 (57)	10 (51)	
% Fluctuation	37.02 (67.05)	28.31 (59.51)	

[1]AUC(0-τ)- AUC for a dosing interval at steady-state
Ratio is based upon the arithmetic means
[2]Log Transformed (LNAUC(0-τ), Ln Cmax)
Ratio is based upon least squares geometric means

Table 39. 90% Confidence Intervals for desacetyldiltiazem based on Ln transformed data(N=23).

Ln AUC(0-τ)	(86.9 97.7)
Ln Cmax	(89.5 99.6)

Table 40

Desmethyldiltiazem Plasma Concentrations (ng/mL)
Following Multiple Dosing of an Oral 300 mg Capsule, n=24
Values are Mean ± (% CV)

[1]Sampling Time (Days)	Sampling Time (Hours)	Test Drug Andrx Pharmaceuticals	Reference Drug Cardizem® CD Marion Merrell Dow
1	0	0	0
2	0	25.35 (33.03)	26.82 (33.81)
3	0	32.82 (29.42)	32.48 (40.75)
4	0	32.92 (36.83)	34.40 (37.19)
5	0	33.24 (32.65)	33.41 (37.99)
6	0	30.95 (36.09)	35.00 (31.91)
6	2	30.01 (39.54)	34.10 (36.13)
6	4	33.30 (36.97)	37.38 (40.09)
6	6	42.05 (31.94)	51.79 (28.74)
6	8	44.13 (30.94)	50.03 (32.22)
6	10	41.90 (31.23)	44.92 (33.67)
6	12	40.17 (30.06)	43.08 (31.73)
6	14	42.90 (32.67)	44.57 (32.25)
6	16	43.37 (33.05)	44.51 (31.14)
6	18	41.46 (35.90)	43.46 (31.66)
6	20	38.14 (37.50)	40.12 (32.85)
6	24	32.20 (37.60)	35.78 (36.37)

[1].Samples on days 1-6 at time 0 are Cmin values.

Table 41
Summary Desmethyldiltiazem
PK Parameters Following Multiple Dosing of an
Oral 300 mg Capsule, n=24
Values are Mean ± (%CV)

Parameter	Test Drug Andrx Pharmaceuticals	Reference Drug Cardizem® CD Marion Merrell Dow	T/R Ratio
AUC (0-τ) (ng.h/ml)[1]	930.5 (31.8)	1014.7 (31.7)	0.92
Ln AUC (0-τ) (ng.h/ml)[2]	6.78 (5.24)	6.86 (5.36)	0.92
Cmax (ng/ml)	49.1 (28.1)	53.7 (28.0)	0.91
Ln Cmax (ng/ml)	3.85 (7.83)	3.94 (7.74)	0.91
Cmin (ng/ml)	30.96 (36.09)	35 (31.91)	0.88
T_{MAX} (h)	12 (40)	9 (44)	
% Fluctuation	71.20 (79.52)	58.00 (39.67)	

[1]AUC(0-τ)- AUC for a dosing interval at steady-state
Ratio is based upon the arithmetic means
[2]Log Transformed (LNAUC(0-τ), Ln Cmax)
Ratio is based upon least squares geometric means

Table 42. 90% Confidence Intervals for desmethyldiltiazem based on Ln transformed data(N=24).

Ln AUC(0-τ)	(87.0 97.1)
Ln Cmax	(86.6 96.5)

All confidence intervals for the parent drug and metabolites were verified by the reviewer

STUDY III

SINGLE-DOSE POST-PRANDIAL STUDY

Objective:

The aim of this study is to compare the oral bioavailability of a 300 mg test capsule formulation of diltiazem HCL to an equivalent oral dose of the reference product, Cardizem^{R} CD capsule manufactured by Marion Merrell Dow following a single 300 mg dose under fasting and non-fasting conditions.

Methods:

The study was conducted at _____ under the direction of _____ M.D. The samples were analyzed by _____ under the direction of _____ Study period I was begun May 17, 1995; study period II started May 24, 1995, while study period III began May 31, 1995. Samples analysis began on June 7, 1995 and concluded on June 19, 1995.

I. Characterization of Study Group:

A. Inclusion criteria

1. All volunteers selected for this study were male volunteers between the ages of 18 and 37 years. Weight range of the volunteers was within ±10% of their desirable height/weight ratio according to the 1983 Metropolitan Insurance Table.

2. All other inclusion criteria were similar to those for the fasting single dose study.

B. Exclusion criteria

1. Same as those for the fasting single dose study.

C. Informed Consent

All prospective volunteers had the study explained by a member of the research team or a member of their staff. The nature of the drug substance to be evaluated was explained together with the potential hazards involving drug allergies and possible adverse

reactions. An acknowledgement of the receipt of this information and the participant's freely-tendered offer to volunteer was obtained in writing from each participant in the study.

II. Study Conduct

The study was conducted as a randomized three-treatment three-period crossover study. 24 subjects were screened and accepted into the study.

A. Subjects fasted 10 hours before dosing. Beginning 15 minutes before their assigned dose time, subjects assigned to the "food effects" groups were given the following high fat meal:

one buttered English muffin
one fried egg
one slice of American cheese
one slice of Canadian bacon
one serving of hash brown potatoes
eight fluid oz. of whole milk
six fluid oz. of orange juice

All subjects were given [redacted] of water at the time of drug administration. Standard meals were provided at 4 and approximately 10 hours after dosing.

B. The products employed in the study treatments were:

1. Treatment A Test(fasting): Andrx Pharmaceuticals 300 mg diltiazem HCL sustained-release capsule, Lot # 600R001A, potency-SR1 beads- [redacted] SR2 beads- [redacted], expiration date 3/97, lot size [redacted] expiration date March 1997.

2. Treatment B Test(post-prandial): Andrx Pharmaceuticals 300 mg diltiazem HCL sustained-release capsule, Lot # 600R001A, potency-SR1 beads- [redacted] SR2 beads- [redacted] expiration date 3/97, lot size [redacted] expiration date March 1997.

3. Treatment C Reference(post-prandial): Cardizem^{R} 300 mg capsule, Lot # P70056, potency-SR1 beads [redacted]; SR2 beads [redacted], expiration date December 1995.

There was a 7 day washout between doses.

C. A 300 mg dose (1 x 300 mg) of each product (test and reference) was administered at time zero with _____ of water. The randomization scheme is presented in Table 43.

Table 43. Random Assignment of 24 subjects

Sequence	SUBJECT
BAC	1,9,14,22
ACB	2,7,15,24
CBA	3,8,13,23
ABC	4,12,16,19
BCA	5,10,18,20
CAB	6,11,17,21

Treatment A:Andrx 1 X 300 mg diltiazem CD capsule
Treatment B:Andrx 1 X 300 mg diltiazem CD capsule
Treatment C: Marion Merrel Dow Cardizem^{R} 1 x 300 mg capsule

D. Blood was collected pre-dose and at the following times post-dose: 2, 4, 6, 7, 8, 10, 12, 14, 16, 18, 20, 24, 30, 36 and 48 hours after dosing.

E. During the study subjects were monitored for adverse reactions. An ECG was obtained at baseline each period to establish reference value for PR interval evaluation. Additional ECG determinations were done at post-dosing hours 4, 6, 8, 14, 16 and 18 within 30 minutes of the blood sample in order to determine drug effect on PR interval prolongation.

III. Analytical

Plasma concentrations of diltiazem, desacetyldiltiazem and desmethyldiltiazem were analyzed by _____ with _____ detection using _____ as an internal standard. Total storage time for samples was approximately 30 days.

DILTIAZEM

Assay sensitivity:
The assay was linear over the range of The limit of sensitivity of the assay was defined as with values less than this reported as zero.

Precision and Reproducibility:
Reproducibility was assessed by comparing the results of standard samples assayed on different days. The coefficient of variation was 6.04% at a concentration of and 7.99% at

Inter-day accuracy was assessed by comparing the results of quality control samples analyzed on different days. The accuracy was 97.6% at and 98% at

DESACETYLDILTIAZEM

Assay sensitivity:
The assay was linear over the range of The limit of sensitivity of the assay was defined as with values less than this reported as zero.

Precision and Reproducibility:
Reproducibility was assessed by comparing the results of standard samples assayed on different days. The coefficient of variation was 5.73% at a concentration of and 2.16% at

Inter-day accuracy was assessed by comparing the results of quality control samples analyzed on different days. The accuracy was 98.4% at and 99% at

DESMETHYLDILTIAZEM

Assay sensitivity:
The assay was linear over the range of The limit of sensitivity of the assay was defined as with values less than this reported as zero.

Precision and Reproducibility:
Reproducibility was assessed by comparing the results of standard samples assayed on different days. The coefficient of variation was 4.84% at a concentration of _____ and 1.93% at_____ g/ml.

Inter-day accuracy was assessed by comparing the results of quality control samples analyzed on different days. The accuracy was 104.0% at 5 ng/ml and 103% at 300 ng/ml.

IV. Pharmacokinetic Methodology

Area under the curve(0-t) and AUC(0-inf) were calculated as well as elimination parameters for each subject and dosing group. Observed values for Tmax and Cmax were also reported.

V. Statistical Evaluation

ANOVA was performed at an alpha=0.05 using the GLM procedure of SAS. The model contained the effects of subject within sequence, period and treatment. Sequence effects were tested against the mean square term for subjects within sequence. All other main effects were tested against the mean square error term. The 90% confidence intervals for the difference between formulations and the power to detect a 20% difference between formulations were calculated for each parameter based upon its ANOVA.

Log-transformed data were submitted for analysis.

RESULTS

Diltiazem

Table 44
Post-Prandial Diltiazem Plasma Concentrations (ng/mL)
Following a Single Oral 300 mg Capsule Dose, n=24
Values are Mean ± (% CV)

Sampling Time (Hours)	Test Drug Fasting Andrx	Test Drug Non-Fasting Andrx	Reference Drug Non-Fasting Cardizem® CD Marion Merrell Dow
0	0	0	0
2	0.08 (489.89)	2.97 (309.47)	1.54 (204.74)
4	33.01 (125.99)	27.66 (159.78)	8.34 (154.57)
6	98.29 (56.25)	78.55 (76.92)	114.63 (47.30)
7	118.45 (36.55)	115.33 (48.91)	134.42 (41.33)
8	109.63 (28.38)	124.62 (41.15)	120.83 (42.93)
10	90.29 (32.62)	103.17 (39.18)	93.53 (49.60)
12	88.12 (31.19)	99.15 (38.26)	87.47 (52.07)
14	113 (33.78)	117.70 (40.92)	109.95 (73.50)
16	129.36 (38.25)	130.39 (38.89)	130.39 (58.32)
18	126.65 (38.90)	125.42 (32.62)	137.07 (54.36)
20	111.17 (38.76)	107.21 (35.53)	121.83 (49.78)
24	88.43 (37.98)	91.52 (41.18)	99.40 (39.98)
30	49.88 (45.79)	52.04 (55.38)	61.71 (58.72)
36	24.06 (50.70)	25.05 (67.55)	29.66 (69.07)
48	6.10 (75.06)	6.99 (84.99)	7.20 (77.34)

Table 45
Summary of PK Parameters for Diltiazem Following a Single Oral 300 mg Capsule Under fasting and non-Fasting Conditions. Values are mean±(CV%)
n=24

Parameter	Test Drug-Fasting Andrx Lot#600R001A	Test Drug-Non-Fasting Andrx Lot#600R001A	Reference Drug Non-Fasting Cardizem® CD Marion Merrel Dow Lot#P70056	Food(T)/Food(R) Ratio
Cmax (ng/ml)	156.9 (29.31)	161.42 (26.68)	161 (47.31)	1.00
Ln Cmax (ng/ml)[1]	5.013 (5.95)	5.04 (5.65)	5.00 (7.44)	1.04
AUC (0-t) (ng.h/ml)[2]	2912.1 (32.80)	2986.1 (32.10)	3162.7 (46.60)	0.94
Ln AUC (0-t)[1] (ng.h/ml)	7.92 (4.32)	7.95 (4.24)	7.97 (5.11)	0.98
AUC(0-inf) (ng.h/ml)[3]	2981.5 (32.80)	3066.9 (32.30)	3237.0 (46.50)	0.95
Ln AUC (0-inf)[1] (ng/mlxhr)	7.94 (4.32)	7.97 (4.20)	7.99 (5.10)	0.98
Tmax (h)	11.59 (44.60)	11.4 (47.00)	12.3 (45.50)	
K_{EL} (1/h)	0.11 (15.88)	0.11 (20.19)	0.12 (18.90)	
$T_{1/2}$ (h)	6.17 (17.41)	6.30 (23.26)	6.01 (19.39)	

[1]Log Transformed (LNAUC (0-t), LNAUC (0-inf), Ln Cmax
Ratio is based upon least squares geometric means
[2]AUC(0-t)=AUC (0 to last measurable concentration)
Ratio is based upon the arithmetic means
[3]AUC(0-inf)=AUC (0 to infinity)

Sample Reassays-
Only 40 samples were reassayed out of a total of 1152(3.4%).

Adverse Effects-
Adverse effects are appended in Table 46. Reported effects were mainly headache and some nausea. Effects were equally distributed between test and reference products.

Table 47
Post-Prandial Desacetyldiltiazem Plasma Concentrations (ng/ml)
Following a Single Oral 300 mg Capsule Dose, n=24
Values are Mean ± (% CV)

Sampling Time (Hours)	Test Drug Fasting Andrx	Test Drug Non-Fasting Andrx	Reference Drug Non-Fasting Cardizem® CD Marion Merrell Dow
0	0	0	0
2	bql	0.17(489.89)	bql
4	0.73(180.27)	0.97(186.09)	bql
6	4.99 (86.78)	3.74 (78.81)	4.56 (59.92)
7	7.18 (64.49)	6.05 (59.29)	6.80 (46.59)
8	8.64 (60.41)	8.24 (49.78)	8.16 (46.60)
10	10.46 (71.05)	10.13 (48.98)	9.41 (47.52)
12	11.34 (84.27)	10.81 (51.15)	9.83 (61.83)
14	13.85 (87.64)	13.12 (53.83)	12.16 (80.12)
16	16.88(103.79)	15.29 (60.07)	15.37 (95.14)
18	19.57(106.66)	17.70 (66.51)	18.43 (103.44)
20	20.99(112.67)	18.39 (73.63)	20.84 (112.26)
24	21.83(105.54)	19.48 (79.89)	22.08 (104.81)
30	18.38(126.24)	17.34(113.35)	20.84 (128.14)
36	11.82(128.63)	11.66(126.80)	13.56 (138.97)
48	4.50(161.84)	6.64(199.75)	5.14 (179.79)

Table 48
Post-Prandial Desacetyldiltiazem Plasma Concentrations Summary
PK Parameters Following a Single Oral 300 mg
Capsule Dose, n=24
Values are Mean(+ %CV)

Parameter	Test Drug-Fasting Andrx	Test Drug-Non-Fasting Andrx	Reference Drug Non-Fasting Cardizem® CD Marion Merrel Dow	Fed(T)/Fed(R) Ratio
Cmax (ng/ml)	23.26(107.70)	22.09 (83.59)	23.57 (109.15)	0.94
Ln Cmax (ng/ml)[1]	2.84 (23.95)	2.89 (19.75)	2.84 (24.21)	1.05
AUC (0-t) (ng.h/ml)[2]	580.7 (110.90)	553.2 (91.20)	596.6 (115.20)	0.93
Ln AUC (0-t)[1] (ng.h/ml)[1]	6.03 (12.05)	6.06 (10.67)	6.04 (12.09)	1.02
AUC (0-inf) (ng.h/ml)[3]	666.9 (110.50)	620.0 (103.00)	696.8 (118.60)	0.88
Ln AUC (0-inf) (ng.h/ml)[1]	6.16 (11.78)	6.15 (10.44)	6.19 (11.70)	0.96
Tmax (h)	22.0 (22.70)	22.8 (30.20)	24.3 (15.10)	
K_{EL} (1/h)	0.08 (19.85)	0.08 (26.85)	0.08 (19.83)	
$T_{1/2}$ (h)	9.20 (20.72)	9.82 (37.15)	9.38 (18.24)	

[1]Log Transformed (LNAUC (0-t), LNAUC (0-inf), Ln Cmax
Ratio is based upon least squares geometric means
[2]AUC(0-t)=AUC (0 to last measurable concentration)
Ratio is based upon the arithmetic means
[3]AUC(0-inf)=AUC (0 to infinity)

Table 49
Post-Prandial Desmethyldiltiazem Plasma Concentrations (ng/mL) Following a Single Oral 300 mg Capsule Dose, n=24
Values are Mean (+ %CV)

Sampling Time (Hours)	Test Drug Fasting Andrx	Test Drug Non-Fasting Andrx	Reference Drug Non-Fasting Cardizem® CD Marion Merrell Dow
0	0	0	0
2	bql	0.20 (489.89)	bql
4	5.64 (120.33)	5.09 (161.52)	0.73 (218.51)
6	20.07 (56.97)	16.79 (76.03)	21.35 (39.91)
7	26.35 (36.23)	24.87 (45.71)	27.92 (28.81)
8	27.24 (28.63)	28.19 (33.53)	28.95 (24.43)
10	27.03 (20.72)	29.02 (28.33)	26.97 (22.92)
12	26.92 (18.73)	29.67 (27.93)	26.35 (25.64)
14	31.05 (19.51)	32.80 (27.88)	28.63 (27.29)
16	34.83 (23.21)	36.46 (27.51)	33.27 (28.72)
18	36.44 (26.07)	37.35 (25.76)	34.70 (26.57)
20	34.51 (26.30)	34.18 (26.04)	34.10 (28.29)
24	30.92 (26.28)	31.33 (26.69)	30.74 (23.22)
30	22.98 (33.01)	23.98 (35.51)	24.75 (30.16)
36	15.14 (35.48)	15.60 (43.69)	16.36 (36.24)
48	5.71 (45.22)	6.21 (57.06)	6.12 (46.34)

Table 50
Post-Prandial Desmethyldiltiazem Plasma Concentration Summary
PK Parameters Following a Single Oral 300 mg
Capsule Dose, n=24
Values are Mean (+ %CV)

Parameter	Test Drug-Fasting Andrx	Test Drug-Non-Fasting Andrx	Reference Drug Non-Fasting Cardizem® CD Marion Merrel Dow	Fed(T)/Fed(R) Ratio
Cmax (ng/ml)	38.40 (19.95)	40.53 (19.17)	37.65 (22.90)	1.07
Ln Cmax (ng/ml)[1]	3.62 (5.60)	3.68 (5.20)	3.60 (5.93)	1.08
AUC (0-t) (ng.h/ml)[2]	987.9 (23.30)	1012.9 (23.8)	991.4 (24.00)	1.02
Ln AUC (0-t) (ng.h/ml)[1]	6.86 (3.59)	6.89 (3.52)	6.87 (3.52)	1.02
AUC (0-inf) (ng.h/ml)[3]	1064.5 (24.70)	1109.0 (24.80)	1078.7 (24.70)	1.03
Ln AUC (0-inf) (ng.h/ml)[1]	6.93 (3.76)	6.98 (3.67)	6.95 (3.56)	1.03
Tmax (h)	15.8 (30.60)	16.3 (22.50)	15.9 (41.60)	
K_{EL} (1/h)	0.08 (16.47)	0.08 (23.43)	0.08 (16.18)	
$T_{1/2}$ (h)	8.82 (17.35)	9.37 (30.08)	8.98 (16.80)	

[1]Log Transformed (LNAUC (0-t), LNAUC (0-inf), Ln Cmax
Ratio is based upon least squares geometric means
[2]AUC(0-t)=AUC (0 to last measurable concentration)
Ratio is based upon the arithmetic means
[3]AUC(0-inf)=AUC (0 to infinity)

Dissolution

The dissolution study for diltiazem was done as follows:

Apparatus:	Paddle,
Media:	buffer)
Volume:	900 ml
No. of Units Analyzed:	12
Specifications:	Interim:

The results are presented in Table 51.

The firm also requested a waiver of the in vivo bioequivalence requirements for their 240 mg, 180 mg and 120 mg CD capsules based upon the same fill weight and potency ratios of the beads as for the 300 mg capsule which underwent the bioequivalence study. The comparative formulations are given in appended Table 52.

Overall Comments:

1. The dissolution data for the test product are acceptable. The firm did not provide dissolution data on the reference product.

2. The 240 mg, 180 mg and 120 mg capsules are compositionally similar to the 300 mg tablet which underwent bioequivalency testing.

3. The 90% confidence intervals for the single dose fasting study for Ln Cmax and Ln AUC(0-t) and AUC(0-inf) were within the acceptable range of of the reference product.

4. The 90% confidence intervals for the multiple dose fasting study for Ln Cmax and Ln AUC(0-τ) were within the acceptable range of of the reference product.

5. The ratio of the geometric means for Ln Cmax, Ln AUC(0-t)

and Ln AUC(0-inf) for the test versus reference product were all within 20% for the post-prandial study.

6. The firm has conducted their dissolution studies in and in SIF using the paddle at pm which are similar to the conditions used by the innovator. However, The Division of Bioequivalence considers the rpm speed to provide excessive agitation in the SIF medium. Therefore, the firm is requested to supply dissolution data at rpm from three production batches before a final dissolution specification in SIF is set for this product.

Recommendation:

1. The Bioequivalence studies conducted by Andrx Pharmaceuticals on its 300 mg diltiazem CD capsule, Lot No. 600R001A, comparing it to Marion Merrell Dow's Cardizem[R] 300 mg CD capsule, Lot No. P70056 has been found to be acceptable by the Division of Bioequivalence. Therefore, Andrx's 300 mg diltiazem CD capsule has been deemed bioequivalent to Cardizem[R] CD, 300 mg capsule, manufactured by Marion Merrell Dow.

2. The dissolution testing conducted by Andrx on the 240 mg strength, Lot No. 599R001, the 180 mg strength Lot No. 598R001 and the 120 strength, Lot No. 597R001 is acceptable. The formulations for the 240, 180 and 120 mg capsules are compositionally similar to the 300 mg tablet which underwent a bioequivalence study. The waivers for the 240 mg, 180 mg and 120 mg capsules are granted. Therefore, Andrx's 240 mg, 180 mg and 120 mg diltiazem capsules are deemed bioequivalent to Cardizem[R], 240 mg, 180 mg and 120 mg capsules manufactured by Marion Merrell Dow.

3. The in vitro dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted using USP 23 Apparatus II (paddle) at The product should also be placed in SIF and sampled from 2 to 24 hours. The test product should meet the following interim specifications:

The firm should receive comments 1-6.

Andre Jackson, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG
FT INITIALED YCHUANG /S/ ----: 7/23/96

Concur: /S/ Date: 7/24/96
Keith Chan, Ph.D.
Director
Division of Bioequivalence

ANDA# 74-752 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-652 (Huang, Jackson), Drug File, Division File

AJJ/032296/dbm/WP# 746752SDW.396
1st Draft 3/22/96

Table 51 . In Vitro Dissolution Testing

Drug (Generic Name):Diltiazem
Dose Strength:300 mg
ANDA No.:74-752
Firm:Andrx
Submission Date:September 22, 1995
File Name:74752SDW.995

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle:x RPM:
No. Units Tested: 12
Medium: Volume: 900 ml
Buffer pH (SIF) volume: 900 ml
Specifications:

Reference Drug: Cardizem
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (hr)	Test Product Lot # 600R001(0.1N HCL) Strength(mg) 300			Reference Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
2	1		14.7			
12	11	2	4.3			
18	49	1	4.4			
24 (12)	78	1	1.9			

SIF

Sampling Times (Minutes)	Test Product Lot # 600R001 Strength(mg) 300			Reference Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
2	41	3	2.2			
12	44	1	3.0			
18	85	1	3.4			
24	97	1	1.9			

II. Results of In Vitro Dissolution Testing:						
Sampling Times (hr)	Test Product Lot # 599R001 Strength (mg) 240			Reference Product Lot # Strength (mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
2	1		10.4			
12	12		3.7			
18	40		4.3			
24	75		2.2			
SIF						
Sampling Times (hr)	Test Product Lot # 599R001 Strength(mg) 240			Reference Product Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
2	39		1.7			
12	42		1.7			
18	76		2.6			
24	93		1.4			

II. Results of In Vitro Dissolution Testing:

Sampling Times (hr)	Test Product Lot # 598R001 Strength(mg) 180			Reference Product Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
2	2		16.5			
12	13		4.7			
18	39		4.2			
24	76		1.6			

SIF

Sampling Times (Minutes)	Test Product Lot # 598R001 Strength(mg) 120			Reference Product Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
2	39		4.0			
12	43		4.1			
18	73		5.8			
24	93		2.2			

II. Results of In Vitro Dissolution Testing:

Sampling Times (hr)	Test Product Lot # 597R001 Strength(mg) 120			Reference Product Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
2	1		23.4			
12	13		5.3			
18	39		5.0			
24	76		2.1			

SIF

Sampling Times (Minutes)	Test Product Lot # 597R001 Strength(mg) 120	Reference Product Lot # Strength(mg)

	Mean %	Range	%CV	Mean %	Range	%CV
2	39		3.8			
12	42		3.9			
18	75		3.3			
24	92		2.6			

TABLE 4 ABSOLUTE RECOVERY FOR DILTIAZEM

OF DILTIAZEM, DESACETYLDILTIAZEM AND

DESMETHYLDILTIAZEM IN HUMAN PLASMA

DILTIAZEM

SAMPLE ID	EXTRACTED PEAK HT.	UNEXTRACTED PEAK HT.	%RECOVERY	MEAN %RECOVERY	%CV
REC 1-1			75.2		
REC 1-2			64.6		
REC 1-3			59.1		
REC 1-4			70.2		
REC 1-5			73.4		
REC 1-6			72.1		
	Mean =	567.97		69.1	8.83
REC 4-1			72.5		
REC 4-2			72.2		
REC 4-3			72.6		
REC 4-4			69.5		
REC 4-5			70.6		
REC 4-6			70.3		
	Mean =	7747.88		71.3	1.84
REC 5-1			66.7		
REC 5-2			66.7	—	
REC 5-3			62.3		
REC 5-4			60.9		
REC 5-5			63.9		
REC 5-6			61.3		
	Mea..	32851.01		63.6	4.11
		Overall Rec (%) =		68.0	

TABLE 9 ABSOLUTE RECOVERY FOR DESACETYLDILTIAZEM

OF DILTIAZEM, DESACETYLDILTIAZEM AND

DESMETHYLDILTIAZEM IN HUMAN PLASMA

DESACETYLDILTIAZEM

SAMPLE ID	EXTRACTED PEAK HT.	UNEXTRACTED PEAK HT.	%RECOVERY	MEAN %RECOVERY	%CV
REC 1-1			76.4		
REC 1-2			63.9		
REC 1-3			60.4		
REC 1-4			73.5		
REC 1-5			74.0		
REC 1-6			74.5		
	Mean =	778.28		70.4	9.35
REC 2-1			72.2		
REC 2-2			70.5		
REC 2-3			69.3		
REC 2-4			67.7		
REC 2-5			65.4		
REC 2-6			72.7		
	Mean	10386.48		69.6	4.01
REC 5-1			66.3		
REC 5-2			65.7		
REC 5-3			61.2		
REC 5-4			60.1		
REC 5-5			63.5		
REC 5-6			60.7		
	Mean =	46235.21		62.9	4.21
		Overall Rec (%) =		67.6	

TABLE 5 ABSOLUTE RECOVERY FOR INTERNAL STANDARD

[redacted]S OF DILTIAZEM, DESACETYLDILTIAZEM AND

DESMETHYLDILTIAZEM IN HUMAN PLASMA

INTERNAL STANDARD

SAMPLE ID	EXTRACTED PEAK HT.	UNEXTRACTED PEAK HT.	%RECOVERY	MEAN %RECOVERY	%CV
REC 1-1			88.2		
REC 1-2			79.0		
REC 1-3			72.8		
REC 1-4			85.1		
REC 1-5			85.3		
REC 1-6			85.3		
	Mean =	7479.07		82.6	6.88

TABLE 6

LONG-TERM STABILITY

OF DILTIAZEM IN HUMAN PLASMA

A set of quality control samples in human plasma prepared on 22 September 1994 and stored at -20° C were analyzed on 10 May 1995 versus a frozen curve prepared on 9 May 1995. Results indicate a frozen stability for at least seven months. Data are presented below.

	QC 1 (ng/mL)	QC 2 (ng/mL)	QC 3 (ng/mL)
N			6
Theoretical Concentration	5.00		300
Mean	4.95	72.4	285
S.D.	0.0563	0.94	4.09
%C.V.	1.14	1.30	1.43
% Difference from Theoretical	-0.950	-3.42	-4.91

TABLE 7 FREEZE-THAW STABILITY FOR DILTIAZEM

OF DILTIAZEM, DESACETYLDILTIAZEM AND

DESMETHYLDILTIAZEM IN HUMAN PLASMA

	F/T 1 (ng/mL)	F/T 4 (ng/mL)	F/T 5 (ng/mL)
Theo conc			
CYCLE 1 24BBB			
Mean	4.88	71.5	287
% Diff from theo	-	-4.70	-4.37
CYCLE 2 24BBB			
Mean	4.87	75.9	277
% Diff from theo	-2.53	1.20	-7.81
CYCLE 3 24BBB			
Mean	4.80	71.0	280
% Diff from theo	-4.08	-4.51	-6.66

TABLE 8 ROOM TEMPERATURE STABILITY FOR DILTIAZEM* OF DILTIAZEM, DESACETYLDILTIAZEM AND DESMETHYLDILTIAZEM IN HUMAN PLASMA

	QC 1 (ng/mL)	QC 4 (ng/mL)	QC5 (ng/mL)
16BBB			
N	3	3	3
Theoretical Concentration	5.00	75.0	300
Mean	4.96	73.7	291
S.D.	0.146	2.74	2.00
%C.V.	2.94	3.72	0.687
%Difference from Theoretical	-0.800	-1.73	-3.00

*

TABLE 10

LONG-TERM STABILITY

DESACETYLDILTIAZEM IN HUMAN PLASMA

A set of quality control samples in human plasma prepared on 22 September 1994 and stored at -20° C were analyzed on 10 May 1995 versus a frozen curve prepared on 9 May 1995. Results indicate a frozen stability for at least seven months. Data are presented below.

	QC 1 (ng/mL)	QC 2 (ng/mL)	QC 3 (ng/mL)
N	6	6	6
Theoretical Concentration	5.00	75.0	300
Mean	4.78	73.4	294
S.D.	0.112	0.919	4.58
%C.V.	2.34	1.25	1.56
% Difference from Theoretical	-4.32	-2.08	-1.87

TABLE 11 FREEZE-THAW STABILITY FOR DESACETYLDILTIAZEM OF DILTIAZEM, DESACETYLDILTIAZEM AND DESMETHYLDILTIAZEM IN HUMAN PLASMA

	F/T 1 (ng/mL)	F/T 2 (ng/mL)	F/T 5 (ng/mL)
Theo conc	5.00	75.0	300
CYCLE 1 24BBB-DA			
Mean	4.96	77.3	301
% Diff from theo	-0.706	3.11	0.175
CYCLE 2 24BBB-DA			
Mean	4.93	72.7	286
% Diff from theo	-1.38	-3.02	-4.74
CYCLE 3 24BBB-DA			
Mean	5.07	75.0	291
% Diff from theo	1.40	-0.0239	-3.04

TABLE 12 ROOM TEMPERATURE STABILITY FOR DESACETYLDILTIAZEM* OF DILTIAZEM, DESACETYLDILTIAZEM AND DESMETHYLDILTIAZEM IN HUMAN PLASMA

	QC 1 (ng/mL)	QC 2 (ng/mL)	QC5 (ng/mL)
16BBB-DA			
N	3	3	3
Theoretical Concentration	5.00	75.0	300
Mean	4.95	71.6	289
S.D.	0.0265	2.17	4.51
%C.V.	0.535	3.03	1.56
%Difference from Theoretical	-1.00	-4.53	-3.66

TABLE 13 ABSOLUTE RECOVERY FOR DESMETHYLDILTIAZEM OF DILTIAZEM, DESACETYLDILTIAZEM AND DESMETHYLDILTIAZEM IN HUMAN PLASMA

DESMETHYLDILTIAZEM

SAMPLE ID	EXTRACTED PEAK HT.	UNEXTRACTED PEAK HT.	%RECOVERY	MEAN %RECOVERY	%CV
REC 1-1			72.5		
REC 1-2			56.0		
REC 1-3			56.5		
REC 1-4			66.7		
REC 1-5			66.0		
REC 1-6			67.2		
	Mean =	623.31		64.1	10.2
REC 3-1			65.8		
REC 3-2			61.4		
REC 3-3			60.9		
REC 3-4			66.0		
REC 3-5			63.7		
REC 3-6			48.4		
	Mean =	8844.45		61.0	10.7
REC 5-1			62.8		
REC 5-2			62.5		
REC 5-3			58.9		
REC 5-4			56.6		
REC 5-5			60.0		
REC 5-6			57.6		
	Mean =	36740.96		59.7	4.26
			Overall Rec (%) =	61.6	

TABLE 14

LONG-TERM STABILITY

F DESMETHYLDILTIAZEM IN HUMAN PLASMA

set of quality control samples in human plasma prepared on
ıtember 1994 and stored at -20° C were analyzed on 10 May 1995 versus a
ı curve prepared on 9 May 1995. Results indicate a frozen stability for
ıst seven months. Data are presented below.

	QC 1 (ng/mL)	QC 2 (ng/mL)	QC 3 (ng/mL)
N	6	6	6
Theoretical Concentration	5.00	75.0	300
Mean	5.02	70.5	286
S.D.	0.0952	0.957	7.35
%C.V.	1.90	1.36	2.57
% Difference from Theoretical	0.437	-5.99	-4.52

Appendix E

TABLE 16 ROOM TEMPERATURE STABILITY FOR DESMETHYLDILTIAZEM*

S OF DILTIAZEM, DESACETYLDILTIAZEM AND

DESMETHYLDILTIAZEM IN HUMAN PLASMA

	QC 1 (ng/mL)	QC 3 (ng/mL)	QC5 (ng/mL)
16BBB-DM			
N	3	3	3
Theoretical Concentration	5.00	75.0	300
Mean	5.34	76.3	294
S.D.	0.266	2.14	5.86
%C.V.	4.98	2.80	1.99
%Difference from Theoretical	6.80	1.73	-2.00

perature

TABLE 17 24 HOUR EXTRACT STABILITY FOR DILTIAZEM*

OF DILTIAZEM, DESACETYLDILTIAZEM AND

DESMETHYLDILTIAZEM IN HUMAN PLASMA

	QC 1 (ng/mL)	QC 4 (ng/mL)	QC5 (ng/mL)
16BBB			
N	3	3	3
Theoretical Concentration	5.00	75.0	300
Mean	4.99	74.6	300
S.D.	0.121	3.20	3.06
%C.V.	2.42	4.29	1.02
%Difference from Theoretical	-0.200	-0.533	0.00

TABLE 18 24 HOUR EXTRACT STABILITY FOR DESACETYLDILTIAZEM* OF DILTIAZEM, DESACETYLDILTIAZEM AND DESMETHYLDILTIAZEM IN HUMAN PLASMA

	QC 1 (ng/mL)	QC 2 (ng/mL)	QC5 (ng/mL)
16BBB-DA			
N	3	3	3
Theoretical Concentration	5.00	75.0	300
Mean	5.28	73.3	298
S.D.	0.263	0.950	1.15
%C.V.	4.98	1.27	0.386
%Difference from Theoretical	5.60	-2.27	-0.667

TABLE 19 24 HOUR EXTRACT STABILITY FOR DESMETHYLDILTIAZEM* OF DILTIAZEM, DESACETYLDILTIAZEM AND DESMETHYLDILTIAZEM IN HUMAN PLASMA

	QC 1 (ng/mL)	QC 3 (ng/mL)	QC5 (ng/mL)
16BBB-DM			
N	3	3	3
Theoretical Concentration	5.00	75.0	300
Mean	5.80	79.1	301
S.D.	0.259	2.70	2.31
%C.V.	4.47	3.41	0.767
%Difference from Theoretical	16.0	5.47	0.333

Table 23

Adverse experiences for subjects in single dose fasting study

Subject	Assigned Drug*	Adverse Event	Severity	Date of Onset	Hours Post-Dose	Time (Hrs) Duration	Comments
	R	Headache	Mild	04/01/95	5.25	1.5	Subject rested; change in severity; possibly drug related.
	R	Headache	Moderate	04/01/95	6.75	4.5	Subject rested; change in severity; possibly drug related.
	R	Headache	Mild	04/01/95	11.25	1	No therapy required; possibly drug related.
	R	Headache	Moderate	04/01/95	14.5	9.75	No therapy required; change in severity; possibly drug related.
	R	Headache	Mild	04/02/95	24.25	26.5	No therapy required; possibly drug related.
	T	Headache	Moderate	04/08/95	4.75	3.5	Subject rested; possibly drug related.
	T	Headache	Moderate	04/08/95	6.75	3	No therapy required; change in severity; possibly drug related.
	T	Headache	Mild	04/08/95	9.75	5	No therapy required; possibly drug related.
	R	Dermal swelling LRQ	Mild	04/09/95	24.5	72	Subject's personal physician diagnosed a muscle strain; not drug related.
	R	Nausea	Mild	04/01/95	4	10 min.	Subject rested and cool cloth applied to forehead; possibly drug related.
	R	Emesis x 1	Mild	04/01/95	4	10 min.	Subject rested and cool cloth applied to forehead; possibly drug related.
	R	Headache	Mild	04/08/95	4.5	5.75	No therapy required; possibly drug related.
	T	Nausea	Moderate	04/01/95	4.25	2.25	Subject rested in supine position with cool cloth applied to forehead; possibly drug related.
	T	Emesis x 1	Moderate	04/01/95	4.25	5 minutes	Possibly drug related.

* Test Drug
Reference Drug

Table 24

Diltiazem HCl 300 mg. Capsule

Early/Late Blood Draw Times

Subject	Period	Day	Post-Dose Hour	# Minutes Early/Late	Reason
	1	3	48	60 - early	School
	1	3	48	60 - early	School
	2	3	48	No sample	Subject did not return
	1	3	48	16 - early	School
	1	3	48	10 - early	Work
	2	3	48	43 - late	Overslept
	2	3	48	25 - late	Overslept
	1	3	48	50 - early	Work
	2	3	48	25 - late	Overslept
	1	3	48	30 - early	School
	1	3	48	27 - early	Work
	1	3	48	7 - late	Traffic
	2	3	48	29 - late	Overslept
	2	3	48	23 - late	Overslept
	1	3	48	3 - late	Overslept
	2	3	48	17 - late	Overslept
	1	3	48	3 - late	Overslept
	2	3	48	5 - late	Overslept
	1	3	48	60 - early	School
	1	3	48	60 - early	School
	2	1	4	45 - late	Original tube broke while centrifuging; another sample drawn 45 minutes late
	2	1	16	5 - late	Difficult phlebotomy

Table 35

Adverse effects observed in the steady-state study

Subject	Assigned Drug*	Adverse Event	Severity	Date of Onset	Hours Post-Dose	Time (Hrs) Duration	Comments
	R	Headache	Mild	07/10/95	2	65	No therapy required. Possibly drug related.
	T	Headache	Mild	07/10/95	2	6	No therapy required. Possibly drug related.
	T	Headache	Mild	07/11/95	2	6	No therapy required. Possibly drug related.
	T	Shoulder Pain	Mild	07/11/95	9	39	No therapy required. Unlikely drug related.
	T	Knee Pain	Mild	07/11/95	9	39	No therapy required. Unlikely drug related.

Table 35 (cont'd)

Subject	Assigned Drug*	Adverse Event	Severity	Date of Onset	Hours Post-Dose	Time (Hrs) Duration	Comments
	T	Headache	Moderate	07/10/95	3.75	17	No therapy required. Possibly drug related.
	T	Headache	Mild	07/11/95	20.75	26	No therapy required. Possibly drug related.
	T	Headache	Moderate	07/10/95	7.75	7	No therapy required. Possibly drug related.
	R	PR Prolongation	Moderate	07/15/95	23.25	2.75	Subject was dropped from the study. Probably drug related.
	T	Headache	Mild	07/10/95	0.75	14	No therapy required. Possibly drug related.
	T	Headache	Moderate	07/10/95	2.75	13	No therapy required. Possibly drug related.
	R	Low back pain	Mild	07/10/95	0.5	70	No therapy required. Unlikely drug related.
	T	Headache	Moderate	07/29/95	1.75	23	No therapy required. Possibly drug related.
	R	Headache	Moderate	07/13/95	5.75	8	No therapy required. Possibly drug related.
	T	Headache	Severe	07/10/95	5.5	68	No therapy required. Possibly drug related.
	T	Nausea	Moderate	07/10/95	14.5	19	No therapy required. Possibly drug related.

Table 35 (cont'd)

004813

Subject	Assigned Drug*	Adverse Event	Severity	Date of Onset	Time (Hrs) Hours Post-Dose	Time (Hrs) Duration	Comments
	T	Headache	Mild	07/13/95	1.5	96	No therapy required. Possibly drug related.
	R	Headache	Mild	07/24/95	4.5	3	No therapy required. Possibly drug related.
	R	Headache	Severe	07/24/95	7.5	10	No therapy required. Possibly drug related.
	R	Nausea	Mild	07/24/95	10.5	181	No therapy required. Possibly drug related.
	R	Headache	Moderate	07/25/95	17.5	174	Subject took 3 doses of 500 mg acetaminophen on 7/25/95; 2 doses of 500 mg acetaminophen on 7/26/95; 1 dose of 500 mg acetaminophen on 7/27/95 and 7/28/95, respectively. Possibly drug related.
	R	Headache	Mild	07/10/95	5.5	8	No therapy required. Possibly drug related.

Drug

Table 36

Diltiazem HCl 300 mg. Capsule

for Multiple Dose Study

Subject	Period	Day	Post-Dose Hour	# Minutes Late	Reason
	1	6	16	3	Difficult phlebotomy
	1	7	24	3	Difficult phlebotomy

Table 46

Adverse effects during Post-Pradnial single dose study

Subject	Assigned Drug*	Adverse Event	Severity	Date of Onset	Hours Post-Dose	Time (Hrs) Duration	Comments
	T	Headache	Moderate	05/17/95	15	14	Cold compress. Possibly drug related.
	T	Headache	Moderate	05/24/95	8	16	No therapy required. Possibly drug related.
	R	Headache	Moderate	05/31/95	5	19	No therapy required. Possibly drug related.
	T	Headache	Moderate	05/24/95	12.5	16.5	No therapy required. Possibly drug related.
	T	Nose bleed	Mild	06/01/95	39	< 1 min.	No therapy required. Unlikely drug related.
	R	Headache	Severe	05/31/95	16.25	7.5	Subject took one 200 mg. ibuprofen. Possibly drug related.

002429

Subject	Assigned Drug*	Adverse Event	Severity	Date of Onset	Hours Post-Dose	Time (Hrs) Duration	Comments
	T	Headache	Mild	05/17/95	13.75	10	No therapy required. Possibly drug related.
	T	Nausea	Mild	05/17/95	9.75	1.5	Subject rested; no other therapy required. Possibly drug related.
	T	Nose bleed	Mild	06/01/95	34.75	5 min.	Applied pressure. No other therapy required. Unlikely drug related.
	R	Headache	Moderate	05/17/95	11.5	17.5	Subject rested; cold compress. No other therapy required. Unlikely drug related.

]
:e Drug

Subject	Assigned Drug*	Adverse Event	Severity	Date of Onset	Hours Post-Dose	Time (Hrs) Duration	Comments
	R	Sweating	Moderate	05/24/95	0.75	8.5	A single dose of 2 x 200 mg ibuprofen given for this AE and the following AE of sinus congestion. Unlikely drug related.
	R	Sinus congestion	Moderate	05/24/95	0.75	8.5	See above.
	R	Headache	Moderate	05/24/95	10.75	7	A single dose of 2 x 200 mg ibuprofen given for this AE and the following AEs of sore throat, chills, and sinus congestion. Possibly drug related.
	R	Sore throat	Moderate	05/24/95	10.75	7	Not drug related.
	R	Chills	Moderate	05/24/95	10.75	7	Not drug related.
	R	Sinus congestion	Moderate	05/24/95	10.75	7	Not drug related.
	R	Headache	Mild	05/25/95	17.75	13	No therapy required. Possibly drug related.
	R	Sore throat	Mild	05/25/95	17.75	13	No therapy required. Not drug related.
	R	Chills	Mild	05/25/95	17.75	13	No therapy required. Not drug related.
	R	Sinus congestion	Mild	05/25/95	17.75	13	No therapy required. Not drug related.
	T	Headache	Moderate	05/17/95	4.75	3	Subject rested; no other therapy required. Possibly drug related. Change in severity.
	T	Headache	Mild	05/17/95	7.75	4	Subject rested; no other therapy required. Possibly drug related. Change in severity.
	T	Headache	Moderate	05/17/95	11.75	2	Subject rested; no other therapy required. Possibly drug related. Change in severity.

Table 52

Dose Proportionality of Pellets and Compositions Between Biobatch (300 mg) and Other Strengths of Diltiazem Hydrochloride Once-A-Day Extended-release Capsule

Pellet Types \ Fill Weight Ratio		300 mg		240 mg		180 mg		120 mg	
		Wt (mg)	%	Wt (mg)	%	Wt (mg)	%	Wt (mg)	%
SR 1 Pellets									
SR 2 Pellets									
Capsule size									
Final Compositions									
Sugar									
Diltiazem HCl, USP									
Ethylcellulose,									
Polysorbate									
Eudragit									
Eudragit									
Talc, USP									
Acetyl tributyl citrate									
	subtotal								
Gelatin,									
	Total	696.9		557.2		437.0		285.0	

TABLE 15 FREEZE-THAW STABILITY FOR DESMETHYLDILTIAZEM OF DILTIAZEM, DESACETYLDILTIAZEM AND DESMETHYLDILTIAZEM IN HUMAN PLASMA

	F/T 1 (ng/mL)	F/T 3 (ng/mL)	F/T 5 (ng/mL)
Theo conc	5.00	75.0	300
CYCLE 1 24BBB-DM			
Mean	5.42	79.6	302
% Diff from theo	8.39	6.07	0.536
CYCLE 2 24BBB-DM			
Mean	5.30	77.5	288
% Diff from theo	5.99	3.30	-3.94
CYCLE 3 24BBB-DM			
Mean	5.44	77.4	287
% Diff from theo	8.74	3.17	-4.34

Div

ANDA 74-752

Andrx Pharmaceuticals, Inc.
Attention: David A. Gardner
4001 S.W. 47th Avenue, # 201
Fort Lauderdale FL 33314

JAN -6 1997

Dear Sir:

This letter supersedes our previous letter dated October 31, 1996, which specified that the Division of Bioequivalence has completed their review and has no further questions. This letter corrects item number 2.

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Diltiazem Hydrochloride Extended-release Capsules 120 mg, 180 mg, 240 mg, and 300 mg.

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

2. The following interim dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted using USP 23 Apparatus II (paddle) at in **The testing should also be conducted simultaneously at in SIF for 24 hours.** The test product should meet the following specifications:

Time	Acid	Time	SIF
2 hr			

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Rabindra Patnaik, Ph.D.
Acting Director,
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-752

Andrx Pharmaceuticals, Inc.
Attention: David A. Gardner
4001 S.W. 47th Avenue, # 201
Fort Lauderdale FL 33314

OCT 31 1996

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Diltiazem Hydrochloride Extended-release Capsules 120 mg, 180 mg, 240 mg, and 300 mg.

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

2. The following interim dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted using USP 23 Apparatus II (paddle) at in **The speed should be reduced to pm and the medium changed to simulated intestinal fluid (SIF) and sampled from 4 hr (based upon time zero in acid) to 24 hours.** The test product should meet the following specifications:

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

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Rabindra Patnaik, Ph.D.
Acting Director,
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ANDA 74-752

Andrx Pharmaceuticals, Inc.
Attention: David A. Gardner
4001 S.W. 47th Avenue, # 201
Fort Lauderdale FL 33314

OCT 31 1996

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Diltiazem Hydrochloride Extended-release Capsules 120 mg, 180 mg, 240 mg, and 300 mg.

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

2. The following interim dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted using USP 23 Apparatus II (paddle) at m in . **The speed should be reduced to . and the medium changed to simulated intestinal fluid (SIF) and sampled from 4 hr (based upon time zero in acid) to 24 hours.** The test product should meet the following specifications:

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Rabindra Patnaik, Ph.D.
Acting Director,
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OCT 28 1996

Diltiazem HCL
300 mg CD Capsule
240 mg CD Capsule
180 mg CD Capsule
120 mg CD Capsule
ANDA# 74752
Reviewer: Andre J. Jackson
WP #74752A.096

Andrx Pharmaceuticals
Fort Lauderdale, Florida
Submission Dated:
October 8, 1996

REVIEW OF ADDENDUM TO A SINGLE DOSE FASTING, MULTIPLE DOSE STEADY-STATE, POST-PRANDIAL SINGLE DOSE BIOEQUIVALENCE STUDIES FOR 300 MG CD CAPSULE AND DISSOLUTION AND WAIVER REQUESTS FOR 240 MG, 180 MG AND 120 MG CAPSULES

BACKGROUND:

The firm submitted a study on September 22, 1995 on their CD capsule which was found to be acceptable to the Division of Bioequivlence pending the resolution of an issue related to the paddle speed for the dissolution testing. The current submission is the firm's submission of dissolution data to address those areas of concern.

FDA Comment:

1. The firm has conducted their dissolution studies in and in SIF using the paddle at m which are similar to the conditions used by the innovator. However, The Division of Bioequivalence considers the pm speed to provide excessive agitation in the SIF medium. Therefore, the firm is requested to supply dissolution data at pm from three production batches before a final dissolution specification in SIF is set for this product.

Firm's Reply-See attached dissolution data tables.

FDA Reply:

The firms reply indicates that the study is more discriminating in describing the dissolution of their products.

Results

Dissolution

The dissolution study for diltiazem was done as follows:

Apparatus:	Paddle,
Media:	buffer pH 3IF)
Volume:	900 ml
No. of Units Analyzed:	12
Specifications:	Interim: Tim 2 hr 2 hr 12 hr 18 hr 24 hr
Assay:	
Wavelength:	

The results are presented in Table 1.

Recommendation:

1. The dissolution testing conducted by Andrx on the 240 mg strength, Lot No. 599R001, the 180 mg strength Lot No. 598R001 and the 120 strength, Lot No. 597R001 is acceptable. The formulations for the 240, 180 and 120 mg capsules are compositionally similar to the 300 mg capsule which underwent a bioequivalence study. The waivers for the 240 mg, 180 mg and 120 mg capsules are granted. Therefore, Andrx's 240 mg, 180 mg and 120 mg diltiazem HCL capsules are deemed bioequivalent to Cardizem®, 240 mg, 180 mg and 120 mg capsules manufactured by Marion Merrell Dow.

2. The in vitro dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted using USP 23 Apparatus II (paddle) at 1 pm in hr. **The speed should be reduced to pm and the medium changed to SIF and sampled from 4 hr(based upon time zero in acid) to 24 hours.** The test product should meet the following specifications:

/S/

Andre Jackson, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG
FT INITIALED YCHUANG /S/ Date: 10/9/96

Concur: /S/ Date: 10/28/96
Keith Chan, PhD.
Director
Division of Bioequivalence

ANDA# 74-752 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-652 (Huang, Jackson), Drug File, Division File

Table 1 . In Vitro Dissolution Testing

Drug (Generic Name):Diltiazem
Dose Strength:300 mg
ANDA No.:74-752
Firm:Andrx
Submission Date:October 8, 1996
File Name:74752A.O96

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle:x RPM:75
No. Units Tested: 12
Medium: 0.1 N HCL Volume: 900 ml
Buffer pH 7.5 (SIF) volume: 900 ml
Specifications:
Proposed by firm:

Reference Drug: Cardizem
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (hr)	Test Product Lot # 600R001(0.1N HCL) Strength(mg) 300			Referenc Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
2	1		13.7			
12	11		3.8			
18	51		4.0			
24	78		1.1			

SIF

Sampling Times (Minutes)	Test Product Lot # 600R001 Strength(mg) 300			Reference Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
2	38		14.7			
12	45		1.6			
18	84		2.7			
24	97		1.3			

II. Results of In Vitro Dissolution Testing:

Sampling Times (hr)	Test Product Lot # 599R001 Strength (mg) 240			Reference Product Lot # Strength (mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
2	1		20.4			
12	11		4.6			
18	43		6.3			
24	78		1.9			

Sampling Times (hr)	Test Product Lot # 599R001 Strength(mg) 240			Reference Product Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
2	33		24.1			
12	43		2.1			
18	76		6.7			
24	92		8.3			

II. Results of In Vitro Dissolution Testing:0.						
Sampling Times (hr)	Test Product Lot # 598R001 Strength(mg) 180			Reference Product Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
2	2		12.6			
12	12		4.4			
18	43		6.3			
24	79		1.7			
SIF						
Sampling Times (Minutes)	Test Product Lot # 598R001 Strength(mg) 180			Reference Product Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
2	33		23.5			
12	44		2.1			
18	74		2.3			
24	92		1.6			

II. Results of In Vitro Dissolution Testing:						
Sampling Times (hr)	Test Product Lot # 597R001 Strength(mg) 120			Reference Product Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
2	2		12.1			
12	11		6.3			
18	43		6.3			
24	77		2.9			
SIF						
Sampling Times (Minutes)	Test Product Lot # 597R001 Strength(mg) 120			Reference Product Lot # Strength(mg)		

	Mean %	Range	%CV	Mean %	Range	%CV
2	34		18.7			
12	41		3.9			
18	71		5.9			
24	88		3.4			

ANDA 74-752

Andrx Pharmaceuticals, Inc.
Attention: David A. Gardner
4001 S.W. 47th Avenue, # 201
Fort Lauderdale FL 33314

JAN -6 1997

Dear Sir:

This letter supersedes our previous letter dated October 31, 1996, which specified that the Division of Bioequivalence has completed their review and has no further questions. This letter corrects item number 2.

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Diltiazem Hydrochloride Extended-release Capsules 120 mg, 180 mg, 240 mg, and 300 mg.

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

2. The following interim dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted using USP 23 Apparatus II (paddle) at pm in **The testing should also be conducted simultaneously at m in SIF for 24 hours.** The test product should meet the following specifications:

Time	Acid	Time	SIF
2 hr			

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Rabindra Patnaik, Ph.D.
Acting Director,
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JAN 2 1997

Diltiazem HCL
300 mg CD Capsule
240 mg CD Capsule
180 mg CD Capsule
120 mg CD Capsule
ANDA# 74752
Reviewer: Andre J. Jackson
WP #74752A-096

Andrx Pharmaceuticals
Fort Lauderdale, Florida
Submission Dated:
October 8, 1996

ADDENDUM TO A SINGLE DOSE FASTING, MULTIPLE DOSE STEADY-STATE, POST-PRANDIAL SINGLE DOSE BIOEQUIVALENCE STUDIES FOR 300 MG CD CAPSULE AND DISSOLUTION AND WAIVER REQUESTS FOR 240 MG, 180 MG AND 120 MG CAPSULES

BACKGROUND:

The firm submitted a study on September 22, 1995 on their CD capsule which was found to be acceptable to the Division of Bioequivlence pending the resolution of issues related to the paddle speed and conditions for the dissolution testing. A letter was sent to the firm based upon their October 8, 1996 submission in which issues related to paddle speed were resolved. The only issue remaining to be resolved related to dissolution conditions since the firm did not change media but conducted the studies for acid and base in parallel. The dissolution recommendation in the reply to the October 8, submission stated:

> The in vitro dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted using USP 23 Apparatus II (paddle) at rpm in r. **The speed should be reduced to rpm and the medium changed to SIF and sampled from 4 hr(based upon time zero in acid) to 24 hours.** The test product should meet the following specifications:

In a telephone conversation with Project Manager (see the attached telephone record, 11/12/96), the firm has indicated that since their product is a beaded capsule that once they have capsule release there is no way of removing product to then place it in the SIF which precludes a quantitative transfer from acidic to the basic medium.

Therefore, the firm's proposed procedure for conducting dissolution studies in parallel is:

Apparatus:	Paddle, 75 RPM
Media:	0.1N HCL-sampling to 2 hrs buffer pH 7.5(SIF)-sampling to 24 hrs
Volume:	900 ml
No. of Units Analyzed:	12

Comment:

1. The dissolution data previously submitted by the firm, for separate dissolution studies done in acid and SIF, on October 8, 1996 is acceptable and indicates that the ___ rpm speed is more discriminating.

Recommendation

1. The Bioequivalence studies conducted by Andrx Pharmaceuticals on its 300 mg diltiazem CD capsule, Lot No. 600R001A, comparing it to Marion Merrell Dow's Cardizem^{R} 300 mg CD capsule, Lot No. P70056 has been found to be acceptable by the Division of Bioequivalence previously on October 7, 1996. Therefore, Andrx's 300 mg diltiazem CD capsule has been deemed bioequivalent to Cardizem^{R} CD, 300 mg capsule, manufactured by Marion Merrell Dow.

2. The dissolution testing conducted by Andrx on the 300 mg capsule, Lot No. 600R001A, is acceptable. The dissolution testing conducted by Andrx on the 240 mg strength, Lot No. 599R001, the 180 mg strength Lot No. 598R001 and the 120 strength, Lot No. 597R001 is also acceptable. The formulations for the 240, 180 and 120 mg capsules are compositionally similar to the 300 mg capsule which underwent a bioequivalence study. The waivers for the 240 mg, 180 mg and 120 mg capsules are granted. Therefore, Andrx's 240 mg, 180 mg and 120 mg diltiazem HCL capsules are deemed bioequivalent to Cardizem^{R}, 240 mg, 180 mg and 120 mg capsules manufactured by Marion Merrell Dow.

3. The in vitro dissolution testing should be incorporated into

the firm's manufacturing controls and stability program. The dissolution testing should be conducted using USP 23 Apparatus II (paddle) at 75 rpm in 0.1N HCL for 2 hr. The testing should also be conducted simultaneously at 75 rpm in SIF for 24 hours. The test product should meet the following specifications:

Time
2 hr

Andre Jackson, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG
FT INITIALED YCHUANG

Date: 12/23/96

Concur:

Date: 12/23/96

Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

ANDA# 74-752 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-652 (Huang, Jackson), Drug File, Division File

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74-752

ADMINISTRATIVE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: December 31, 1992
See OMB Statement on Page 3.

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	**NDA/ANDA NO. ASS.**

NOTE: No application may be filed unless a completed application form has been received (21 CFR Part 314).

NAME OF APPLICANT
Andrx Pharmaceuticals, Inc.

DATE OF SUBMISSION
May28, 1997

ADDRESS (Number, Street, City, State and Zip Code)
4001 S.W. 47th Avenue, #201
Fort Lauderdale, FL 33314

TELEPHONE NO. (Include Area Code)
(954) 581-7500

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued)
74-752

DRUG PRODUCT

ESTABLISHED NAME (e.g., USP/USAN)
DILTIAZEM HYDROCHLORIDE EXTENDED-RELEASE

PROPRIETARY NAME (If any)

CODE NAME (If any)

CHEMICAL NAME

DOSAGE FORM
Capsules

ROUTE OF ADMINISTRATION
Oral

STRENGTH(S)
120mg, 180mg 240mg & 300mg

PROPOSED INDICATIONS FOR USE
Indicated for the treatment of hypertension. May be used alone or in combination with other antihypertensive medications. Indicated for the management of chronic stable angina and angina due to coronary artery spasm.

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), AND DRUG MASTER FILES (21 CFR 314.420) REFERRED TO IN THIS APPLICATION:

MAY 30 199

INFORMATION ON APPLICATION

TYPE OF APPLICATION (Check one)

☐ THIS SUBMISSION IS A FULL APPLICATION (21 CFR 314.50) ☒ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG
Cardizem CD

HOLDER OF APPROVED APPLICATION
Marion Merrel Dow, Inc.

TYPE SUBMISSION (Check one)

☐ PRESUBMISSION ☒ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION
☐ ORIGINAL APPLICATION ☐ RESUBMISSION (Facsimile)

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION (e.g., Part 314.70(b)(2)(iv)) _____

PROPOSED MARKETING STATUS (Check one)

☐ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT (Rx) ☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT (OTC)

000001

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

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TELEPHONE NO. (Include Area Code)
(954) 581-7500

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Fort Lauderdale, FL 33314

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued)
74-752

DRUG PRODUCT

ESTABLISHED NAME (e.g., USP/USAN)
DILTIAZEM HYDROCHLORIDE EXTENDED-RELEASE

PROPRIETARY NAME (If any)

CODE NAME (If any)

CHEMICAL NAME

DOSAGE FORM
Capsules

ROUTE OF ADMINISTRATION
Oral

STRENGTH(S)
120mg, 180mg 240mg & 300mg

PROPOSED INDICATIONS FOR USE
Indicated for the treatment of hypertension. May be used alone or in combination with other antihypertensive medications. Indicated for the management of chronic stable angina and angina due to coronary artery spasm.

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), AND DRUG MASTER FILES (21 CFR 314.420) REFERRED TO IN THIS APPLICATION:

INFORMATION ON APPLICATION

TYPE OF APPLICATION (Check one)

☐ THIS SUBMISSION IS A FULL APPLICATION (21 CFR 314.50) ☒ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG
Cardizem CD

HOLDER OF APPROVED APPLICATION
Marion Merrel Dow, Inc.

TYPE SUBMISSION (Check one)

☐ PRESUBMISSION ☒ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION
☐ ORIGINAL APPLICATION ☐ RESUBMISSION (Facsimile)

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION (e.g., Part 314.70(b)(2)(iv)) _____

PROPOSED MARKETING STATUS (Check one)

☐ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT (Rx) ☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT (OTC)

000001

CONTENTS OF APPLICATION

This application contains the following items: *(Check all that apply)*

	1. Index
	2. Summary (21 CFR 314.50 (c))
	3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d) (1))
	4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)
	b. Methods Validation Package (21 CFR 314.50 (e) (2) (i))
■	c. Labeling (21 CFR 314.50 (e) (2) (ii))
	i. draft labeling *(4 copies)*
	ii. final printed labeling (12 copies)
	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))
	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))
	7. Microbiology section (21 CFR 314.50 (d) (4))
	8. Clinical data section (21 CFR 314.50 (d) (5))
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))
	10. Statistical section (21 CFR 314.50 (d) (6))
	11. Case report tabulations (21 CFR 314.50 (f) (1))
	12. Case reports forms (21 CFR 314.50 (f) (1))
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. OTHER *(Specify)* Facsimile Amendment

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
David A. Gardner	David A. Gardner	May 28, 1997

ADDRESS (Street, City, State, Zip Code)	TELEPHONE NO. *(Include Area Code)*
4001 S.W. 47th Avenue, #201 ort Lauderdale, FL 33314	(954) 581-7500

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec.1001.)

000002

RECORD OF TELEPHONE CONVERSATION

I initiated a call to Andrx Pharmaceuticals, Inc. and spoke with Mr. David Gardner. I informed him of the following labeling comments regarding the submission dated May 28, 1997.

Labeling Deficiencies:

INSERT

The package insert is satisfactory in printer's proof. However, before submitting final printed insert labeling, please make the following minor and editorial changes.

a. DESCRIPTION
   i. Revise the molecular formula to consist with USP 23.
   ii. You may delete the following from your list inactive ingredients, _____

b. CLINICAL PHARMACOLOGY (Hemodynamic and Electrophysiologic Effects)
   In the third sentence of the fourth paragraph, delete the extra spaces between, "day" and "dosage".

Prepare and submit twelve copies of final printed container labels.

In addition, I informed Mr. Gardner to submit a total of twelve copies of printer's proof insert labeling and that the above revisions were not required for tentative approval. He expressed his appreciated for the information received regarding this ANDA.

DATE 6/17/97

ANDA NUMBER
74-752

IND NUMBER

TELECON

INITIATED BY **MADE**
_ **APPLICANT/ SPONSOR** _ **BY TELE.**
_x_ **FDA** _ **IN PERSON**

PRODUCT NAME Diltiazem Hydrochloride Extended-release Capsules USP, (Once-a-dayDosage) 120mg, 180mg, 240mg&300mg

FIRM NAME Andrx Pharmaceuticals, Inc.

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Mr. David Gardner

SIGNATURE

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, these drug products 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 W. Ames, Project Manager, at (301) 827-5849, for further instructions.

Sincerely yours,

/S/ 9/14/87

Roger L. Williams, M.D.
Deputy Center Director
for Pharmaceutical Science
Center for Drug Evaluation and Research

MAY 19 1997

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

ANDA Number: 74-752

Date of Submission: February 27, 1997

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

Labeling Deficiencies:

1. CONTAINER

   Upon further review, we request that you delete the following text from your container labels:

   AB to Cardizem CD®

   Cardizem CD® is a registered trademark of Hoechst Marion Rousell

   Diltiazem hydrochloride Extended-release Capsules USP which exhibit different pharmacokinetics are also marketed. Please confirm you are dispensing the prescribed formulation.

2. INSERT

   a. General Comment

      Delete the text "a marketed" prior to the established name, "Diltiazem hydrochloride Extended-release Capsules (Once A Day Dosage)", where it appears throughout the labeling.

   b. DESCRIPTION

      i. Increase the print size of the structural and molecular formulas. We find both of them difficult to read.

      ii. Include the dyes in the imprinting ink in your list of inactive ingredients.

c. ADVERSE REACTIONS

i. To increase the clarity and readably of the table we encourage you to use bold print throughout the entire table.

ii. In the first sentence following the table revise "diltiazem hydrochloride once-a day" to read "Diltiazem hydrochloride Extended-release Capsules (Once A Day Dosage)"

d. OVERDOSAGE

i. Bradycardia

Delete the terminal zero following the decimal point.
["1 mg" instead of 1.0 mg"].

ii. Hypotension

Revise "Levarterenol bitartrate" to read "norepinephrine".

e. DOSAGE AND ADMINISTRATION (Concomitant Use With Other Cardiovascular Agents)

i. Sublingual NTG

A). Revise "Sublingual NTG" to read "Sublingual Nitroglycerin".

B). In the first sentence, revise "diltiazem hydrochloride" to read "Diltiazem hydrochloride Extended-release Capsules (Once A Day Dosage)".

ii. Prophylactic Nitrate Therapy

See comment d(i)(B) above.

iii. Antihypertensives

Revise "(once-a-day)" to read "(Once A Day Dosage)".

f. HOW SUPPLIED

i. We note you have listed a package size of in this section. However, you have not submitted any information regarding the container and closure system for this package size. Please delete from your HOW

SUPPLIED section and/or submit the required data.

ii. We acknowledge your comment regarding your package configuration of However, it is not acceptable for marketing as submitted. Therefore, delete from your HOW SUPPLIED section.

iii. Upon further review we request that you delete the following paragraph:

Diltiazem Hydrochloride Extended-release Capsules USP which exhibit different pharmacokinetics are also marketed. Please confirm you are dispensing the prescribed formulation.

Please revise your labels and labeling, as instructed above, and submit in draft.

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.

/S/

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

ANDA: 74-752 FIRM: Andrx Pharmaceuticals, Inc.
DRUG PRODUCT: Diltiazem Hydrochloride Extended-release Capsules

FACSIMILE Deficiencies

Labeling Deficiencies

All comments and corrections that were suggested regarding the labels for the containers and the insert have been made.

Copies of approved label copy for all strengths and all package sizes are attached at pages 4 through 7. Included at pages 8 through 15 is a side-by-side comparison of the label copy from the facsimile amendment which was submitted on February 27, 1997 vs. the revised label copy being submitted with this facsimile amendment. Also included is a draft label for each package size of each strength that will be marketed.

Attached at pages 16 through 23 is a copy of the revised insert. At pages 24 through 36 is a side-by-side comparison of the insert submitted with the facsimile amendment on February 27, 1997 vs. the insert being submitted with this facsimile amendment. Also included is a draft "printer's proof" for the insert.

Please Note:

As agreed in a teleconference on May 7, 1997, the will be used only for of product.

ANDA 74-752

Andrx Pharmaceuticals, Inc.
Attention: David A. Gardner
4001 S.W. 47th Avenue, Suite 201
Ft. Lauderdale, FL 33314

NOV 17 1995

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated September 22, 1995, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Diltiazem Hydrochloride Extended-release Capsules, 120 mg, 180 mg, 240 mg and 300 mg.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

> You are required to completely package your exhibit batches in containers proposed for marketing. Partial packaging, packaging into bulk storage containers, or a packaging for which you are not seeking approval is not acceptable unless a protocol has been submitted and approved prior to submission of the application. Please provide documentation to confirm that the portion of the test batches packaged in the containers proposed for marketing are representative of the entire batch. Such documentation should include testing results for in-process or packaged product that demonstrate homogeneity of the manufactured product. Please refer to the letters to the industry from the Director, Office of Generic Drugs, dated November 8, 1991, and August 4, 1993. In addition, we refer you to the Office of Generic Drugs' Policy and Procedure Guide #41-95, dated February 8, 1995.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

In addition, while we note that you have provided a list of convictions, you have failed to include information regarding convictions of affiliated persons responsible for the development and submission of the application in addition to employees of the applicant. Please note that contractors responsible for the development of data and other information used to support approval of an application are "affiliated persons". Please provide a revised list of convictions with an original signature.

Also, in the interim, please submit three additional copies of the analytical methods and descriptive information needed to perform the tests on the samples (both the bulk active ingredient(s) and finished dosage form) and validate the analytical methods. Please do not send samples unless specifically requested to do so. If samples are required for validation, we will inform your where to send them in a separate communication.

If the above methodology is not submitted, the review of the application will be delayed.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CAR 314.101(a)(3)If you do so, the application shall be filed over protest under 21 CAR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

Harvey Greenberg
Consumer Safety Officer
(301) 594-0315

Sincerely yours,

/S/

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

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

ANDA Number: **74-752** Date of Submission: **August 22, 1996**

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**

Labeling Deficiencies:

1. GENERAL COMMENT:

   Comment B(1)(a) of our letter dated July 11, 1996 was in error. The drug name should have read "Diltiazem Hydrochloride Extended-release Capsules (Once-a-day dosage)". We are sorry for any inconvenience this error may have caused.

2. CONTAINER (30s, [redacted] 500s and

   a. We acknowledge your statements regarding your concern for a pharmacist's confusion in determining for which of the three available diltiazem hydrochloride extended-release capsules (once-a-day dosage) your product may be substituted. Please add the following statements to the label:

      i. AB to Cardizem CD®

      ii. Cardizem CD® is a registered trademark of Hoechst Marion Rousell.

      Please note that the use of these statements is currently being evaluated by the Agency. Further changes may be requested in the future.

   b. ...prescription. (spelling)

3. INSERT

   a. DESCRIPTION

      Insert the following as the last paragraph:

      USP Drug release test pending.

b. ADVERSE REACTIONS

Paragraph 2 - ...360 mg... (rather than "60 mg").

c. DOSAGE AND ADMINISTRATION

First sentence - ...controlled... (spelling).

Please revise your container labels and package insert labeling, as instructed above, and submit final printed package insert labeling and container labels.

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.

/S/ for/

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

Center for Drug Evaluation and Research

This Tentative Approval Summary supersedes the Tentative Approval Summary dated July 17, 1997

— Tentative Approval Summary

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

ANDA Number: **74-752** Date of Submission: **February 18, 1998**

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**

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

Do you have 12 Final Printed Labels and Labeling? Yes - 9 of each labeling piece in blue jacket - 3 of each piece in red
N.B. - Firm has submitted printer's proof PI - they need to submit FPL prior to full approval

Container Labels: 120 mg, 180 mg, 240 mg & 300 mg: 30s & 500s -
Satisfactory in FPL as of 6/20/97 submission.

Professional Package Insert Labeling:
Satisfactory in Printer's Proof as of 2/18/98 submission.

Revisions needed post-approval: Replace "CAUTION: Federal law..." statement with symbol "Rx only" or "℞ only".

BASIS OF APPROVAL:

Was this approval based upon a petition? No

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

NDA Number: 20-062

NDA Drug Name:
Diltiazem Hydrochloride Extended-release Capsules USP

NDA Firm: Marion Merrell Dow Inc.

Date of Approval of NDA Insert and supplement #: NDA 20-062/S-019 and S-021 ~~/revised July~~ 1995, approved 4/2/96.

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: RLD

Basis of Approval for the Carton Labeling: RLD

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

~~[Most of info from previous review]~~

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter? [USP added]	x		
Is this product a USP item? If so, USP supplement in which verification was assured. [USP/supp.6]	x		
Is this name different than that used in the Orange Book?		X	
Error Prevention Analysis			
PROPRIETARY NAME			
Has the firm proposed a proprietary name? NO		X	
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR. [See 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	
Error Prevention Analysis: *LABELING* (Continued)	**Yes**	**No**	**N.A.**
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? [Some of the inactives differ from the RLD]	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. Insert labeling based on the approved insert labeling of Cardizem® CD, revised July 1995, approved 4/2/96 (NDA 20-062/S-019 and S-021).

2. The firm has modeled this application after Cardizem® CD.

3. The 17th ed. Of the Approved Drug Products book lists six patents and two exclusivities for the listed drug. The firm's patent certification and exclusivity statement references only four patents and one exclusivity. The previous reviewer indicated that a note was made to the chemist regarding this issue.

4. The firm revised their list of inactive ingredients in the DESCRIPTION section and it is now consistent with their components and composition statement.
[Vol. B1.2, p. 6785, 6788 & 6790, also Vol. B2.1 p. 3 to 9]

5. The four capsule strengths will be distinguished by color:

120 mg	white/orange	180 mg	yellow/orange
240 mg	light brown/orange	300 mg	orange/orange

6. Capsules imprint:

The color of 120 mg, 180 mg, 240 mg, and 300 mg capsules are listed in the HOW SUPPLIED section and is consistent with the firm's description of the appearance of their capsules in the application under the Manufacturing and Processing, [instead of the finished dosage form section].
[V0l. B 1.2, P. 7037, 7104, 7163 & 7226].
See NOTES TO THE CHEMIST [Vol. B1.4 section XIV]

7. The package size of [redacted] were deleted from the HOW SUPPLIED section. This is acceptable.

Note the following from a previous labeling review:
In response to our labeling comment regarding the package size of the firm indicated that this package size is intended for distribution They also indicated that they have submitted stability studies for this package size.
[Vol. B2.1, 3/19/97 correspondence/p.128]
This in not acceptable (per chemist). The chemist [acting team leader] plans to notify the firm via phone regarding the package size and also

the package size of . See comments under HOW SUPPLED.

8. CLOSURE

120 mg, 180 mg, 240 mg and 300 mg
30s - CRC
500s - nonCRC
[Vol. 1.4, Section XIII]

9. Marketing: TABLET STRENGTHS/PACKAGE SIZE

NDA- 120 mg, 180 mg, 240 mg & 300 mg: 30s, & 100s UP
ANDA-120 mg, 180 mg, 240 mg & 300 mg: 30s & 500s

10. STORAGE/DISPENSING statements

STORAGE:

USP: Preserve in tight containers

NDA: Store at controlled room temperature (59-86°F)15-30°C. Avoid excessive humidity.

ANDA:Store at controlled room temperature 15-30°C (59-86°F). Avoid excessive humidity.

DISPENSING:

USP: Dispense in tight containers

ANDA:Dispense in tight, light resistant container as defined in USP.

11. USP labeling requirements:

Indicate the Drug Release test with which the product complies.

12. The firm has deleted the text "**A marketed**" as requested.
Note the following from a previous labeling review:
I was informed by the Team Leader John Grace, R.Ph. that the text "**A marketed**", Diltiazem Hydrochloride Extended-release Capsule (Once-a-day Dosage) should not appear generic firms insert labeling.

13. Differences between the RLD and ANDA insert labeling:

a. OVERDOSAGE (Hypotension)

"Levarterenol bitartrate" instead of "norepinephrine".

b. DOSAGE AND ADMINISTRATION (Concomitant Use With Other Cardiovascular Agents)

Sublingual NTG

"Sublingual NTG" instead of "Sublingual Nitroglycerin".

[These requests were made in a previous review].

14. The firm deleted the following text per our request.
Note from a previous review.
I was informed by the team leader, John Grace, R.Ph. to request generic firms to delete the following text:

-AB to Cardizem CD®

-Cardizem CD® is a registered trademark of Hoechst Marion Rousell

-Diltiazem hydrochloride Extended-release Capsules USP which exhibit different pharmacokinetics are also marketed. Please confirm you are dispensing the prescribed formulation.

NOTE:
-This differs and supersedes the labeling review of 1/2/97 and FTR of ANDA 74-752 for submission date 8/22/96 [Andrx/Diltiazem hydrochloride Extended-release Capsules]
-In addition, this differs supersedes the Diltiazem hydrochloride Extended-release Capsules (Twice A Day Dosage) Labeling guidance dated 9/95].

15. Generic firms may retain the text "(Once a day dosage)". This is acceptable per Team Leader, John Grace R.Ph.

16. The following is from a previous review/reviewer's FTR.

    a. ~~This issue~~ of product differentiation was discussed and is described in the 9/95 revised labeling guidance for Diltiazem Hydrochloride Capsules USP (Twice-a-Day Dosage). Further discussion among J. Phillips, J. Grace and A. Vezza resulted in the decision to defer comment at this time regarding this issue. A conference represented by DDMAC, the Labeling and Nomenclature Committee and OGD tentatively concluded that the phrase "Drug X is AB to Drug Y." will be used to designate to which approved drug an ANDA will be bioequivalent to. This is not official as of the present time. Upon further discussion between J. Phillips, J. Grace and A Vezza, the decision was made to tell ANDRX to place the statements "AB to Cardizem CD®" on the front panel under the strength and "Cardizem CD® is a registered trademark of Hoechst Marion Rousell." on the side panel of the container label. **[N.B. The decision to implement this now was later reversed, however a guidance with this statement is currently under development.]**

    b. This is a first generic.

    c. The insert labeling of the listed drug references a food effect. The applicant has done a single dose food/fasting 3 way crossover study.

    d. The 30s, and 500s container sizes are (white) while the

       impervious to light per chemist R. Rajagopalan. **[N.B. The container sizes were withdrawn from this application.]**

17. The purpose of the firm's 2/18/98 Minor Amendment is to update the PI with the minor and editorial revisions which were related to the firm on June 17, 1997 by Dr. J. White (see telecon). Despite the fact that Dr. White stated that these revisions were not necessary to make for their drug product to be tentatively approved the firm made the decision to revise anyway.

18. This review was done with the red jacket.

Date of Review: 2-25-98 Date of Submission: 2-18-98

Primary Reviewer: Adolph Vezza /S/ Date: 2/26/98

Team Leader: Charlie Hoppes /S/ Date: 2/26/98

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

ANDA Number: **74-752** Dates of Submission: **February 26, May 8 and June 2, 1998**

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**

Labeling Deficiencies:

1. GENERAL COMMENT

   Please note that the following comments refer only to your last labeling amendment (June ~~10~~ 2, 1998).

2. CONTAINER 30s and 500s

   a. Please note that the established name for this drug product is "Diltiazem HCl Extended-release Capsules USP". Where the established name shall be placed in direct conjunction with the proprietary name, the established name (rather than the name of the drug substance) must be surrounded by brackets. We refer you to 21 CFR 201.15(g)(1). Revise to enclose the entire established name of your product in parentheses.

   b. The established name must be at least half as large as the letters comprising the proprietary name. We refer you to 21 CFR 201.10(g)(2) for guidance.

   c. We are concerned that some of the established name is being obscured by the "XT" water mark. Please refer to 21 CFR 201.15(a)(6).

   d. Increase the prominence and size of the established name - see comments (a), (b), and (c) above.

   Please revise your container labels, as instructed above, and submit final printed container labels.

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.

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

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: 120 mg, 180 mg, 240 mg & 300 mg: 30s & 500s -

Professional Package Insert Labeling:
Satisfactory in FPL as of 5/8/98 submission.

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

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

NDA Number: 20-062

NDA Drug Name:
Diltiazem Hydrochloride Extended-release Capsules USP

NDA Firm: Marion Merrell Dow Inc.

Date of Approval of NDA Insert and supplement #: NDA 20-062/S-019 and S-021/revised July 1995, approved 4/2/96.

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: RLD

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

[Most of info from previous review]

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter? [USP added]	x		
Is this product a USP item? If so, USP supplement in which verification was assured. [USP/supp.6]	x		
Is this name different than that used in the Orange Book?		X	
Error Prevention Analysis			

PROPRIETARY NAME			
Has the firm proposed a proprietary name? NO		X	
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR. [See 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	
Error Prevention Analysis: *LABELING* (Continued)	**Yes**	**No**	**N.A.**
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? [Some of the inactives differ from the RLD]	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. Insert labeling based on the approved insert labeling of Cardizem® CD, revised July 1995, approved 4/2/96 (NDA 20-062/S-019 and S-021).

2. The firm has modeled this application after Cardizem® CD.

3. The list of inactive ingredients in the DESCRIPTION section is consistent with the components and composition statement. [Vol. B1.2, p. 6785, 6788 & 6790, also Vol. B2.1 p. 3 to 9]

4. The four capsule strengths will be distinguished by color:

120 mg	white/orange	180 mg	yellow/orange
240 mg	light brown/orange	300 mg	orange/orange

5. Capsules imprint:

The color of 120 mg, 180 mg, 240 mg, and 300 mg capsules are listed in the HOW SUPPLIED section and is consistent with the firm's description of the appearance of their capsules in the application under the Manufacturing and Processing, [instead of the finished dosage form section]. [Vol. B 1.2, P. 7037, 7104, 7163 & 7226]. See NOTES TO THE CHEMIST [Vol. B1.4 section XIV]

6. The package size of were deleted from the HOW SUPPLIED section. This is acceptable.

Note the following from a previous labeling review:
In response to our labeling comment regarding the package size of the firm indicated that this package size is intended for distribution They also indicated that they have submitted stability studies for this package size. [Vol. B2.1, 3/19/97 correspondence/p.128] This in not acceptable (per chemist). The chemist [acting team leader] plans to notify the firm via phone regarding the package size [I was informed that the cap closure of the is not satisfactory for marketing and storage in a retail pharmacy, where it can be opened and closed on repeated bases. Also, there is an issue regarding the and a tampering issue. No data was submitted for the package size of See comments under HOW SUPPLED.

7. CLOSURE

120 mg, 180 mg, 240 mg and 300 mg .. 30s (CRC) 500s (nonCRC) [Vol. 1.4, Section XIII]

8. Marketing: TABLET STRENGTHS/PACKAGE SIZE

NDA- 120 mg, 180 mg, 240 mg & 300 mg: 30s, & 100s UP
ANDA-120 mg, 180 mg, 240 mg & 300 mg: 30s & 500s

9. STORAGE/DISPENSING statements

USP: Preserve in tight containers

NDA: Store at controlled room temperature (59-86°F)15-30°C. Avoid excessive humidity.

ANDA: Store at controlled room temperature 15-30°C (59-86°F). Avoid excessive humidity.

USP: Dispense in tight containers

ANDA: Dispense in tight, light resistant container as defined in USP.

10. USP labeling requirements:

Indicate the Drug Release test with which the product complies.

11. The firm has deleted the text **"A marketed"** as requested.
Note the following from a previous labeling review:
I was informed by the Team Leader John Grace, R.Ph. that the text **"A marketed"**, Diltiazem Hydrochloride Extended-release Capsule (Once-a-day Dosage) should not appear generic firms insert labeling.

12. Differences between the RLD and ANDA insert labeling:

a. OVERDOSAGE (Hypotension)

"Levarterenol bitartrate" instead of "norepinephrine".

b. DOSAGE AND ADMINISTRATION (Concomitant Use With Other Cardiovascular Agents)

Sublingual NTG

"Sublingual NTG" instead of "Sublingual Nitroglycerin".

[These requests were made in a previous review].

13. The firm deleted the following text per our request.
Note from a previous review:
I was informed by the team leader, John Grace, R.Ph. to request generic firms to delete the following text:

-AB to Cardizem CD®

-Cardizem CD® is a registered trademark of Hoechst Marion Rousell

-Diltiazem hydrochloride Extended-release Capsules USP which exhibit different pharmacokinetics are also marketed. Please confirm you are dispensing the prescribed formulation.

NOTE:
-This differs and supersedes the labeling review of 1/2/97 and FTR of ANDA 74-752 for submission date 8/22/96 [Andrx/Diltiazem hydrochloride Extended-release Capsules]
-In addition, this differs supersedes the Diltiazem hydrochloride Extended-release Capsules (Twice A Day Dosage) Labeling guidance dated 9/95].

14. Generic firms may retain the text "(Once a day dosage)". This is acceptable per Team Leader, John Grace R.Ph.

15. The following is from a previous review/reviewer's FTR.

    a. ~~This issue of~~ product differentiation was discussed and is described in the 9/95 revised labeling guidance for Diltiazem Hydrochloride Capsules USP (Twice-a-Day Dosage). Further discussion among J. Phillips, J. Grace and A. Vezza ~~resulted in the~~ decision to defer comment at this time regarding this issue. A conference represented by DDMAC, the Labeling and Nomenclature Committee and OGD tentatively concluded that the phrase "Drug X is AB to Drug Y." will be used to designate to which approved drug an ANDA will be bioequivalent to. ~~This is not~~ official as of the present time. Upon further discussion between J. Phillips, J. Grace and A Vezza, the decision was made to tell ANDRX to place the statements "AB to Cardizem ~~CD® on the front panel under the strength and~~ "Cardizem CD® is a registered trademark of Hoechst Marion Rousell." on the side panel of the container label. **[N.B. The decision to implement this now was later reversed, however a guidance with this statement ~~is currently under development.~~]**

    b. This is a first generic.

    c. The insert labeling of the listed drug references a food effect. The applicant has done a single dose food/fasting 3 way crossover study.

    d. The 30s, and 500s container sizes are HDPE (white) while the with the capsules in a The are impervious to light per chemist R. Rajagopalan. **[N.B. The ~~container sizes were withdrawn~~ from this application.]**

16. The purpose of the firm's 2/18/98 Minor Amendment is to update the PI with the minor and editorial revisions which were related to the firm on ~~June~~ 17, 1997 by Dr. J. White (see telecon). Despite the fact that Dr. White stated that these revisions were not necessary to make for their drug product to be tentatively approved the firm made the decision to revise anyway.

17. Despite our "TA" letter out to the firm dated 9-15-97 they chose to revise their labeling no less than four times (1) 2-18-98 - submitted printer's proof PI. (2) 2-26-98 - submitted container labels with "CARTIA *XT*" [PI remains without proprietary name] (3) 5-8-98 - submitted PI with "Rx only" (4) 6-2-98 - submitted "newly dressed" container labels". At this point only the PI is acceptable for approval. The container labels have the established name wrong and the large "XT" is obscuring the "D" in Diltiazem.

18. Andrx filed under Paragraph IV. Court found that Andrx found that Andrx could not go to market until 30 months after they notified both Carderm and Hoechst Marion Roussel (12-30-95) - (7-2-98) of their intentions.

Date of Review: 6-23-98 Dates of Submission: 2-26, 5-8 & 6-2-98

Primary Reviewer: Adolph Vezza /S/ Date: 6/24/98

Team Leader: Charlie Hoppes /S/ Date: 6/24/98

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cc:

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

ANDA Number: 74-752

Date of Submission: May 28, 1997

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

Labeling Deficiencies:

INSERT

The package insert is satisfactory in printer's proof. However, before submitting final printed insert labeling, please make the following minor and editorial changes.

a. DESCRIPTION

i. Revise the molecular formula to consist with USP 23.

ii. You may delete the following from your list inactive ingredients,

b. CLINICAL PHARMACOLOGY (Hemodynamic and Electrophysiologic Effects)

In the third sentence of the fourth paragraph, delete the extra spaces between, "day" and "dosage".

Prepare and submit twelve copies of final printed container labels.

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.

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

NOTE TO THE CHEMIST

1. The firm has revised their list of inactive ingredients. Do you concur?

   Chemist's RR answer: Yes. 6/10/97

2. Do you concur with labeling comment 1(a)(ii) under DESCRIPTION?

   Chemist's RR answer: Yes. 6/10/97

3. Are you aware that the firm has deleted the package sizes of 90s and 5000s from the HOW SUPPLIED section?

   Chemist's RR answer: Yes, I am aware. 6/10/97

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter? [USP added]	X		
Is this product a USP item? If so, USP supplement in which verification was assured. [USP/supp.6]	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?			
Error Prevention Analysis			
PROPRIETARY NAME			
Has the firm proposed a proprietary name? If yes, complete this subsection.	X		
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?			X
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?			X
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR. [See 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	

If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			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	
Error Prevention Analysis: *LABELING* (Continued)	Yes	No	N.A.
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	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			x
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			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? [Some of the inactives differ from the RLD]	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.			
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:

1. Insert labeling based on the approved insert labeling of Cardizem® CD, revised July 1995, approved 4/2/96 (NDA 20-062/S-019 and S-021).

2. The firm has modeled this application after Cardizem® CD.

3. The 17th ed. Of the Approved Drug Products book list six patents and two exclusitvies for the listed drug. The firm's patent certification and exclusivity statement references only four patents and one exclusivity. The previous reviewer indicated that a note was made to the chemist regarding this issue. I will also include a statement under NOTE TO THE CHEMIST.

4. The firm revised their list of inactive ingredients in the DESCRIPTION section and it is now consistent with their components and composition statement.
[Vol. B1.2, p. 6785, 6788 & 6790, also Vol. B2.1 p. 3 to 9]

5. The four capsule strengths will be distinguished by color:

120 mg	white/orange	180 mg	yellow/orange
240 mg	light brown/orange	300 mg	orange/orange

6. Capsules imprint:

The color of 120 mg, 180 mg, 240 mg, and 300 mg capsules are listed in the HOW SUPPLIED section and is consistent with the firm's description of the appearance of their capsules in the application under the Manufacturing and Processing, [instead of the finished dosage form section].
[V01. B 1.2, P. 7037, 7104, 7163 & 7226].
See NOTES TO THE CHEMIST [Vol. B1.4 section XIV]

7. The package size of were deleted from the HOW SUPPLIED section. This is acceptable.
Note the following from my previous labeling review:
In response to our labeling comment regarding the package size of the firm indicated that this package size is intended for distribution They also indicated that they have submitted stability studies for this package size.
[Vol. B2.1, 3/19/97 correspondence/p.128]
This in not acceptable (per chemist). The chemist [acting team leader] plans to notify the firm via phone regarding the package size and also
[I was informed that the cap closure of the is not satisfactory for marketing and storage in a retail pharmacy, where it can be opened and closed on repeated bases. Also, there is an issue regarding the
and a tampering issue. No data was submitted for the package size of . See comments under HOW SUPPLED.

8. CLOSURE

120 mg, 180 mg, 240 mg and 300 mg
30s - CRC
500s - nonCRC
[Vol. 1.4, Section XIII]

9. Marketing: TABLET STRENGTHS/PACKAGE SIZE

NDA- 120 mg, 180 mg, 240 mg & 300 mg: 30s, & 100sUD
ANDA-120 mg, 180 mg, 240 mg & 300 mg: 30s & 500s

10. STORAGE/DISPENSING statements

STORAGE:

USP: Preserve in tight containers

NDA: Store at controlled room temperature (59-86°F)15-30°C. Avoid excessive humidity.

ANDA:Store at controlled room temperature 15-30°C (59-86°F). Avoid excessive humidity.

DISPENSING:

USP: Dispense in tight containers

ANDA:Dispense in tight, light resistant container as defined in USP.

11. USP labeling requirements:

Indicate the Drug Release test with which the product complies.

12. The firm has deleted the text "**A marketed**" as requested.
Note the following from my previous labeling review:
I was informed by the Team Leader John Grace, R.Ph. that the text "**A marketed**", Diltiazem Hydrochloride Extended-release Capsule (Once-a-day Dosage) should not appear generic firms insert labeling.

13. Differences between the RLD and ANDA insert labeling:

a. OVERDOSAGE (Hypotension)

"Levarterenol bitartrate" instead of "norepinephrine".

b. DOSAGE AND ADMINISTRATION (Concomitant Use With Other Cardiovascular Agents)

Sublingual NTG

"Sublingual NTG" instead of "Sublingual Nitroglycerin".

[These requests were made in my previous review].

14. The firm deleted the following text per our request.
Note from my previous review.
I was informed by the team leader, John Grace, R.Ph. to request generic firms to delete the following text:

-AB to Cardizem CD®

-Cardizem CD® is a registered trademark of Hoechst Marion Rousell

-Diltiazem hydrochloride Extended-release Capsules USP which exhibit different pharmacokinetics are also marketed. Please confirm you are dispensing the prescribed formulation.

NOTE:
-This differs and supersedes the labeling review of 1/2/97 and FTR of ANDA 74-752 for submission date 8/22/96 [Andrx/Diltiazem hydrochloride Extended-release Capsules]
-In addition, this differs supersedes the Diltiazem hydrochloride Extended-release Capsules (Twice A Day Dosage) Labeling guidance dated 9/95].

15. Generic firms may retain the text "(Once a day dosage)". This is acceptable per Team Leader, John Grace R.Ph.

16. The following is from a previous review/reviewer's FTR.

    a. This issue of product differentiation was discussed and is described in the 9/95 revised labeling guidance for Diltiazem Hydrochloride Capsules USP (Twice-a-Day Dosage). Further discussion among J. Phillips, J. Grace and A. Vezza resulted in the decision to defer comment at this time regarding this issue. A conference represented by DDMAC, the Labeling and Nomenclature Committee and OGD tentatively concluded that the phrase "Drug X is AB to Drug Y." will be used to designate to which approved drug an ANDA will be bioequivalent to. This is not official as of the present time. Upon further discussion between J. Phillips, J. Grace and A Vezza, the decision was made to tell ANDRX to place the statements "AB to Cardizem CD®" and "Cardizem CD® is a registered trademark of Hoechst Marion Rousell." on the container label.

    b. This is a first generic.

    c. The insert labeling of the listed drug references a food effect. The applicant has done a single dose food/fasting 3 way crossover study.

    d. The 30s, and 500s container sizes are HDPE (white) while the are of with the capsules in The are impervious to light per chemist R. Rajagopalan.

Date of Review: June 10, 1997

Date of Submission: May 28, 1997

/S/

Primary Reviewer — Date: 6-11-97

/S/

Secondary Reviewer — Date: 6/11/97

/S/

Team Leader
Labeling Review Branch — Date: 6/23/97

cc:

.L

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74752

CORRESPONDENCE

Andrx
PHARMACEUTICALS, INC.

June 25, 1998

ORIG AMENDMENT
1/AE

Mr. Douglas Sporn, Director
OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FACSIMILE AMENDMENT

Re: **Facsimile Amendment ANDA 74-752: Diltiazem Hydrochloride Extended-release Capsules, USP (Once-a-day Dosage) 120mg, 180 mg, 240 mg & 300mg.**

Dear Director Sporn:

Andrx Pharmaceuticals, Inc. ("Andrx"), today submits twelve (12) **color printer's proof** container labels for an original abbreviated new drug application ("ANDA") for Diltiazem Hydrochloride Extended-release Capsules, USP (Once-a-day Dosage) 120 mg, 180 mg, 240 mg and 300 mg dated September 22, 1995. This ANDA received tentative approval on September 15, 1997. Changes were made to the container labels based on labeling deficiencies received via facsimile on Wednesday June 24, 1998. A copy of that facsimile correspondence is attached.

Andrx is providing two copies of this facsimile amendment to the Office of Generic Drugs, an Archival Copy in a blue folder and a Chemistry Review Copy in a red folder.

This also certifies that, concurrent with the filing of this amendment, a true copy of the amendment along with a certification that the contents are a true copy was sent to our local district office in Maitland, Florida. This copy was sent as a Field Submission Chemistry Section in a maroon folder.

Please direct any communications regarding this submission to me at the following address:

4001 S. W. 47 Avenue
Ft. Lauderdale, FL 33314

If you need to telephone or send a facsimile, my numbers are (954) 581-7500 and (954) 327-5389 (Fax).

RECEIVED
JUN 26 1998
GENERIC DRUGS

Thank you for your prompt handling of this amendment.

Sincerely,

David A. Gardner
V. P., Regulatory Affairs/QA/QC

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

File
74-752

Andrx PHARMACEUTICALS, INC.

June 23, 1998

Office of Generic Drugs, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: ANDA 74-752; Diltiazem Hydrochloride Extended release Capsules, 120, 180, 240 and 300 mg.

Dear Director, Office of Generic Drugs:

We previously informed your office that the legal action filed against our company by Carderm Capital L.P. and Hoechst Marion Roussel, Inc. (the "Plaintiffs") for patent infringement. That action was filed on January 31, 1996, alleges that the Andrx product infringes United States Patent No. 5,470,584 (Plaintiffs did not sue for infringement of any of the five other patents listed in Andrx Pharmaceuticals' certification), and remains pending at the District Court.

If your office has any questions regarding this information, please call me at (954) 321 5214.

Sincerely,

Scott Lodin
Vice President and General Counsel

SL:aal

G:\SWAP\ANDRX\LEGAL\ANDX\PHARM\FDA3.LTR

4.1 Andrx

CC: DLS
GS
DH
CP
JP
Rickman
Beers-Block
74-752

Andrx
PHARMACEUTICALS, INC.

June 10, 1998

Mr. Douglas Sporn
Office of Generic Drugs, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: ANDA 74-752: *Diltiazem Hydrochloride Extended-release Capsules [generic Cardizem® CD]*
Final Approval Date

Dear Director, Office of Generic Drugs:

On December 29, 1995, in connection with the referenced ANDA, Andrx Pharmaceuticals, Inc. ("Andrx") forwarded Paragraph IV certifications, in the form attached hereto as Exhibit A, to Marion Merrell Dow, Inc. [the NDA holder and exclusive licensee of the patents], Carderm Capital L.P. [the owner of certain patents], and Elan Corporation [the owner of other certain patents], the persons required to receive those certifications pursuant to 21 CFR 314.94(a)(12)(i)(A) (4). As evidenced by the copies of their signed return receipts, attached hereto as composite Exhibit B, those certifications were received by Marion Merrell Dow, Inc. (now known as Hoechst Marion Roussel, Inc.) and Elan Corporation on December 30, 1995 and by Carderm Capital L.P. on January 2, 1996. Following receipt of those certifications, Hoechst Marion Roussel, Inc. and Carderm Capital Ltd. initiated legal action against Andrx alleging infringement of United States Patent No. 5,470,584.

That Complaint was filed on January 31, 1996, within the 45 day time frame required by 21 CFR §314.107(f), and remains pending. Accordingly, while the FDA tentatively approved the Andrx ANDA on September 16, 1997, the FDA has been unable to make that approval effective until "the expiration of the thirty-month period beginning on the date of the receipt of the notice provided under paragraph (2)(B)(i)"[1]. 21 CFR 355(4)(B)(iii). Pursuant to Regulation §314.107(b)(3), **"approval may be made effective 30 months after the date of the receipt of the notice of certification by the patent owner or by the exclusive licensee (or their representatives)."**

Andrx believes that its ANDA may be approved by the FDA on or after **June 30, 1998**, 30 months after the December 30, 1995 date its certifications were received by Marion Merrell Dow, Inc. and Elan Corporation. In forming this belief, we note that the foregoing statute permits the FDA to approve the ANDA following the expiration of the 30 month period (which began on December 30, 1995) and the regulation uses the term "or" (rather than "and") when referring to the receipts by the patent owner and exclusive licensee.

---

[1] While the statute provides that this period may be extended or shortened by the Court, no such order has been entered by the District Court and all of the parties to that litigation have agreed that they will not seek the extension or shortening of such period.

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

If there are any questions regarding this information please contact me by telephone at (954) 584-0300 and/or by fax at (954)792-1034.

Sincerely,

Chih-Ming Chen, Ph.D.
President

Andrx
PHARMACEUTICALS, INC.

Labeling Verified: drafted on 6/23/98 alizza 6/5/98

June 2, 1998

ORIG AMENDMENT
N LAM

RECEIVED
JUN 03 1998
GENERIC DRUGS

Mr. Douglas Sporn, Director
OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MINOR AMENDMENT

Re: **Minor Amendment ANDA 74-752: Diltiazem Hydrochloride Extended-release Capsules, USP (Once-a-day Dosage) 120mg, 180 mg, 240 mg & 300mg.**

Dear Director Sporn:

Andrx Pharmaceuticals, Inc. ("Andrx"), today submits twelve (12) **final** printed container labels for an original abbreviated new drug application ("ANDA") for Diltiazem Hydrochloride Extended-release Capsules, USP (Once-a-day Dosage) 120 mg, 180 mg, 240 mg and 300 mg dated September 22, 1995. This ANDA received tentative approval on September 15, 1997.

With this amendment, all requirements for final approval as detailed in the September 15, 1997 tentative approval letter have been satisfied:

1. **Expiration of 30-month period (July 3, 1998) provided for in section 505(j)(4)(B)(iii) since the date of receipt (Jan. 2, 1996) of the 45-day notice required under section 505(j)(2)(B)(i);**

2. **Final printed package insert submitted May 8, 1998** (Minor amendment);

3. **Final printed container labels provided with this submission, and**

4. **There have been no changes in the chemistry, manufacturing and control data or any other conditions that were outlined in the abbreviated new drug application since the date of tentative approval on Sept. 15, 1977.**

Therefore, I would like to request that the Office of Generic Drugs change the tentative approval for this product to a **final approval on July 3, 1998.**

Andrx is providing two copies of this minor amendment to the Office of Generic Drugs, an Archival Copy in a blue folder and a Chemistry Review Copy in a red folder.

This also certifies that, concurrent with the filing of this amendment, a true copy of the amendment along with a certification that the contents are a true copy was sent to our local district office in Maitland, Florida. This copy was sent as a Field Submission Chemistry Section in a maroon folder.

Nadine 6-5-98

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

Please direct any communications regarding this submission to me at the following address:

4001 S. W. 47 Avenue
Ft. Lauderdale, FL 33314

If you need to telephone or send a facsimile, my numbers are (954) 581-7500 and (954) 327-5389 (Fax).

Thank you for your prompt handling of this amendment.

Sincerely,

David A. Gardner
V. P., Regulatory Affairs/QA/QC

Andrx
PHARMACEUTICALS, INC.

labeling review
dictated 6/23/98
(on 6/2/98 submission)

May 8, 1998

ORIG AMENDMENT
N/A

Office of Generic Drugs, CDER, FDA
DOCUMENT CONTROL ROOM
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MINOR AMENDMENT

Re: **ANDA 74-752: Diltiazem Hydrochloride Extended-release Capsules, USP 120mg, 180 mg, 240 mg & 300mg (Once-a-day Dosage)**

Dear Director Sporn:

Andrx Pharmaceuticals, Inc. ("Andrx"), today submits twelve (12) final printed copies of the package insert for an original abbreviated new drug application ("ANDA") for Diltiazem Hydrochloride Extended-release Capsules, USP 120 mg, 180 mg, 240 mg and 300 mg (Once-a-day Dosage) dated September 22, 1995. The ANDA received tentative approval on September 15, 1997. This submission is in response to a telephone conversation with Timothy W. Ames on April 3, 1998 and is a follow up to a labelling Minor Amendment that was submitted on February 18, 1998.

In addition, as required in the Tentative Approval letter, Andrx states the following:

> There have been no changes in the chemistry, manufacturing and control data or any other conditions that were outlined in the abbreviated new drug application since the date of tentative approval on September 15, 1997.

Andrx is providing two copies of this minor amendment to the Office of Generic Drugs, an Archival Copy and a Chemistry Review Copy.

This also certifies that, concurrent with the filing of this amendment, a true copy of the amendment along with a certification that the contents are a true copy was sent to our local district office in Maitland, Florida. This copy was sent as a Field Submission Chemistry Section.

Please direct any communications regarding this submission to me at the following address:

4001 S. W. 47 Avenue
Ft. Lauderdale, FL 33314

If you need to telephone or send a facsimile, my numbers are (954) 581-7500 and (954) 327-5389 (Fax).

RECEIVED
MAY 11 1998
GENERIC DRUGS

Andrx
PHARMACEUTICALS INC.

February 6, 1998

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MINOR AMENDMENT

Re: **Minor Amendment to ANDA 74-752: Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day Dosage) 120mg, 180 mg, 240 mg & 300mg**

Dear Director Sporn, Office of Generic Drugs:

Andrx Pharmaceuticals, Inc. ("Andrx"), today submits a minor amendment to an original abbreviated new drug application ("ANDA") for Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day Dosage) 120 mg, 180 mg, 240 mg and 300 mg dated September 22, 1995. This ANDA received **tentative approval** on September 15, 1997.

This minor amendment is being filed in order to provide container/closure information for a ninety count package size for all four strengths that was inadvertently omitted from the original application. The ANDA received tentative approval with a thirty (30) count and a five hundred (500) count package for each strength. The bottles being used for the ount packages are from the same manufacturer as those used for the 30 and 500 counts. The CRC closure that is used on all four strengths is the same as the closure used on the 240 mg and 300 mg 30 count bottles which have received tentative approval. All of the appropriate specifications and testing information are provided with this amendment. In addition, copies of the packaging records for each strength are also included.

Andrx is filing two copies of this minor amendment, an Archival Copy in a blue folder and a Chemistry Review Copy in a red folder. This submission consists of 126 pages which are numbered at the bottom of each page.

This also certifies that, concurrent with the filing of this amendment, a true copy of the amendment along with a certification that the contents are a true copy is being sent to our local district office in Orlando, Florida. This copy will be sent in a Field Submission Chemistry Section maroon folder.

4001 S.W. 47th AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • (954) 581-7500 • FAX (954) 587-1054

Please direct any communications regarding this amendment to me at the following address:

4001 S. W. 47 Avenue, Suite #201
Ft. Lauderdale, FL 33314

If you need to telephone or send a facsimile, my numbers are (954) 581-7500 and (954) 327-5389 (Fax).

Thank you for your prompt handling of this amendment.

Sincerely,

David A. Gardner

David A. Gardner
V. P., Regulatory Affairs/QA/QC

Andrx
PHARMACEUTICALS, INC.

February 26, 1998

Labeling rec'd 6/23/98
drafted 6/12/98 submitted
(on 6/2/98)
/S/

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MINOR AMENDMENT

ORIG AMENDMENT

Re: **Minor Amendment ANDA 74-752: Diltiazem Hydrochloride Extended-release Capsules, USP (Once-a-day Dosage) 120mg, 180 mg, 240 mg & 300mg.**

Dear Director Sporn:

Andrx Pharmaceuticals, Inc. ("Andrx"), today submits twelve (12) **draft** copies of the revised final printed container labels - using a **brand** name - for an original abbreviated new drug application ("ANDA") for Diltiazem Hydrochloride Extended-release Capsules, USP (Once-a-day Dosage) 120 mg, 180 mg, 240 mg and 300 mg dated September 22, 1995. This ANDA received tentative approval on September 15, 1997.

On June 20, 1997, Andrx submitted to the Office of Generic Drugs twelve (12) **final** printed labels for each container size for each strength for this ANDA. Those labels were accepted with "no further changes" prior to the tentative approval using the generic name - *Diltiazem Hydrochloride* - for the product. Since the tentative approval, Andrx has decided to market the generic version of Cardizem CD under the brand name of **CARTIA *XT***. This brand name approach will definitely help avoid the confusion for pharmacists who are trying to dispense among all of the extended-release products of diltiazem hydrochloride. There is also possible confusion when one particular company, e.g. Andrx, is manuacturing and marketing more than one diltiazem extended-release product. The following influenced this decision:

1) As shown in the attached table, there are a total of **eight (8)** extended-release products of diltiazem hydrochloride that have been approved by FDA. Seven (7) of the eight products are currently on the market and the eighth will be marketed by Andrx once we receive final approval for the product and the proposed labeling in this amendment.

2) In addition, purchased from and began marketing the generic version of in October of 1997 using *Diltiazem Hydrochloride Extended-release Capsules* for the name of the product on the label. There is no "once-a-day dosage" on the label of generic product, and in fact, the label is exactly the same as that of Diltiazem HCl ER Capsule which is taken twice daily (see attachment following table). This is yet another extended-release diltiazem product on the market to cause confusion for the pharmacist when trying to properly fill a prescription for this product dosage form.

RECEIVED
FEB 27 1998
GENERIC DRUGS

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

Hence, as indicated earlier, Andrx is proposing to use "CARTIA *XT*" as the brand name to avoid confusion with other diltiazem ER products.

Andrx is providing two copies of this minor amendment to the Office of Generic Drugs, an Archival Copy in a blue folder and a Chemistry Review Copy in a red folder.

This also certifies that, concurrent with the filing of this amendment, a true copy of the amendment along with a certification that the contents are a true copy was sent to our local district office in Orlando, Florida. This copy was sent as a Field Submission Chemistry Section in a maroon folder.

Please direct any communications regarding this submission to me at the following address:

4001 S. W. 47 Avenue
Ft. Lauderdale, FL 33314

If you need to telephone or send a facsimile, my numbers are (954) 581-7500 and (954) 327-5389 (Fax).

Thank you for your prompt handling of this amendment.

Sincerely,

David A. Gardner
V. P., Regulatory Affairs/QA/QC

Andrx
PHARMACEUTICALS, INC.

February 18, 1998

ORIG AMENDMENT
UNIT

Office of Generic Drugs, CDER, FDA
DOCUMENT CONTROL ROOM
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MINOR AMENDMENT

Re: **ANDA 74-752: Diltiazem Hydrochloride Extended-release Capsules, USP (Once-a-day Dosage) 120mg, 180 mg, 240 mg & 300mg**

Dear Director Sporn:

Andrx Pharmaceuticals, Inc. ("Andrx"), today submits twelve (12) "printer's proof" copies of the draft package insert for an original abbreviated new drug application ("ANDA") for Diltiazem Hydrochloride Extended-release Capsules, USP (Once-a-day Dosage) 120 mg, 180 mg, 240 mg and 300 mg dated September 22, 1995. The ANDA received tentative approval on September 15, 1997. This submission is in response to a telephone conversation with Dr. J. D. White at approximately 11:30 am on June 17, 1997 and is a follow up to a Telephone Amendment that was submitted on June 20, 1997.

Andrx is providing two copies of this minor amendment to the Office of Generic Drugs, an Archival Copy and a Chemistry Review Copy.

This also certifies that, concurrent with the filing of this amendment, a true copy of the amendment along with a certification that the contents are a true copy was sent to our local district office in Orlando, Florida. This copy was sent as a Field Submission Chemistry Section.

Please direct any communications regarding this submission to me at the following address:

4001 S. W. 47 Avenue, Suite #201
Ft. Lauderdale, FL 33314

If you need to telephone or send a facsimile, my numbers are (954) 581-7500 and (954) 327-5389 (Fax).

Thank you for your prompt handling of this amendment.

RECEIVED
FEB 19 1998
GENERIC DRUGS

Sincerely,
David A. Gardner
V. P., Regulatory Affairs/QA/QC

ANDA: 74-752 FIRM: Andrx Pharmaceuticals, Inc.

DRUG PRODUCT: Diltiazem Hydrochloride Extended-release Capsules, USP, 120 mg, 180 mg, 240 mg & 300 mg (Once-a-day Dosage)

Based on a telephone conversation on the morning of June 17, 1997 with Dr. J. D. White regarding the package insert for ANDA 74-752, the following is being submitted:

Twelve (12) "printer's proof" copies of the draft package insert.

The following changes were made to the package insert:

DESCRIPTION:

1.) Molecular formula corrected to include the "S" which was omitted.

2.) Following were deleted from the list of inactive ingredients:

CLINICAL PHARMACOLOGY

Hemodynamic and Electrophysiologic Effects

3.) Fourth paragraph, third sentence: extra spaces between "day" and "dosage" in "(once-a-day dosage)" were deleted.

HOW SUPPLIED

4.) Rev date for the insert changed to 02/98.

There were no changes to any other sections of the insert!

Attached at pages 3 through 10 is a copy of the revised insert. Attached at pages 11 through 23 is a side-by-side comparison of the insert submitted with the June 20, 1997 amendment vs. the insert being submitted with this amendment. The differences between the insert submitted with this amendment vs. the insert submitted with the June 20, 1997 amendment have been highlighted. In addition, the side-by-side comparison of the two inserts has been annotated using the numbers **1.** through **4.** which correspond to the numbers assigned to the changes detailed above.

Andrx
PHARMACEUTICALS INC.

February 6, 1998

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MINOR AMENDMENT

Re: **Minor Amendment to ANDA 74-752: Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day Dosage) 120mg, 180 mg, 240 mg & 300mg**

Dear Director Sporn, Office of Generic Drugs:

Andrx Pharmaceuticals, Inc. ("Andrx"), today submits a minor amendment to an original abbreviated new drug application ("ANDA") for Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day Dosage) 120 mg, 180 mg, 240 mg and 300 mg dated September 22, 1995. This ANDA received **tentative approval** on September 15, 1997.

This minor amendment is being filed in order to provide container/closure information for a ninety count package size for all four strengths that was inadvertently omitted from the original application. The ANDA received tentative approval with a thirty (30) count and a five hundred (500) count package for each strength. The bottles being used for the count packages are from the same manufacturer as those used for the 30 and 500 counts. The CRC closure that is used on all four strengths is the same as the closure used on the 240 mg and 300 mg 30 count bottles which have received tentative approval. All of the appropriate specifications and testing information are provided with this amendment. In addition, copies of the packaging records for each strength are also included.

Andrx is filing two copies of this minor amendment, an Archival Copy in a blue folder and a Chemistry Review Copy in a red folder. This submission consists of 126 pages which are numbered at the bottom of each page.

This also certifies that, concurrent with the filing of this amendment, a true copy of the amendment along with a certification that the contents are a true copy is being sent to our local district office in Orlando, Florida. This copy will be sent in a Field Submission Chemistry Section maroon folder.

RECEIVED
FEB 0 9 1998
GENERIC DRUGS

4001 S.W. 47th AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • (954) 581-7500 • FAX (954) 587-1054

Please direct any communications regarding this amendment to me at the following address:

4001 S. W. 47 Avenue, Suite #201
Ft. Lauderdale, FL 33314

If you need to telephone or send a facsimile, my numbers are (954) 581-7500 and (954) 327-5389 (Fax).

Thank you for your prompt handling of this amendment.

Sincerely,

David A. Gardner

David A. Gardner
V. P., Regulatory Affairs/QA/QC

Andrx
PHARMACEUTICALS INC.

NEW CORRESP

January 14, 1998

Mr. Douglas Sporn, Director
Office of Generic Drugs, CDER, FDA
DOCUMENT CONTROL ROOM
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Attention: Timothy Ames
Withdrawal of Amendment dated November 6, 1997

Re: **ANDA 74-752 Withdrawal of Amendment dated November 6, 1997** to: ***Diltiazem Hydrochloride Extended-release Capsules, USP, 120 mg, 180 mg, 240 mg & 300 mg (Once-a-day Dosage).***

Dear Mr. Sporn:

Andrx Pharmaceuticals, Inc. ("Andrx"), is today submitting this letter in order to **withdraw** an amendment to an original abbreviated new drug application ("ANDA") for Diltiazem Hydrochloride Extended-release Capsules, 120 mg, 180 mg, 240 mg and 300 mg dated September 22, 1995. This ANDA received **tentative approval** on September 15, 1997. The amendment was dated November 6, 1997 and was originally submitted as a Special Supplement - Changes Being Effected but was converted to an amendment because this ANDA has only received tentative approval and not final approval.

The amendment was originally submitted in order to revise the specification for the dissolution test which is performed on our in-process extended-release (SR2) beads from not less than .o not less than at 18 hours. Based on a discussion on the afternoon of January 12, 1998 with Timothy Ames, Radhika Rajagopalan, et. al., if this specification is changed at this time, the validity of the bio-batch could be questioned because the in-process SR2 beads used to produce the product tested between and at 18 hours in Therefore, based on this conversation, Andrx is withdrawing the amendment. The specification for the in-process SR2 beads will remain not less than . at 18 hours in As indicated in the April 4, 1996 Minor Amendment, this dissolution test was added solely for patent infringement purposes.

This also certifies that, concurrent with the filing of this amendment withdrawal letter, a true copy of the letter along with a certification that the content is a true copy was sent to our local district office.

If there are any questions regarding this information please contact me at (954) 327-4413 (direct dial) and/or (954) 327-5389 (Fax).

RECEIVED
JAN 15 1998
GENERIC DRUGS

Sincerely,

David A. Gardner
V.P., Regulatory Affairs/QA/QC

4001 S.W. 47th AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • (954) 581-7500 • FAX (954) 587-1054

Andrx
PHARMACEUTICALS INC.

Acceptable
PRE Rickman
9/15/97

September 15, 1997

Office of Generic Drugs, CDER, FDA
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773
Attention: Peter Rickman

RE: ANDA 74-752 (Generic Cardizem CD)

Dear Mr. Rickman:

Per your request this morning, I hereby certify that to the best of my knowledge, **no** lawsuit has been filed against Andrx Pharmaceuticals, Inc. for any alleged infringement of the following five patents:

U.S. 5,439,689 - Expiration Date August 8, 2012

U.S. 5,364,620 - Expiration Date November 14, 2011

U.S. 5,286,497 - Expiration Date May 20, 2011

U.S. 5,002,776 - Expiration Date March 26, 2008

U.S. 4,894,240 - Expiration Date January 16, 2007

Please advise if any additional information is required.

Very truly yours,

Chih-Ming Chen, Ph.D.
President

4001 S.W. 47th AVENUE, SUITE 201 FORT LAUDERDALE, FLORIDA 33314 • (954) 581-7500 • FAX (954) 587-1054

Andrx
PHARMACEUTICALS, INC.

NAI
Hardcopy of Telephone Amendment
9/10/97
9/18/97

September 10, 1997

NEW CORRESP

Office of Generic Drugs, CDER, FDA
DOCUMENT CONTROL ROOM
Attention: Peter Rickman
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE REQUEST

Re: **ANDA 74-752**: *Diltiazem Hydrochloride Extended-release Capsules, USP, 120 mg, 180 mg, 240 mg & 300 mg (Once-a-day Dosage)*

Dear Director, Office of Generic Drugs:

As required by 21 CFR 314.95(b), Andrx Pharmaceuticals, Inc. ("Andrx"), today submits additional information to an original abbreviated new drug application ("ANDA") for Diltiazem Hydrochloride Extended-release Capsules, USP, 120 mg, 180 mg, 240 mg and 300 mg dated September 22, 1995.

This submission is in response to a telephone conversation with Peter Rickman on September 9, 1997. Mr. Rickman requested information to confirm that an additional notification of a paragraph IV certification had been sent to Marion Merrell Dow, Inc. (a.k.a. Hoechst Marion Roussel, Inc.), Carderm Capital L. P. and Elan Corporation, plc by **registered or certified mail, return receipt requested.** The original notifications were sent by **express mail, return receipt. requested.**

This is a certification that a *Notice of Certification of Non - Infringement* was sent by **certified** letter to each person identified under 21 CFR 314.95(a) and that the notice met the content requirements of 21 CFR 314.95(c). Copies of the letter, the proofs of mailing dated July 9, 1996 and the signed return receipts are attached.

Andrx is providing three (3) copies of this submission (12 pages), an Archival Copy and two (2) review copies - one copy for the Chemistry Section and one copy for the Pharmacokinetic Section.

This also certifies that, concurrent with the filing, a true copy of this submission along with a certification that the content is a true copy was sent to our local district office.

RECEIVED
SEP 11 1997
GENERIC

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

If there are any questions regarding this information please contact me at (954) 581-7500 extension 1413 and/or (954) 587-1054 (Fax).

Sincerely,

David A. Gardner

David A. Gardner
V.P., Regulatory Affairs/QA/QC

Andrx
PHARMACEUTICALS, INC.

May 28, 1997

NEW CORRESP
NC

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FACSIMILE AMENDMENT

Re: **Facsimile Amendment to ANDA 74-752: Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day Dosage) 120mg, 180 mg, 240 mg & 300mg**

Dear Director, Office of Generic Drugs:

Andrx Pharmaceuticals, Inc. ("Andrx"), today submits a facsimile amendment to an original abbreviated new drug application ("ANDA") for Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day Dosage) 120 mg, 180 mg, 240 mg and 300 mg dated September 22, 1995. This amendment is in response to a facsimile received on May 19, 1997.

In addition to providing a facsimile copy of this amendment to the Office of Generic Drugs, Andrx is also filing two (2) copies of this amendment, an Archival Copy in a blue folder and a Chemistry Review Copy in a red folder. These copies will be sent by overnight courier on May 29, 1997.

This also certifies that, concurrent with the filing of this amendment, a true copy of the amendment along with a certification that the contents are a true copy is being sent to our local district office in Orlando, Florida. This copy will be sent in a Field Submission Chemistry Section maroon folder.

Please direct any communications regarding this amendment to me at the following address:

4001 S. W. 47 Avenue, Suite #201
Ft. Lauderdale, FL 33314

If you need to telephone or send a facsimile, my numbers are (954) 581-7500 and (954) 587-1054 (Fax).

Thank you for your prompt handling of this facsimile amendment.

MAY 30 1997

Sincerely,

David A. Gardner
V. P., Regulatory Affairs/QA/QC

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

Andrx
PHARMACEUTICALS, INC.

October 8, 1996

Office of Generic Drugs, CDER, FDA
DOCUMENT CONTROL ROOM
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855 - 2773

nda B
BIOAVAILABILITY
TELEPHONE AMENDMENT NEW CORRESP
BIOEQUIVALENCE
NC/BIO

Re: ***Minor Amendment*** to ANDA 74-752: *Diltiazem Hydrochloride Extended-release Capsules, 120 mg, 180 mg, 240 mg and 300 mg*

Dear Director, Office of Generic Drugs:

Based on a telephone conversation with Drs. Keith K. Chan, Jason A. Gross and Andre J. Jackson of the Bioequivalence Section of OGD on Tuesday August 27, 1996, the following information is being submitted as a minor amendment to ANDA 74-752, *Diltiazem Hydrochloride Extended - release Capsules. 120 mg, 180 mg, 240 mg and 300 mg* that was submitted by Andrx Pharmaceuticals, Inc.:

Dissolution data at pm for all four strengths of the drug product (120 mg, 180 mg, 240 mg and 300 mg) in the following media:

Andrx is providing two (2) copies of the amendment (14 pages) - an Archival Copy and a Pharmacokinetic/Bioequivalence review copy.

If there are any questions regarding this information please contact me at (954) 581-7500 and/or (954) 587-1054 (FAX).

Thank you for your prompt attention to the processing of this information.

RECEIVED
OCT 0 9 1996
GENERIC DRUGS

Sincerely,

David A. Gardner

David A. Gardner
V. P., Regulatory Affairs/QA/QC

Andrx
PHARMACEUTICALS, INC.

February 27, 1997

NEW CORRESP

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FACSIMILE AMENDMENT

Re: **Facsimile Amendment to ANDA 74-752: Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day Dosage) 120mg, 180 mg, 240 mg & 300mg**

Dear Director, Office of Generic Drugs:

Andrx Pharmaceuticals, Inc. ("Andrx"), today submits a facsimile amendment to an original abbreviated new drug application ("ANDA") for Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day Dosage) 120 mg, 180 mg, 240 mg and 300 mg dated September 22, 1995. This amendment is in response to a facsimile received on January 30, 1997.

In addition to providing a facsimile copy of this amendment to the Office of Generic Drugs, Andrx is also filing two (2) copies of this amendment, an Archival Copy in a blue folder and a Chemistry Review Copy in a red folder.

This also certifies that, concurrent with the filing of this amendment, a true copy of the amendment along with a certification that the contents are a true copy was sent to our local district office in Orlando, Florida. This copy was sent in a Field Submission Chemistry Section maroon folder.

Please direct any communications regarding this amendment to me at the following address:

RECEIVED

4001 S. W. 47 Avenue, Suite #201
Ft. Lauderdale, FL 33314

FEB 28 1997

If you need to telephone or send a facsimile, my numbers are (954) 581-7500 and (954) 587-1054 (Fax).

GENERIC DRUGS

Thank you for your prompt handling of this facsimile amendment.

Sincerely,

David A. Gardner

David A. Gardner
V. P., Regulatory Affairs/QA/QC

Andrx
PHARMACEUTICALS, INC.

March 19, 1997

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room
Attn.: Radhika Rajagopalan
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE REQUEST
Addition to
FACSIMILE AMENDMENT

Re: **ANDA 74-752: Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day Dosage) 120mg, 180 mg, 240 mg & 300mg**

Dear Director, Office of Generic Drugs:

Andrx Pharmaceuticals, Inc. ("Andrx"), today submits up-dated specifications to an original abbreviated new drug application ("ANDA") for Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day Dosage) 120 mg, 180 mg, 240 mg and 300 mg dated September 22, 1995. This submission is in response to a telephone conversation with Ms. Radhika Rajagopalan this morning, March 19, 1997 and is an addition to the Facsimile Amendment filed on February 27, 1997.

In addition to providing a facsimile copy of this information to the Office of Generic Drugs, Andrx is also filing two (2) additional copies, an Archival Copy and a Chemistry Review Copy.

This also certifies that, concurrent with the filing of this amendment, a true copy of the amendment along with a certification that the contents are a true copy was sent to our local district office in Orlando, Florida. This copy was sent as a Field Submission Chemistry Section.

Please direct any communications regarding this submission to me at the following address:

4001 S. W. 47 Avenue, Suite #201
Ft. Lauderdale, FL 33314

If you need to telephone or send a facsimile, my numbers are (954) 581-7500 and (954) 587-1054 (Fax).

Thank you for your prompt handling of this addition to our facsimile amendment.

Sincerely,

David A. Gardner
V. P., Regulatory Affairs/QA/QC

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

Andrx
PHARMACEUTICALS, INC.

NEW CONNECT

March 10, 1997

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room
Attn.: Radhika Rajagopalan
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE REQUEST
Addition to
FACSIMILE AMENDMENT

Re: **ANDA 74-752: Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day Dosage) 120mg, 180 mg, 240 mg & 300mg**

Dear Director, Office of Generic Drugs:

Andrx Pharmaceuticals, Inc. ("Andrx"), today submits up-dated specifications to an original abbreviated new drug application ("ANDA") for Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day Dosage) 120 mg, 180 mg, 240 mg and 300 mg dated September 22, 1995. This submission is in response to a telephone conversation with Ms. Radhika Rajagopalan this morning, March 10, 1997 and is an addition to the Facsimile Amendment filed on February 27, 1997.

In addition to providing a facsimile copy of this information to the Office of Generic Drugs, Andrx is also filing two (2) additional copies, an Archival Copy and a Chemistry Review Copy.

This also certifies that, concurrent with the filing of this amendment, a true copy of the amendment along with a certification that the contents are a true copy was sent to our local district office in Orlando, Florida. This copy was sent as a Field Submission Chemistry Section.

Please direct any communications regarding this submission to me at the following address:

4001 S. W. 47 Avenue, Suite #201
Ft. Lauderdale, FL 33314

If you need to telephone or send a facsimile, my numbers are (954) 581-7500 and (954) 587-1054 (Fax).

Thank you for your prompt handling of this addition to our facsimile amendment.

RECEIVED
MAR 1 1 1997
GENERIC DRUGS

Sincerely,
David A. Gardner
David A. Gardner
V. P., Regulatory Affairs/QA/QC

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

ANDA: 74-752 FIRM: Andrx Pharmaceuticals, Inc.
DRUG PRODUCT: Diltiazem Hydrochloride Extended-release Capsules

The following up-dated specifications are being submitted as requested by Ms. Radhika Rajagopalan:

Diltiazem Hydrochloride Extended-release , Code #
Diltiazem Hydrochloride Extended-release , Blended Code #

Diltiazem Hydrochloride Extended-release , Code #
Diltiazem Hydrochloride Extended-release P), Blended Code #

The change to these specifications occurred in the dissolution test. Except for the dissolution test on the SR2 pellets (code #s) in , the paddle speed for all of the other tests was changed from .

Andrx
PHARMACEUTICALS, INC.

September 22, 1995

Office of Generic Drugs
CDER, Food and Drug Administration
Metro Park North
7500 Standish Place, Room 150
Rockville, MD 20855

Re: ANDA for *Diltiazem Hydrochloride Once - A - Day Extended - Release Capsules*

Dear Director, Office of Generic Drugs:

Andrx Pharmaceuticals, Inc. ("Andrx") today submits an original abbreviated new drug application ("ANDA") seeking approval to market 120 mg, 180 mg, 240 mg and 300 mg Diltiazem Hydrochloride Extended - Release Capsules based on a 300 mg capsule that is bioequivalent to the reference listed drug, Cardizem CD, manufactured by Marion Merrell Dow, Inc. (also known as Hoechst Marion Roussell, Inc.) pursuant to NDA: 20-062.

This ANDA consists of twenty-two (22) volumes - sixteen (16) volumes for bioequivalence and six (6) for the remaining technical information. Andrx is filing an archival copy (blue folders) of the ANDA that contains all of the information required for the ANDA. In addition, a review copy of the ANDA is being submitted which contains all of the information found in the archival copy and is color coded as follows:

Orange: Bioequivalence which contains Sections I - VII

Red: Chemistry, Manufacturing & Controls which contains Sections I - V and VII - XIX.

For more detailed information on the organization of this ANDA, please refer to page Intro v of the ANDA, "Executive Summary - Organization of the ANDA".

Please direct any written communications regarding this ANDA to me at the address listed below. If you need to telephone or send a facsimile, my numbers are (954) 327-4413 (direct dial) and (954) 587-1054 (fax).

This also certifies that, concurrent with the filing of this ANDA, a true copy of the technical sections of the ANDA (including a copy of the 356h form and a certification that the contents are a true copy of those filed with the Office of Generic Drugs) was sent to our local district office. This "field copy" was also sent in red folders.

Thank you for your prompt handling of this submission.

RECEIVED
SEP 22 1995
GENERIC DRUGS

Sincerely,
David A. Gardner
V. P., Regulatory Affairs/QA/QC

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 305-581-7500 • FAX: 305-587-1054

ORIGINAL

Andrx
PHARMACEUTICALS INC.

November 22, 1995

Office of Generic Drugs, CDER, FDA
DOCUMENT CONTROL ROOM
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

AA

Re: Amendment to ANDA 74-752: *Diltiazem Hydrochloride Once-A-Day Extended-release Capsules*

Dear Director, Office of Generic Drugs:

Andrx Pharmaceuticals, Inc. ("Andrx"), today submits an amendment to an original abbreviated new drug application ("ANDA") for Diltiazem Hydrochloride Extended-release Capsules, 120 mg, 180 mg, 240 mg and 300 mg dated September 22, 1995.

The amendment consists of one volume which is divided as follows:

I. Packaging Records
1. Packaging reconciliation for all product strengths and all package sizes Page 1.
2. Completed packaging records for 120 mg strength
597R001A Pages 2 - 13
597R001B Pages 14 - 24
597R001C Pages 25 - 35
3. Completed packaging records for 180 mg strength
598R001A Pages 36 - 47
598R001B Pages 48 - 58
598R001C Pages 59 - 69
4. Completed packaging records for 240 mg strength
599R001A Pages 70 - 81
599R001B Pages 82 - 92
599R001C Pages 93 - 103

RECEIVED
NOV 24 1995
GENERIC DRUGS

II. Certification Required by Generic Drug Enforcement Act of 1992
Page 104

Andrx is filing two (2) copies of the amendment, an archival copy in a blue folder and a review copy in a red folder.

This also certifies that, concurrent with the filing of this amendment, a true copy of the

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 305-581-7500 • FAX: 305-587-1054

amendment along with a certification that the contents are a true copy was sent to our local district office. This "field copy" was also sent in a red folder.

Please direct any communications regarding this amendment to me at the following address:

4001 S.W. 47th Avenue, Suite 201
Ft. Lauderdale, FL 33314

If you need to telephone or send a facsimile, my numbers are (954) 327-4413 (direct dial) and (954) 587-1054 (fax).

Thank you for your prompt handling of this amendment.

Sincerely,

David A. Gardner

David A. Gardner
V.P., Regulatory Affairs/QA/QC

Andrx
PHARMACEUTICALS INC.

November 22, 1995

RECEIVED
NOV 24 1995
GENERIC DRUGS

Office of Generic Drugs, CDER, FDA
DOCUMENT CONTROL ROOM
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Amendment to ANDA 74-752: *Diltiazem Hydrochloride Once-A-Day Extended-release Capsules* based on a refuse to file letter dated NOV 17,1995.

Dear Director, Office of Generic Drugs:

On November 17,1995, the Office of Generic Drugs issued a "refuse to file" letter for an abbreviated new drug application for Diltiazem Hydrochloride Extended-release Capsules, 120 mg, 180 mg, 240 mg and 300 mg which was submitted by Andrx Pharmaceuticals, Inc. on September 22, 1995. A review and response will be presented for each of the reasons listed for refusing to file. Following that will be a listing of the information/documents that are being submitted to supplement the application.

A review of the two reasons listed for refusing to file with our responses follows:

#1 Listed Reason:
You are required to completely package your exhibit batches in containers proposed for marketing. Partial packaging, packaging into bulk storage containers, or a packaging for which you are not seeking approval is not acceptable unless...dated February 8, 1995.

Response:
There appears to be a mis-interpretation or mis-understanding of documents that were submitted with the application regarding the packaging of this product into containers of The packaging of the product into : was not done for the purpose of , Andrx Pharmaceuticals intends to market a container of In support of this fact, the following pages from the original submission have been attached:

7295 - Production flow chart which indicates that the product - lot 600R001- is to be packaged into three different sizes - bottles of 30, bottles of 500 and . (For convenience, product/packaging reconciliation has been added to the flow chart, which shows that all the product was packaged.)

7309 - Page from manufacturing record - lot 600R001 - showing bulk product yield prior to packaging - capsules.

7440 - First page of master packaging record for lot 600R001A - bottles of 30.

7446 - Page from lot 600R01A showing the number of bottles of 30 packaged - 220.

7452 - First page of master packaging record for lot 600R001B - bottles of 500.

7458 - Page from lot 600R001B showing the number of bottles of 500 packaged - 172.

7464 - First page of master packaging record for lot 600R001C -

7470 - Page from lot 600R001C showing the number of packaged - 3.

7788 - Section one describes the container closure systems used for packaging the product.

7790 - 7792 - Exact description of the container/closure system used for each of the three package sizes for all four strengths of the product.

162 - Last page of the proposed package insert for the product which indicates that the product will be supplied in a for each strength.

40 - Proposed container label for for 120 mg strength

56 - Proposed container label for for 180 mg strength

72 - Proposed container label for for 240 mg strength

88 - Proposed container label for r 300 mg strength

8225 & 8278 - Accelerated and room temperature stability results for 300 mg strength in

8453 & 8502 - Accelerated and room temperature stability results for 240 mg strength in 00.

8675 & 8724 - Accelerated and room temperature stability results for 180 mg strength in

8909 & 8955 - Accelerated and room temperature stability results for 120 mg strength in

All of the information and data on the pages cited do indicate that Andrx Pharmaceuticals intends to market a capsules for each strength of the product and that none of the product was packaged exclusively for

Since the entire batch for each strength was packaged, the test results that were provided in the original submission for each of the four strengths are valid - pages 8084 through 8087. (Copy of each page attached.)

#2 Listed Reason:
In addition, while we note that you have provided a list of convictions, you have failed to include information regarding convictions of affiliated persons responsible for the development and submission of the application in addition to employees of the applicant. Please note that contractors responsible for the development of data and other information used to support approval of an application are "affiliated persons". Please provide a revised list of convictions with an original signature.

Response:
A revised list of convictions with an original signature will be provided in the amendment to the original application.

Please note that pages 6869, 6870 and 6871 of the original submission were certifications provided by our contract testing laboratories as required by the Generic Drug Enforcement Act of 1992. Copies of the appropriate pages are attached.

As requested in the letter, three (3) additional copies of the analytical methods with validation for the bulk drug substance and the finished dosage form are also being submitted.

Andrx Pharmaceuticals, Inc. is also amending the original submission with the following information:

A packaging reconciliation sheet that shows the bulk product yield for each strength and the number of capsules for each strength of product that were packaged into each size container - bottles of 30, bottles of 500 and

Completed packaging records for 120 mg strength:
597R001A - Bottles of 30
597R001B - Bottles of 500
597R001C -

Completed packaging records for 180 mg strength:

598R001A - Bottles of 30
598R001B - Bottles of 500
598R001C - ____

Completed packaging records for 240 mg strength:

599R001A - Bottles of 30
599R001B - Bottles of 500
599R001C - ____

A revised list of convictions with an original signature.

Please direct any written communications regarding this information to me at the following address:

4001 S.W. 47th Avenue,Suite 201
Ft. Lauderdale, FL 33314

If you need to telephone or send a facsimile, my numbers are (954)327-4413 (direct dial) and (954)587-1054 (fax).

Thank you for your prompt attention to the processing of this information.

Sincerely,

David A. Gardner

David A. Gardner
V.P., Regulatory Affairs/QA/QC

ANDA 74-752

Andrx Pharmaceuticals, Inc.
Attention: David A. Gardner
4001 S.W. 47th Avenue, Suite 201
Ft. Lauderdale, FL 33314

DEC - 8 1995

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to our "Refuse to File" letter dated November 17, 1995, and your amendment dated November 22, 1995.

NAME OF DRUG: Diltiazem Hydrochloride Extended-release Capsules, 120 mg, 180 mg, 240 mg and 300 mg

DATE OF APPLICATION: September 22, 1995

DATE OF RECEIPT: September 22, 1995

DATE ACCEPTABLE FOR FILING: November 24, 1995

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
Consumer Safety Officer
(301) 594-0350

/s/

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

ANDA 74-752
cc:

Enc

Andrx
PHARMACEUTICALS, INC.

January 17, 1996

Office of Generic Drugs, CDER, FDA
DOCUMENT CONTROL ROOM
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP NEW CORRESP
NC

RECEIVED
JAN 22 1996
GENERIC DRUGS

Re: Amendment to ANDA 74-752: *Diltiazem Hydrochloride Once-A-Day Extended-release Capsules*

Dear Director, Office of Generic Drugs:

As required by 21 CFR 314.95(b), Andrx Pharmaceuticals, Inc. ("Andrx"), today submits an amendment to an original abbreviated new drug application ("ANDA") for Diltiazem Hydrochloride Extended-release Capsules, 120 mg, 180 mg, 240 mg and 300 mg dated September 22, 1995.

The amendment is a certification that a *Notice of Certification of Non - Infringement* was sent by certified mail to each person identified under 21 CFR 314.95(a) and that the notice met the content requirements of 21 CFR 314.95(c). Copies of the letter and the signed return receipts are included in the amendment.

Andrx is providing three (3) copies of the amendment (nine pages), an archival copy and and two (2) review copies.

This also certifies that, concurrent with the filing of this amendment, a true copy of the amendment along with a certification that the content is a true copy was sent to our local district office.

If there are any questions regarding this information please contact me at (954) 327-4413 (direct dial) and/or (954) 587-1054 (Fax).

Sincerely,

David A. Gardner
V.P., Regulatory Affairs/QA/QC

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

Andrx
PHARMACEUTICALS, INC.

February 5, 1996

RECEIVED

FEB 06 1996

GENERIC DRUGS

Office of Generic Drugs, CDER, FDA
Attention: Tim Ames, HFD-600
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRES

Re: ANDA 74-752: *Diltiazem Hydrochloride Once-A-Day Extended-release Capsules*

Dear Director, Office of Generic Drugs:

As required by 21 CFR 314.107(f)(2)(i - iv), Andrx Pharmaceuticals, Inc. ("Andrx"), today submits information regarding legal action which has been filed against Andrx by Hoechst Marion Roussel, Inc. and Carderm Capital L. P. for patent infringement.

With regard to this matter, Andrx provides the following information:

(i) ANDA number: 74-752

(ii) Name of abbreviated new drug: *Diltiazem Hydrochloride Once-A-Day Extended - release Capsules*

(iii) Established name, strength and dosage form: *Diltiazem Hydrochloride Extended - release Capsules, 120 mg, 180 mg, 240 mg and 300 mg.*

(iv) Certification of patent infringement filing:

This is to certify that Hoechst Marion Roussel, Inc. and Carderm Capital L. P. (Plaintiffs) have filed legal action against Andrx Pharmaceuticals, Inc. (Defendant) alleging infringement of United States Patent No. 5,470,584. The complaint was filed in United States District Court for the Southern District of Florida - Miami on January 31, 1996 and has been given case number: 96-06121 (CIV- ROETTGER).

If there are any questions regarding this information please contact me at (954) 327-4413 (direct dial) and/or (954) 587-1054 (Fax).

Sincerely,

David A. Gardner

David A. Gardner
V.P., Regulatory Affairs/QA/QC

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

Andrx
PHARMACEUTICALS, INC.

March 25, 1996

Office of Generic Drugs, CDER, FDA
DOCUMENT CONTROL ROOM
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855 - 2773

MAR 26 1996

Re: ***Minor Amendment*** to ANDA 74-752: *Diltiazem Hydrochloride Extended-release Capsules, 120 mg, 180 mg, 240 mg and 300 mg*

Dear Director, Office of Generic Drugs:

Based on a telephone conversation with Jason A. Gross of the Bioequivalence Section of OGD on Friday March 22, 1996, the following information is being submitted as a minor amendment to ANDA 74-752, *Diltiazem Hydrochloride Extended - release Capsules* that was submitted by Andrx Pharmaceuticals, Inc.:

Subjects were dropped from the multiple dose bioequivalence study for the following reasons:

Subject
On day six (6) of Period I, prior to dosing, Subject had a PR interval of 216. At this time the sponsor's monitor was contacted and it was decided to discontinue this subject's participation in the study for safety reasons. This subject was released from the clinic later that day after his PR interval returned to within normal limits.

The following support information is being submitted for Subject
Page 4814 from the original ANDA filing
Page 5637 from the original ANDA filing
Memorandum from arch
Copy of ECG from

Subject #
Subject , dropped from the study prior to initial dosing of Period II for personal reasons.

The following support information is being submitted for Subject #
Page 4814 from the original ANDA filing
Page 5659 from the original ANDA filing
Memorandum from

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

As requested, copies of the following are also included:

Release specifications for the 300 mg Diltiazem Hydrochloride Once-A-Day Extended-release Capsule which includes the dissolution specification.
(Page 8030 from the original ANDA filing.)

Dissolution Standard Test Method for the 300 mg Diltiazem Hydrochloride Once-A-Day Extended-release Capsule.
(Pages 8079 through 8083 from the original ANDA filing.)

If there are any questions regarding this information please contact me at (954) 581-7500 and/or (954) 587-1054 (FAX).

Thank you for your prompt attention to the processing of this information.

Sincerely,

David A. Gardner

David A. Gardner
V. P., Regulatory Affairs/QA/QC

Andrx
PHARMACEUTICALS, INC.

April 4, 1996

RECEIVED

APR 0 5 1996

GENERIC DRUGS

Office of Generic Drugs, CDER, FDA
DOCUMENT CONTROL ROOM
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: **Minor Amendment** to ANDA 74-752: *Diltiazem Hydrochloride Once-A-Day Extended-release Capsules, 120 mg, 180 mg, 240 mg & 300 mg.*

AA

Dear Director, Office of Generic Drugs:

Andrx Pharmaceuticals, Inc. ("Andrx"), today submits an amendment to an original abbreviated new drug application ("ANDA") for Diltiazem Hydrochloride Extended-release Capsules, 120 mg, 180 mg, 240 mg and 300 mg dated September 22, 1995.

The amendment is being submitted in order to revise the specifications for our in-process extended-release (SR2) beads. Specifically, we are proposing to add a dissolution test in ı ɔ the Diltiazem HCl Extended-release Pellets (SR2) - product code and Diltiazem HCl Extended-release Pellets (SR2), Blended - product code ? We are proposing a single sampling time at eighteen (18) hours. The explanation and rationale for this additional test are attached to this letter.

Andrx is providing three (3) copies of the amendment (23 pages) - an Archival Copy and two (2) review copies (one copy for the Pharmacokinetic Section and one copy for the Chemistry Section).

This also certifies that, concurrent with the filing of this amendment, a true copy of the amendment along with a certification that the content is a true copy was sent to our local district office.

If there are any questions regarding this information please contact me at (954) 327-4413 (direct dial) and/or (954) 587-1054 (Fax).

Sincerely,

David A. Gardner

David A. Gardner
V.P., Regulatory Affairs/QA/QC

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

ANDA 74-752

Andrx Pharmaceuticals, Inc.
Attention: Mr. David A. Gardner
4001 S. W. 47th Avenue, Suite 201
Fort Lauderdale, FL 33314

JUL 11 1996

Dear Mr. Gardner:

This is in reference to your abbreviated new drug application dated September 22, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Diltiazem Hydrochloride Extended-release Capsules USP, (once a day dosage) 120 mg, 180 mg, 240 mg and 300 mg.

Reference is also made to your amendments dated November 22, 1995 and April 4, 1996.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

Page(s) 3

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

B. LABELING DEFICIENCIES

1. GENERAL COMMENTS:

a. Revise the established name of your product to read as follows where it appears on container labels and throughout the package insert labeling:

Diltiazem Hydrochloride Capsules USP
(Once-a-day dosage)

Please note that "USP" is encouraged as this product is the subject of a USP monograph.

b. Revise your storage statement to read, "...temperature 15-30°C(59-86°F).".

2. CONTAINER (30s, 90s, 500s and 5000s)

a. We note that you have included container labels for a package size of 5000s (drums). Is this package size for distribution? If so, please identify the end user. How is it

possible for the provider to maintain USP standards with this container closure system (tight, light-resistant container)

b. We encourage the use of boxing, contrasting colors, other means to differentiate the strengths of your products.

c. We acknowledge that you have proposed two versions of container labels. However, we prefer that you revise the container label as described in the first GENERAL COMMENT.

d. Please include the following statement on the container label:

> Diltiazem Hydrochloride Extended-release Capsules USP which exhibit different pharmacokinetics are also marketed. Please confirm you are dispensing the prescribed formulation.

3. INSERT

a. GENERAL

i. Italicize "*in vivo*" and "*in vitro*" throughout your insert labeling.

ii. Your choice of format for paragraph breaks makes it very difficult in some instances to determine where one paragraph ends and another starts, e.g., the last two paragraphs in the Hemodynamic and Electrophysiologic Effects subsection of CLINICAL PHARMACOLOGY. Please consider a different format for distinguishing paragraphs.

b. TITLE

See general comment.

c. DESCRIPTION

i. Revise the third sentence to read:

> The structural formula is:

ii. Include the molecular formula ($C_{22}H_{26}N_2O_4S \cdot HCl$).

iii. Make the following revision, "...molecular weight of 450.99.".

iv. Revise the third sentence of the second paragraph as follows:

> Each diltiazem hydrochloride extended-release capsule (once daily dosage), for oral administration, is formulated...

v. Regarding the use of the phrase "and other ingredients". We refer you to USP XXIII General Information, Chapter <1091>. Labeling of Inactive Ingredients, which states that a trade secret may be omitted from the list of inactive ingredients if the list states "and other ingredients". The chapter further states that an ingredient is considered to be a trade secret only if its presence confers a significant competitive advantage AND its identity cannot be ascertained by the use of modern analytical technology. If you still elect to use the phrase "and other ingredients", please provide supporting data concerning the "trade secret" status of these ingredients, if not, revise your labeling to include all ingredients in the list.

vi. You may delete the last line of this section.

d. CLINICAL PHARMACOLOGY

i. Hemodynamic and Electrophysiologic Effects

A). Add the following text as the second and third sentences of the third paragraph:

> In a double-blind, parallel, dose-response study utilizing doses ranging from 90 to 540 mg once daily, a marketed

diltiazem hydrochloride extended-release capsule (once-a-day dosage) lowered supine diastolic blood pressure in an apparent linear manner over the entire dosage range studied. The changes in diastolic blood pressure, measured at trough, for placebo, 90 mg, 180 mg, 360 mg, and 540 mg were -2.9, -4.5, -6.1, -9.5, and -10.5 mm Hg, respectively.

B). We acknowledge your comment regarding the deletion of the fourth paragraph of this subsection since they refer to a specific study using the brand product. This text should be retained in your labeling with the following revision in the first sentence, "...once daily, a marketed diltiazem hydrochloride extended-release capsule (once-a-day dosage), increased...".

ii. Pharmacokinetics and Metabolism

We acknowledge your comment regarding the deletion of the last paragraph of this subsection. As this paragraph contains useful comparative information, please retain it in your insert labeling. Refer to "CARDIZEM tablets" as "diltiazem tablets" and "CARDIZEM CD" as "diltiazem hydrochloride extended-release capsules (once-a-day dosage).

e. WARNINGS (Cardiac Conduction)

Make the following revision to the last sentence of the first paragraph, "...of diltiazem. (See ADVERSE REACTIONS.)

f. ~~PRECAUTIONS~~

i. Carcinogenesis, Mutagenesis, Impairment of Fertility

A). Revise the first sentence as follows:

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.

B). Revise the last sentence as follows:

...rats at oral dosages of up to 100 mg/kg/day.

ii. Pediatric Use

...in pediatric patients...

g. ADVERSE REACTIONS

i. Make the following revision to the second paragraph,

...trials in patients receiving a marketed diltiazem hydrochloride extended-release capsule (once-a-day dosing) product up to 60 mg with rates in placebo patients shown for comparison.

ii. Make the following revisions to the table:

A). Revise the title to read, "Diltiazem Hydrochloride Extended-release Capsule (once-a-day) Placebo...

B). Revise the second column heading to read, "Diltiazem Extended-release Capsule (once-a-day)".

iii. Make the following revision in the paragraph following the table:

> ...involving over 3200 patients, the most...

iv. Other (second paragraph)

A). Make the following revisions in the first sentence:

> ...diltiazem: allergic reactions, alopecia, angioedema (including facial or periorbital edema), asystole, erythema multiforme (including Stevens-Johnson syndrome, toxic epidermal necrolysis), exfoliative...

B). Make the following revision in the penultimate sentence, "...generalized rash, some characterized...".

h. OVERDOSAGE

Add the following sentence as the penultimate sentence of the sixth paragraph:

> Limited data suggest that plasmapheresis or charcoal hemoperfusion may hasten diltiazem elimination following overdose.

i. DOSAGE AND ADMINISTRATION (Angina)

Make the following revision in the first sentence of the last paragraph:

> 4. **Antihypertensives.** Diltiazem hydrochloride extended-release capsules (once-a-day) have...

j. HOW SUPPLIED

i. See comment regarding the container size of under CONTAINER.

ii. Include the, "CAUTION: Federal law...", statement as it appears on your container labels.

iii. Include the, "Manufactured by:", statement consistent with your container labels.

iv. Include the revision date for your package insert labeling.

v. We encourage the inclusion of the dispensing recommendations appearing on your container and the statement which appears under the last comment for CONTAINER.

Please revise your container labels and package insert labeling, as instructed above, and submit final printed (or printers proof) package insert labeling and final printed container labels. Please note that final printed insert labeling is not required for tentative approval of an application if it is granted with more than 90 days remaining from the date when full approval can be considered. We will accept final "printers proof" for the insert only.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon further 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.

In addition to the above comments please be aware of the following note:

The drug product dissolution specifications and in-process specifications are currently under review by the Division of Bioequivalence. This division will communicate to the chemistry reviewer the results of the interim in-vitro dissolution test(s) and tolerances. These will be compared against the tolerances proposed by the firm and any discrepancies will be communicated to you. At that time the labeling review will address the DESCRIPTION section of the package insert to the effect that the dissolution test(s) and tolerances are pending.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. The response to this letter will be considered a MAJOR amendment and should be so designated in your cover letter. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. You will be notified in a separate letter of any deficiencies identified in the Bioequivalence portion of your application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 7/11/96

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOAVAILABILITY
NEW CORRESP
N46

Andrx
PHARMACEUTICALS, INC.

RECEIVED
MAY 03 1996
GENERIC DRUGS

May 2, 1996

Office of Generic Drugs, CDER, FDA
DOCUMENT CONTROL ROOM
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855 - 2773

TELEPHONE AMENDMENT
BIOEQUIVALENCE

Re: ***Minor Amendment*** to ANDA 74-752: *Diltiazem Hydrochloride Extended-release Capsules, 120 mg, 180 mg, 240 mg and 300 mg*

Dear Director, Office of Generic Drugs:

Based on a telephone conversation with Jason A. Gross of the Bioequivalence Section of OGD on Wednesday April 24, 1996, the following information is being submitted as a minor amendment to ANDA 74-752, *Diltiazem Hydrochloride Extended - release Capsules, 120 mg, 180 mg, 240 mg and 300 mg* that was submitted by Andrx Pharmaceuticals, Inc.:

1) A summary of the in-vitro dissolution test results for all four stregths of the product in nd SIF at sampling time points of 2, 12, 18 and 24 hours. As requested, the data includes the average, range and coefficient of variation at each time point in each medium. A discussion of the information being submitted is also provided.

2) Finished product release specifications for 120 mg (180 mg (, 240 mg and 300 mg Diltiazem HCl Once-A-Day Extended-release Capsules which includes the dissolution specification.

   (**Note:** Per your request, we provided dissolution data in t 2, 12, 18 and 24 hours but the specification submitted was for a single sampling time of 2 hours only.)

Andrx is providing two (2) copies of the amendment (12 pages) - an Archival Copy and a review copy for Pharmacokinetics/Bioequivalence.

If there are any questions regarding this information please contact me at (954) 581-7500 and/or (954) 587-1054 (FAX).

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

Thank you for your prompt attention to the processing of this information.

Sincerely,

David A. Gardner

David A. Gardner
V. P., Regulatory Affairs/QA/QC

Andrx
PHARMACEUTICALS, INC.

Orig NDA ORIG AMENDMENT Vol AC

Labeling /S/ 10/9/96 /S/

August 22, 1996

RECEIVED
AUG 23 1996
GENERIC DRUGS

Office of Generic Drugs, CDER, FDA
DOCUMENT CONTROL ROOM
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MAJOR AMENDMENT

Re: **Major Amendment to ANDA 74-752:** ***Diltiazem Hydrochloride Extended-release Capsules USP (once-a-day dosage).***

Dear Director, Office of Generic Drugs:

Andrx Pharmaceuticals, Inc. ("Andrx"), today submits a major amendment to an original abbreviated new drug application ("ANDA") for Diltiazem Hydrochloride Extended-release Capsules USP (once-a-day dosage) 120 mg, 180 mg, 240 mg and 300 mg dated September 22, 1995. This amendment is in response to a Chemistry and Labelling deficiency letter dated July 11, 1996.

Andrx is filing two (2) copies of the amendment, an Archival Copy in a blue folder and a Chemistry Review Copy in a red folder.

This also certifies that, concurrent with the filing of this amendment, a true copy of the amendment along with a certification that the contents are a true copy was sent to our local district office. This "Field Copy" was sent in a maroon - Field Submission Chemistry Section - folder.

Please direct any communications regarding this amendment to me at the following address:

4001 S. W. 47 Avenue, Suite #201
Ft. Lauderdale, FL 33314

If you need to telephone or send a fasimile, my numbers are (954)581-7500 and (954) 587-1054 (FAX).

Thank you for your prompt handling of this amendment.

Sincerely,

David A. Gardner
V. P., Regulatory Affairs/QA/QC

P 807 663 471

RECEIPT FOR CERTIFIED MAIL

NO INSURANCE COVERAGE PROVIDED
NOT FOR INTERNATIONAL MAIL
(See Reverse)

Sent to Marion Merrell Dow, Inc.
aka Hoechst Marion Roussel, Inc.

Street and No.
2110 East Galbraith Road

P.O., State and ZIP Code
Cincinnati OH 45215-6300

Postage	55
Certified Fee	110
Special Delivery Fee	
Restricted Delivery Fee	
Return Receipt showing to whom and Date Delivered	110
Return Receipt showing to whom, Date, and Address of Delivery	
TOTAL Postage and Fees	$

Postmark or Date

PS Form 3800, June 1985

000009

SENDER: Complete items 1 and 2 when additional services are desired, and complete items 3 and 4.

Put your address in the "RETURN TO" space on the reverse side. Failure to do this will prevent this card from being returned to you. The return receipt fee will provide you the name of the person delivered to and the date of delivery. For additional fees the following services are available. Consult postmaster for fees and check box(es) for additional service(s) requested.

1. ☐ Show to whom delivered, date, and addressee's address. 2. ☐ Restricted Delivery.

3. Article Addressed to:

Marion Merrell Dow, Inc.
aka Roehst Marion Roussel, Inc.
Attn: Michael Dixon
Corporate Counsel
9300 East Calbraith Road
Kansas City, OH 45215-6300

4. Article Number

P 807 663 471

Type of Service:

☐ Registered ☐ Insured
☒ Certified ☐ COD
☐ Express Mail

Always obtain signature of addressee or agent and DATE DELIVERED.

5. Signature — Addressee

X

6. Signature — Agent

X Elizabeth Coleman

7. Date of Delivery

8. Addressee's Address (ONLY if requested and fee paid)

CINCINNATI OH JUL 27 1988 LOCKLAND BR

PS Form 3811, Feb. 1986 DOMESTIC RETURN RECEIPT

P 507 663 472

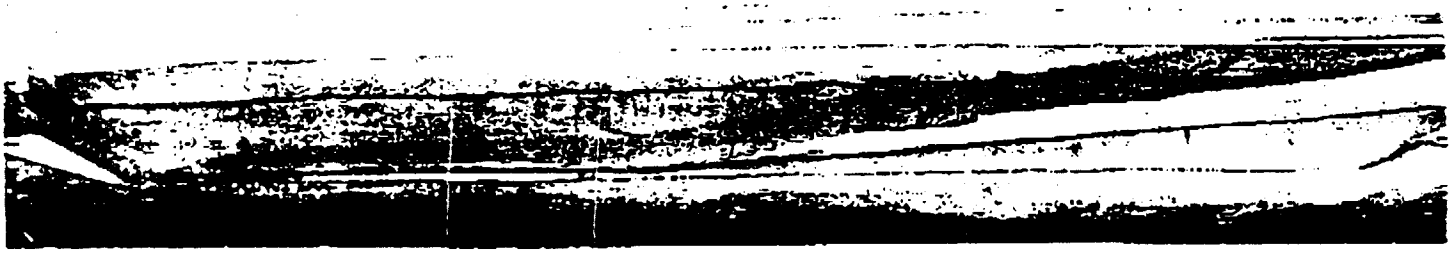
RECEIPT FOR CERTIFIED MAIL

NO INSURANCE COVERAGE PROVIDED
NOT FOR INTERNATIONAL MAIL

(See Reverse)

Sent to Carderm Capital L.P.	
Street and No. Kleinfeld, Kaplan et al 1140 Nineteenth Street	
P.O. State and ZIP Code Washington, DC 20036	
Postage	$ .55
Certified Fee	.110
Special Delivery Fee	
Restricted Delivery Fee	
Return Receipt showing to whom and Date Delivered	.110
Return Receipt showing to whom, Date, and Address of Delivery	
TOTAL Postage and Fees	$
Postmark or Date	

PS Form 3800, June 1985



SENDER: Complete items 1 and 2 when additional services are desired, and complete items 3 and 4. Put your address in the "RETURN TO" space on the reverse side. Failure to do this will prevent this card from being returned to you. The return receipt fee will provide you the name of the person delivered to and the date of delivery. For additional fees the following services are available. Consult postmaster for fees and check box(es) for additional service(s) requested.

1. ☐ Show to whom delivered, date, and addressee's address. 2. ☐ Restricted Delivery.

3. Article Addressed to:
Carderm Capital L.P.
c/o Mr. Peter Safir, Agent
Kleinfeld, Kaplan and Becker
1140 Nineteenth Street, N.W.
Washington, DC 20036-6601

4. Article Number
P 807 663 472

Type of Service:
☒ Registered ☐ Insured
☐ Certified ☐ COD
☐ Express Mail

Always obtain signature of addressee or agent and DATE DELIVERED.

5. Signature — Addressee
X

6. Signature — Agent
X

7. Date of Delivery
11 Oct 96

8. Addressee's Address (ONLY if requested and fee paid)

PS Form 3811, Feb. 1986 DOMESTIC RETURN RECEIPT

000012

[redacted]

SENDER: Complete items 1 and 2 when additional services are desired, and complete items 3 and 4.

Put your address in the "RETURN TO" space on the reverse side. Failure to do this will prevent this card from being returned to you. The return receipt fee will provide you the name of the person delivered to and the date of delivery. For additional fees the following services are available. Consult postmaster for fees and check box(es) for additional service(s) requested.

1. ☐ Show to whom delivered, date, and addressee's address. 2. ☐ Restricted Delivery.

3. Article Addressed to:

Elan Corporation, PLC
c/o Mr. Gary Frischling, Agent
Irell & Manella
1800 Avenue of the Stars
Los Angeles, CA 90067-4276

4. Article Number

P 807 663 473

Type of Service:

☐ Registered ☐ Insured
☒ Certified ☐ COD
☐ Express Mail

Always obtain signature of addressee or agent and DATE DELIVERED.

5. Signature — Addressee

X

6. Signature — Agent

X

7. Date of Delivery

8. Addressee's Address *(ONLY if requested and fee paid)*

PS Form 3811, Feb. 1986 DOMESTIC RETURN RECEIPT

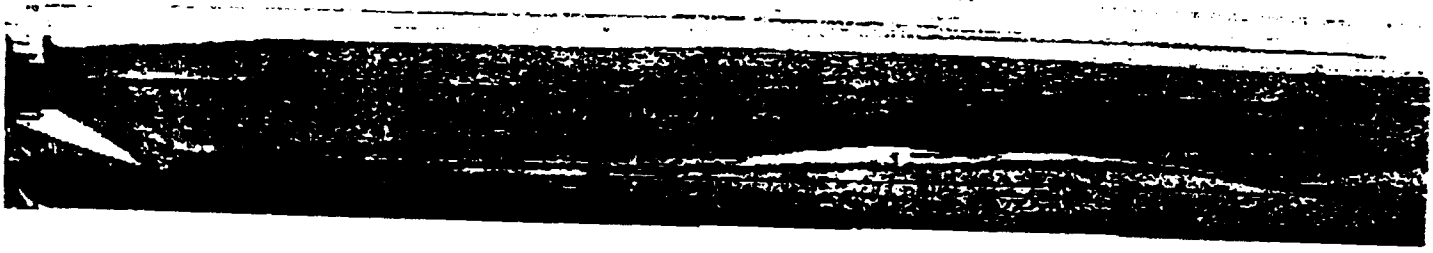
P 807 663 473

RECEIPT FOR CERTIFIED MAIL

NO INSURANCE COVERAGE PROVIDED
NOT FOR INTERNATIONAL MAIL
(See Reverse)

Sent to Elan Corporation, PLC Ireil & Manella	
Street and No. 1800 Avenue of the Stars	
P.O., State and ZIP Code Los Angeles, CA 90067	
Postage	$ 53
Certified Fee	
Special Delivery Fee	
Restricted Delivery Fee	
Return Receipt showing to whom and Date Delivered	110
Return Receipt showing to whom, Date, and Address of Delivery	
TOTAL Postage and Fees	$
Postmark or Date	

PS Form 3800, June 1985



It is hereby certified that a copy of this Notice has been sent by certified mail, return receipt requested to:

Holder of New Drug Application for Cardizem CD
Marion Merrell Dow,Inc.
and Hoechst Marion Roussel, Inc.
9110 East Galbraith Road
Cincinnati, OH 45215-6300

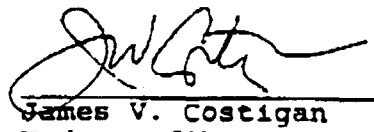
Owner of U.S. Letters Patent No. 5,286,497; 5,439,689 and 5,470,584

Cardeem Capital L.P.
c/o Mr. Peter Safir, Agent
Kleinfeld, Kaplan and Becker
1140 Nineteenth Street
Washington, DC 20036-6601

Owner of U.S. Letters Patent Nos. 4,894,240; 5,002,776 and 5,364,620

Elan Corporation, PLC
c/o Mr. Gary Frischling, Agent
Irell & Manella
1800 Avenue of the Stars
Los Angeles, CA 90067-4276

Andrx Pharmaceuticals, Inc.

By: 

James V. Costigan
Hedman, Gibson & Costigan
1185 Avenue of the Americas
New York, NY 10036-2601
(212) 302-8989

which does not come within each of the ten (10) particular ranges of percent dissolution under the conditions of claim 1 of U.S. 5,439,689 because it has a different dissolution profile. Claims 2-13 and 22 of U.S. 5,439,689 are directly or indirectly dependent on claim 1 of U.S. 5,439,689, and are not infringed because claim 1 of U.S. 5,439,689 is not infringed. Claims 14-21 are not infringed because they are directed to a delayed release composition where the release profile has three (3) particular ranges. The Andrx product has an in vitro dissolution profile which does not come within each of the three (3) particular ranges of percent dissolution under the conditions of claim 14 of U.S. 5,439,689 because it has a different dissolution profile. Claims 15-21 of U.S. 5,439,689 are directly or indirectly dependent on claim 14 of U.S. 5,439,689, and are not infringed because claim 14 of U.S. 5,439,689 is not infringed.

Claims 1-28 of U.S. 4,894,240 will not be infringed by the making, using or selling of the Andrx product because the Andrx product does not contain a core comprising diltiazem or a pharmaceutically acceptable salt thereof in association with an organic acid which is a limitation that is in claim 1 of U.S. 4,894,240. Claims 2-27 are all directly or indirectly dependent on claim 1 of U.S. 4,894,240 and are not infringed because claim 1 of U.S. 4,894,240 is not infringed.

Claims 1-20 of U.S. 5,002,776 will not be infringed by the making, using or selling of the Andrx product because the Andrx product does not contain a core comprising diltiazem or a pharmaceutically acceptable salt thereof in association with an organic acid which is a limitation that is in claim 1 of U.S. 5,002,776. Claims 2-20 are all directly or indirectly dependent on claim 1 of U.S. 5,002,776 and are not infringed because claim 1 of U.S. 5,002,776 would not be infringed by the Andrx product.

Claims 1-5 of U.S. 5,364,620 will not be infringed by the making using or selling of the Andrx product because the Andrx product is not a formulation comprising pellets having a core comprising diltiazem or a pharmaceutically acceptable salt thereof in association with an organic acid which is a limitation that is in claim 1 of U.S. 5,364,620. Claims 2-20 are all directly or indirectly dependent on claim 1 of U.S. 5,002,776 and are not infringed because claim 1 of U.S. 5,002,776 would not be infringed by the Andrx product. Each of the claims of U.S. 5,364,620 is directed to a method of treating, controlling or preventing either blood pressure or angina attacks in particular subjects by using a formulation comprising pellets having a core comprising diltiazem or a pharmaceutically acceptable salt thereof in association with an organic and Andrx will not make, use or sell a product having a core which contains an organic acid

The United States Food and Drug Administration has received an abbreviated new drug application from Andrx which contains bioequivalence data which shows that the Andrx once a day diltiazem product is bioequivalent to Cardizem CD.

The Andrx Abbreviated New Drug Application Serial No. is 74-752.

The established name for the proposed drug product is Diltiazem Hydrochloride Extended-Release Capsule.

The active ingredient for the proposed drug product is diltiazem hydrochloride; the dosage forms are a once a day oral capsule that will be sold in multiple strengths of 120mg; 180mg and 300mg.

The following patents which have been listed in Approved Drug Products are known to Andrx and are invalid and will not be infringed by the making using or selling of the Andrx diltiazem hydrochloride product (Andrx product):

- 5,286,497 - Expiration Date May 20, 2011
- 5,439,689 - Expiration Date August 8, 2012
- 5,470,584 - Expiration Date May 20, 2011
- 4,894,240 - Expiration Date January 16, 2007
- 4,752,476 - Expiration Date March 26, 2008
- 5,364,620 - Expiration Date November 14, 2011

The patents which have been listed in Approved Drug Products will not be infringed by the Andrx product for the following reasons:

Claim 13 of U.S. 5,286,497 will not be infringed by the making, using or selling of the Andrx product because the Andrx product does not exhibit the patented in-vitro dissolution profile under the conditions of measurement that are set forth in the claims of U.S. 5,286,497 and is therefore outside of the scope of the invention which is patented by U.S. 5,286,497. Claim 1 of U.S. 5,286,497 is limited to a blend of two types of diltiazem beads which either separately or in combination exhibit certain particular ranges of percent dissolution of total

diltiazem in vitro under test conditions which are set forth in claim 1. The Andrx product has an in vitro dissolution profile which does not come within each of the ten (10) particular ranges of percent dissolution under the conditions of claim 1 of U.S. 5,286,497 because it has a different dissolution profile. Claims 2-11 of U.S. 5,286,497 are directly or indirectly dependent on claim 1 of U.S. 5,286,497, and are not infringed because claim 1 of U.S. 5,286,497 is not infringed.

Claims 1-9 of U.S. 5,470,584 will not be infringed by the making, using or selling of the Andrx product because the Andrx delayed release product does not exhibit the patented in-vitro dissolution profile under the conditions of measurement that are set forth in the claims of U.S. 5,470,584 and is therefore outside of the scope of the invention which is patented by U.S. 5,470,584. Claim 1 of U.S. 5,470,584 recites a delayed release diltiazem formulation that has three (3) particular ranges of percent dissolution of total diltiazem in vitro under test conditions which are set forth in claim 1. The Andrx product has an in vitro dissolution profile which does not come within each of the three (3) particular ranges of percent dissolution under the conditions of claim 1 of U.S. 5,470,584 because it has a different dissolution profile. Claims 2-9 of U.S. 5,470,584 are directly or indirectly dependent on claim 1 of U.S. 5,470,584, and are not infringed because claim 1 of U.S. 5,470,584 is not infringed. Claims 1-9 of U.S. 5,470,584 are invalid because they are unpatentable under 35 U.S.C.§102 or 35 U.S.C.§103 over U.S. 4,364,620 which discloses diltiazem pellets which are the same as the subject matter of the claims of U.S. 5,470,584. Claims 1-9 of U.S. 5,470,584 are also invalid under 35 U.S.C.§112 because they are indefinite and fail to point out what the applicant regards as the invention by failing to provide an antecedent basis for the terms diltiazem bead and diltiazem core; and by failing to disclose the best mode for the practice of the invention by failing to provide in Example 3 a description of how to make the preferred formulation. Claims 1-9 are invalid under 35 U.S.C.§132 for introducing new matter in that the term "delayed release diltiazem formulation" was not disclosed in the originally filed application.

Claims 1-22 of U.S. 5,439,689 will not be infringed by the making, using or selling of the Andrx product, which will be sold for the treatment of hypertension and angina, because the Andrx delayed release bead does not exhibit the in-vitro dissolution profile under the conditions of measurement that are set forth in the claims of U.S. 5,439,689 and is therefore outside of the scope of the invention which is patented by U.S. 5,439,689. Claim 1 of U.S. 5,439,689 is limited to a delayed release bead that has ten (10) particular ranges of percent dissolution of total diltiazem in vitro under test conditions which are set forth in claim 1. The Andrx product has an in vitro dissolution profile

Supplemental Patent Certification Under 21 CFR §314.94 and Supplemental Notice of Certification of Invalidity or Noninfringement of a Patent Under 21 CFR §314.95

1. Andrx Pharmaceuticals, Inc., (Andrx) having a place of business at 4001 S.W. 47th Avenue, Fort Lauderdale, FL 33314 hereby certifies to the following persons that it has filed an Abbreviated New Drug Application under 21 U.S.C.§505(j)(2)(B)ii for permission to sell a once a day diltiazem hydrochloride product which is bioequivalent to Cardizem CD:

a. Holder of New Drug Application for Cardizem CD

Marion Merrell Dow, Inc.
and Hoechst Marion Roussel, Inc.
c/o J. Michael Dixon
Corporate Counsel
9110 East Galbraith Road
Cincinnati, OH 45215-6300

b. Owner of U.S. Letters Patent Nos. 5,286,497; 5,439,689 and 5,371,084

Biogerm Capital L.P.
c/o Mr. Peter Safir, Agent
Weinfeld, Kaplan and Becker
1110 Nineteenth Street
Washington, DC 20036-6601

c. Owner of U.S. Letters Patent Nos. 4,894,240; 5,002,776 and 5,364,620

Elan Corporation, PLC
c/o Mr. Gary Frischling, Agent
Orrick & Manella
1300 Avenue of the Stars
Los Angeles, CA 90067-4276

Andrx
PHARMACEUTICALS, INC.

July 28, 1997

Mr. Douglas L. Sporn
Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: **ANDA 74-752** Diltiazem Hydrochloride Extended-release Capsules, USP (Once-daily) 120, 180, 240 and 300 mg **(Reference Drug - Cardizem CD™)**

ANDA 74-852 Diltiazem Hydrochloride Extended-release Capsules, USP (Once-daily) 120, 180 and 240 mg **(Reference Drug - Dilacor XR™)**

Dear Mr. Sporn:

We are writing to ascertain the status of the above ANDA 74-752 and 74-852.

David Gardner, Vice President of Regulatory Affairs of Andrx Pharmaceuticals, Inc., has been in continuous contact with various members of the OGD staff who have provided constant assistance. He has now been verbally assured that both ANDAs are in the final process of being approved.

However, based on the chronology of the major events for these two ANDAs (see enclosed tables), we feel that the final processing by the OGD may be taking more time than expected. It would be appreciated if you would review the status of these ANDAs so that we do not encounter any unnecessary delays during this final approval stage.

Thank you in advance for any assistance that you can provide.

Sincerely,

Chih-Ming Chen, Ph.D.
President

Enclosures

cc: D.A. Gardner - Regulatory Affairs

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

Andrx
PHARMACEUTICALS, INC.

September 10, 1997

Office of Generic Drugs, CDER, FDA
DOCUMENT CONTROL ROOM
Attention: **Peter Rickman**
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE REQUEST

NEW CORRESP

Re: ANDA 74-752 *Diltiazem Hydrochloride Extended-release Capsules, USP, 120 mg, 180 mg, 240 mg & 300 mg (Once-a-day Dosage)*

Dear Director, Office of Generic Drugs:

As required by 21 CFR 314.95(b), Andrx Pharmaceuticals, Inc. ("Andrx"), today submits additional information to an original abbreviated new drug application ("ANDA") for Diltiazem Hydrochloride Extended-release Capsules, USP, 120 mg, 180 mg, 240 mg and 300 mg dated December 22, 1995.

This submission is in response to a telephone conversation with Peter Rickman on September 9, 1997. Mr. Rickman requested information to confirm that an additional notification to Paragraph IV certification had been sent to Marion Merrell Dow, Inc. (a.k.a. Hoechst Marion Roussel, Inc.), Carderm Capital L. P. and Elan Corporation, plc by **registered or certified mail, return receipt requested.** The original notifications were sent by **express mail, return receipt requested.**

This is a certification that a *Notice of Certification of Non - Infringement* was sent by certified mail to each person identified under 21 CFR 314.95(a) and that the notice met the content requirements of 21 CFR 314.95(c). Copies of the letter, the proofs of mailing dated September 9, 1997 and the signed return receipts are attached.

Andrx is providing three (3) copies of this submission (12 pages), an Archival Copy and two (2) copies - one copy for the Chemistry Section and one copy for the Pharmacokinetic Section.

Andrx also certifies that, concurrent with the filing, a true copy of this submission along with a confirmation that the content is a true copy was sent to our local district office.

4955 ORANGE DRIVE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

If there are any questions regarding this information please contact me at (954) 581-7500 extension 1413 and/or (954) 587-1054 (Fax).

Sincerely,

David A. Gardner

David A. Gardner
V.P., Regulatory Affairs/QA/QC

ORIGINAL

ANDRX PHARMACEUTICALS, INC.

June 20, 1997

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT

Re: **ANDA 74-752: Diltiazem Hydrochloride Extended-release Capsules, USP (Once-a-day Dosage) 120mg, 180 mg, 240 mg & 300mg**

Dear Director, Office of Generic Drugs:

Andrx Pharmaceuticals, Inc. ("Andrx"), today submits twelve (12) copies of final printed container labels and eleven (11) copies of the draft insert for an original abbreviated new drug application ("ANDA") for Diltiazem Hydrochloride Extended-release Capsules, USP (Once-a-day Dosage) 120 mg, 180 mg, 240 mg and 300 mg dated September 22, 1995. This submission is in response to a telephone conversation with Dr. J. D. White at approximately 11:30 am on June 17, 1997.

Andrx is providing two copies of this telephone amendment to the Office of Generic Drugs, an Archival Copy and a Chemistry Review Copy.

This also certifies that, concurrent with the filing of this telephone amendment, a true copy of the amendment along with a certification that the contents are a true copy was sent to our local district office in Orlando, Florida. This copy was sent as a Field Submission Chemistry Section.

Please direct any communications regarding this submission to me at the following address:

4001 S. W. 47 Avenue, Suite #201
Ft. Lauderdale, FL 33314

If you need to telephone or send a facsimile, my numbers are (954) 581-7500 and (954) 587-1054 (Fax).

Thank you for your prompt handling of this telephone amendment.

RECEIVED
JUN 23 1997
GENERIC DRUGS

Sincerely,
David A. Gardner
David A. Gardner
V. P., Regulatory Affairs/QA/QC

ANDA: 74-752 FIRM: Andrx Pharmaceuticals, Inc.

DRUG PRODUCT: Diltiazem Hydrochloride Extended-release Capsules, USP, 120 mg, 180 mg, 240 mg & 300 mg (Once-a-day Dosage)

Based on a telephone conversation on the morning of June 17, 1997 with Dr. J. D. White regarding the labeling for ANDA 74-752, the following is being submitted:

1) Twelve (12) final printed labels for each container size for each strength.

Per Dr. White, the label copy submitted with the May 28, 1997 Facsimile Amendment was acceptable - no further changes.

2) Eleven (11) black and white draft copies of the package insert.

Per Dr. White, the following changes will be required in the package insert:

DESCRIPTION:

Correct the molecular formula to include the "S" which was omitted.

Delete the following from the list of inactive ingredients:

15

CLINICAL PHARMACOLOGY

Hemodynamic and Electrophysiologic Effects

Fourth paragraph, third sentence: delete the extra spaces between "day" and "dosage" in "(once-a-day dosage)".

Per Dr. White, **the above revisions will not have to be made prior to tentative approval of the ANDA but will, of course, be required for full approval.**