CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

74-752/S-001 to S-018

Trade Name: Cartia XT

Generic Name: (Diltiazem Hydrochloride Extended-release Capsules, 120 mg; 180 mg; 240 mg; 300 mg)

Sponsor: Andrx Pharmaceuticals, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-752/S-001 to S-018

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-752/S-001 to S-018

APPROVAL LETTERS

ANDA 74-752/S-001, S-002, S-003, 007

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

JUN 8

Dear Sir:

This is in reference to your supplemental new drug applications dated August 18, 1998, submitted pursuant to 21 CFR 314.70, regarding your abbreviated new drug application for Cartia-XT (Diltiazem Hydrochloride Extended-release Capsules, USP); 120 mg, 180 mg, 240 mg and 300 mg.

Reference is also made to your amendment dated April 23, 1999.

The supplemental applications provide for:

S-001: Packaging Addition - the addition of 90 count container/closure systems, 1000 count container closure systems, and changes in container sizes for the 120 mg x 30 capsule, 240 mg x 30 capsule, and 240 mg x 500 capsule packaging.

S-002: Packaging Revision - a change in the [redacted]

S-003: Packaging Revision - a change in the [redacted]

S-007: Labeling Revision.

We have completed the review of these supplemental applications, and they are approved.

Regarding the Labeling Revision:

Container: 90s and 1000s

1. Relocate "RX only" to the main panel.

2. Revise the storage temperature recommendations as follows:

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

These revisions may be done in an annual report provided that the changes are described in full.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

/S/ 6/8/99

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

APPEARS THIS WAY
ON ORIGINAL

ANDA 74-752/S-004, S-006

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

JUN 8

Dear Sir:

This is in reference to your supplemental new drug applications dated September 11, 1998, submitted pursuant to 21 CFR 314.70, regarding your abbreviated new drug application for Cartia-XT (Diltiazem Hydrochloride Extended-release Capsules, USP); 120 mg, 180 mg, 240 mg and 300 mg.

Reference is also made to your correspondence dated February 23 and March 26, 1999, and your amendments dated April 14 and May 20, 1999.

The supplemental applications provide for:

S-004: Formulation Change -

[redacted]

S-006: Labeling Revision.

From a labeling standpoint the insert labeling has been satisfactorily revised to reflect the addition of magnesium stearate to the listing of inactive ingredients in the DESCRIPTION section.

We have completed the review of these supplemental applications, and they are approved.

Please note that the listed drug referenced in your application is subject to periods of patent protection which expire on January 16, 2007 (Pat.#4,894,240), March 26, 2008, (Pat.#5,002,776), May 20, 2011 (Pat.#5,286,497), November 14, 2011, (Pat.#5,364,620), August 8, 2012 (Pat.#5,439,689) and May

20, 2011 (Pat.#5,470,584), respectively. Your application contains patent certifications under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, or sale of this drug product will not infringe on any of these patents. Section 505(j)(5)(B)(iii) of the Act provides that approval shall be made effective immediately unless an action is brought for infringement of the patent(s) which are the subject of the certifications before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(I) is received. You have notified the Agency that Andrx Pharmaceuticals Inc. has complied with the requirements of Section 505(j)(2)(B) of the Act and that no action for patent infringement was brought against Andrx Pharmaceuticals Inc. within the statutory forty-five day period.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

/S/ 6/8/99

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

APPEARS THIS WAY
ON ORIGINAL

ANDA 74-752/S-005

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

APR 2 1999

Dear Sir:

This is in reference to your supplemental new drug application dated October 23, 1998, submitted pursuant to 21 CFR 314.70 regarding your abbreviated new drug application for CARTIA XT™ (Diltiazem Hydrochloride Extended-release Capsules, USP); 120 mg, 180 mg, 240 mg and 300 mg.

The supplemental application provides for final printed container labels for each size and strength.

We have completed the review of this supplemental application and it is approved.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

/S/ 3/31/99

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

ANDA 74-752/S-008

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

JUL 18 2000

Dear Diane Servello:

This is in reference to your supplemental new drug application dated June 24, 1999, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act, regarding your abbreviated new drug application for Diltiazem Hydrochloride Extended-release Capsules USP, 120 mg, 180 mg, 240 mg and 300 mg.

Reference is also made to your amendments dated January 27, April 3 and June 16, 2000.

The supplemental application submitted as a "Prior Approval Supplement", provides for the use of

We have completed the review of this supplemental application and it is approved.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

/S/ 7/18/00

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

ANDA 74-752/S-009

MAY 12

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

Dear Diane Servello:

This is in reference to your supplemental new drug application dated June 24, 1999, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act, regarding your abbreviated new drug application for Diltiazem Hydrochloride Extended-release Capsules USP, 120 mg, 180 mg, 240 mg, and 300 mg.

Reference is also made to your amendments dated January 27, and April 3, 2000, and April 26, 2000.

The supplemental application submitted as "Prior Approval Supplement", provide for the

We have completed the review of this supplemental application, and it is approved.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

/S/ 5/12/00

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

ANDA 74-752/S-011 (120 mg, 180 mg, 240 mg and 300 mg)
74-852/S-004 (120 mg, 180 mg and 240 mg)

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

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Dear Madam:

This is in reference to your supplemental new drug applications dated February 28, 2000, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act, regarding your abbreviated new drug application for Diltiazem Extended-release Capsules, USP.

The supplemental applications submitted as "Prior Approval Supplements", provide for:

S-011, S-004:

We have completed the review of these supplemental applications, and they are approved.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

/S/

for Florence S. Fang 8/15/00
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-752/S-012

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

JAN 8 2001

Dear Diane Servello:

This is in reference to your supplemental new drug application dated July 19, 2000, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act, regarding your abbreviated new drug application for Diltiazem Hydrochloride Extended-release Capsules USP, 120 mg, 180 mg, 240 mg and 300 mg.

The supplemental application submitted as a "Supplement-Changes Being Effected", provides for an additional in-process dissolution test for Diltiazem HCl Extended-release

We have completed the review of this supplemental application and it is approved.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

/S/

1/4/01

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

ANDA 74-752/S-013

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

JAN 8 2001

Dear Diane Servello:

This is in reference to your supplemental new drug application dated July 28, 2000, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act, regarding your abbreviated new drug application for Diltiazem Hydrochloride Extended-release Capsules USP, 120 mg, 180 mg, 240 mg and 300 mg.

The supplemental application submitted as a "Supplement-Changes Being Effected in 30 days", provides for an improvement to the process for Diltiazem HCl Extended-release

We have completed the review of this supplemental application and it is approved.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

/S/ 1/4/01

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

ANDA 74-752/S-015

Andrx Pharmaceuticals, Inc.
Attention: Diane Servello
4955 Orange Drive
Fort Lauderdale, FL 33314

FEB 27 2002

Dear Diane Servello:

This is in reference to your supplemental new drug application dated August 21, 2001, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act, regarding your abbreviated new drug application for Diltiazem Hydrochloride Extended-release Capsules USP, 120 mg, 180 mg, 240 mg and 300 mg.

The supplemental application submitted as "Prior Approval Supplement", provides for a revision of the in-process dissolution specifications for Diltiazem HCl Extended-release

We have completed the review of this supplemental application and it is approved.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

/S/ 2/25/02

for

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

ANDA 74-752/S-016

Andrx Pharmaceuticals, Inc.
Attention: Diane Servello
4955 Orange Drive
Fort Lauderdale, FL 33314

OCT 11 2002

Dear Diane Servello:

This is in reference to your supplemental new drug application dated June 4, 2002, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act, regarding your abbreviated new drug application for Diltiazem Hydrochloride Extended-release Capsules USP, 120 mg, 180 mg, 240 mg and 300 mg.

The supplemental application submitted as a "Supplement-Changes Being Effected in 30 days", provides for the addition of

We have completed the review of this supplemental application and it is approved.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

/S/ 10/11/02

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

74-752/S-017

DEC 24 2002

ANDA - See Attached List

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

Dear Ms. Vaughn:

This is in reference to your supplemental new drug applications dated June 24, 2002, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act, regarding your abbreviated new drug applications for the drug products listed in the appendix.

These supplemental applications, submitted as "Supplements-Changes Being Effected in 30 Days", provide for the addition of

We have completed the review of these supplemental applications, and they are approved.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

/S/ 12/24/02

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

ANDA 74-752/S-018

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

NOV 18 2003

Dear Janet Vaughn:

This is in reference to your supplemental new drug application dated June 30, 2003, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act, regarding your abbreviated new drug application for Cartia XT Capsules USP, 120 mg, 180 mg, 240 mg and 300 mg.

Reference is also made to your amendment dated October 24, 2003.

The supplemental application, submitted as a "Prior Approval Supplement", provides for

We have completed the review of this supplemental application and it is approved.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

for /S/ 11/18/03.

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

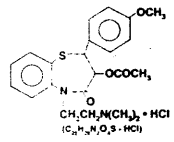
74-752/S-001 to S-018

Final Printed Labeling

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

R Only

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:



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

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, ammonomethacrylate copolymer-NF, D & C Red #28, D & C Yellow #10, D & C Yellow #10 Aluminum Lake, ethylcellulose, FD & C Blue #1 Aluminum Lake, FD & C Blue #2 Aluminum Lake, FD & C Red #40, FD & C Red #40 Aluminum Lake, gelatin-NF, magnesium stearate, methacrylic acid copolymer-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 (once-a-day dosage) are due 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 change 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 by 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 vascular beds, 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) [illegible] ischemic and nonischemic

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Actions Diltiazem Hydrochloride Extended-release Capsules USP (once-a-day dosage) has been shown to produce changes in exercise tolerance, probably related to its ability to reduce myocardial oxygen demand. This is accomplished by reductions in heart rate and systemic blood pressure at submaximal and maximal exercise 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

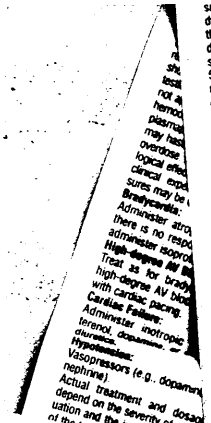
Like other calcium channel antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

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 systolic pressure, 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 a change in urinary sodium-potassium ratio.

In a double-blind, parallel dose-response study of doses from 60 mg to 480 mg once daily, diltiazem hydrochloride extended-release capsule (once-a-day dosage) increased time to termination of exercise in a linear manner over the entire dose range studied. The improvement in time to termination of exercise utilizing a Bruce exercise protocol, measured at trough, for placebo, 60 mg, 120 mg, 240 mg, 360 mg, and 480 mg was 29, 40, 56, 51, 69 and 68 seconds, respectively. As doses of diltiazem hydrochloride extended-release capsule (once-a-day dosage) were increased, overall angina frequency was decreased. Diltiazem hydrochloride extended-release capsule (once-a-day dosage), 180 mg once daily, or placebo was administered in a double-blind study to patients receiving concomitant treatment with long-acting nitrates and/or beta-blockers. A significant increase in time to termination of exercise and a significant decrease in overall angina frequency was observed. In this trial the overall frequency of adverse events in the diltiazem hydrochloride extended-release capsule (once-a-day dosage) treatment group was the same as the placebo group.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods by approximately 20%. In a study involving single oral doses of 300 mg of diltiazem hydrochloride in six normal volunteers, the average maximum 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 pro-



duces 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 in heart 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 a change in urinary sodium/potassium ratio.

In a double-blind, parallel dose-response study of doses from 60 mg to 480 mg once daily, diltiazem hydrochloride extended-release capsule (once-a-day dosage) increased time to termination of exercise in a linear manner over the entire dose range studied. The improvement in time to termination of exercise utilizing a Bruce exercise protocol, measured at trough, for placebo, 60 mg, 120 mg, 240 mg, 360 mg, and 480 mg was 29, 40, 56, 51, 69 and 68 seconds, respectively. As doses of diltiazem hydrochloride extended-release capsule (once-a-day dosage) were increased, overall angina frequency was decreased. Diltiazem hydrochloride extended-release capsule (once-a-day dosage), 180 mg once daily, or placebo was administered in a double-blind study to patients receiving concomitant treatment with long-acting nitrates and/or beta-blockers. A significant increase in time to termination of exercise and a significant decrease in overall angina frequency was observed. In this trial the overall frequency of adverse events in the diltiazem hydrochloride extended-release capsule (once-a-day dosage) treatment group was the same as the placebo group.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods by approximately 20%. In a study involving single oral doses of 300 mg of diltiazem hydrochloride in six normal volunteers, the average maximum 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 3.0 to 4.5 hours. Desacetyl 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.

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-tne-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

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.

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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 Hydrochloride Extended-release Capsule (once-a-day) n=3291	Placebo n=991
Edema	4.6%	1.5%
Headache	4.6%	3.6%
Dizziness	3.5%	1.9%
Asthenia	2.8%	1.3%
AV block, First-Degree	2.4%	0.6%
Bradycardia	1.7%	1.3%
Flushing	1.4%	0.5%
Nausea	1.2%	1.3%

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:

Amblyopia, 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 disease in these patients. A number of well-documented cases of granulocytic 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 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 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 360 mg/kg.

The toxic dose in man is not known. Due to extensive metabolism, blood levels after a standard dose of diltiazem can vary over 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 patient 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.

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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. Read 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

ride 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 Nitroglycerin.** 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 btl	62037-597-30	White/orange opaque capsule imprinted with "Andrx 597" on one end and "120 mg" on the other.
	90 btl	62037-597-90	
	500 btl	62037-597-05	
	1000 btl	62037-597-10	
180 mg	30 btl	62037-598-30	Yellow/orange opaque capsule imprinted with "Andrx 598" on one end and "180 mg" on the other.
	90 btl	62037-598-90	
	500 btl	62037-598-05	
	1000 btl	62037-598-10	
240 mg	30 btl	62037-599-30	Light brown/orange opaque capsule imprinted with "Andrx 599" on one end and "240 mg" on the other.
	90 btl	62037-599-90	
	500 btl	62037-599-05	
	1000 btl	62037-599-10	
300 mg	30 btl	62037-600-30	Orange/orange opaque capsule imprinted with "Andrx 600" on one end and "300 mg" on the other.
	90 btl	62037-600-90	
	500 btl	62037-600-05	
	1000 btl	62037-600-10	

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

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

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

Rev. date: 04/99

7000

NDC 62037-597-30

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
30 CAPSULES

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

7001 (08/98)

N 3 62037-597-30 5

LOT: APR - 2 1999

EXP:

NDC 62037-598-30

ONCE DAILY CartiaXT

(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 (08/98)

N 3 62037-598-30 2

LOT: APR - 2 1999

EXP:

NDC 62037-599-30

ONCE DAILY CartiaXT

(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 (08/98)

N 3 62037-599-30 9

LOT: APR - 2 1999

EXP:

NDC 62037-600-30

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
30 CAPSULES

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

7013 (08/98)

N 3 62037-600-30 2

LOT: APR - 2 1999

EXP:

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AN ANDRX COMPANY

NDC 62037-597-05

7003 (08/98)

Andrx
PHARMACEUTICALS, INC.

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

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N 3 62037-597-05 3

LOT:
EXP:

NDC 62037-598-05

7007 (08/98)

Andrx
PHARMACEUTICALS, INC.

ONCE DAILY
CartiaXT™
(diltiazem HCl extended-release capsules, USP)

ONCE-A-DAY DOSAGE

EACH CAPSULE CONTAINS:
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Fort Lauderdale, FL 33314

UNAUTHORIZED
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AN ANDRX COMPANY

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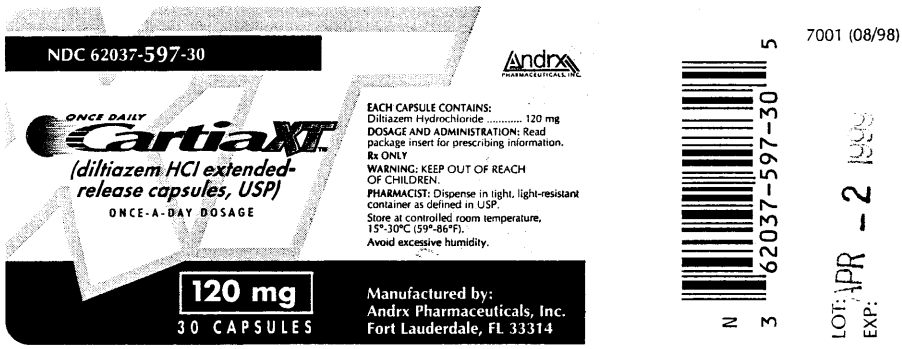
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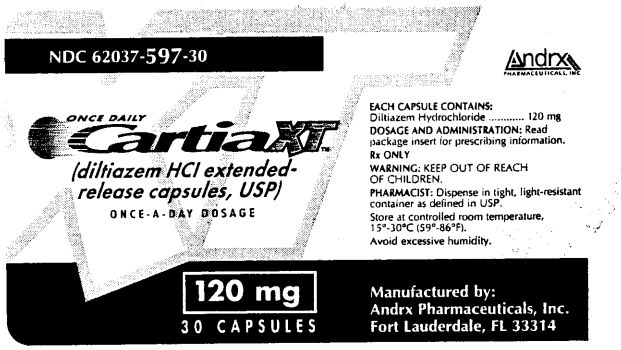
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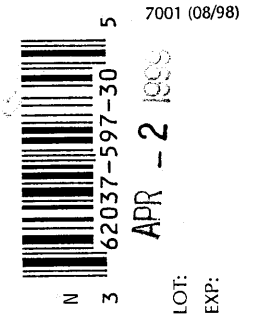
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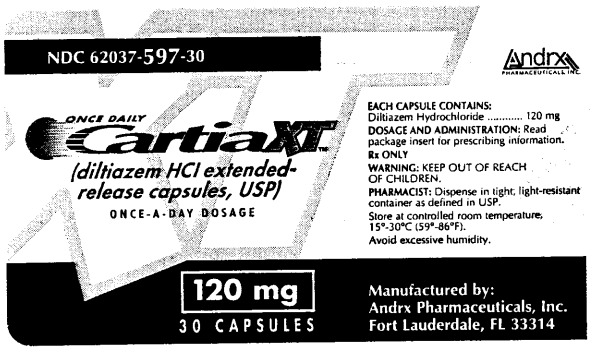
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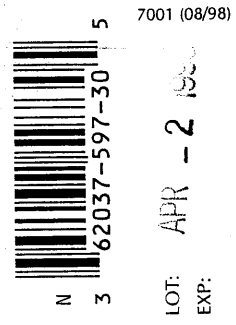
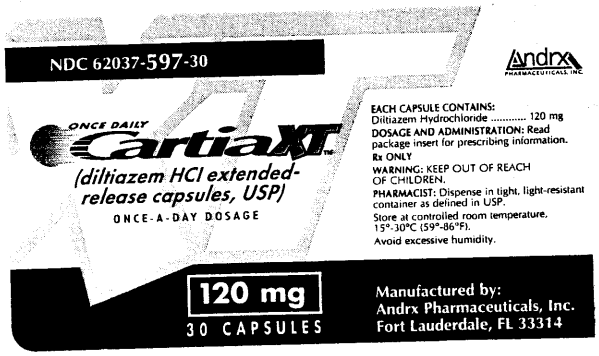
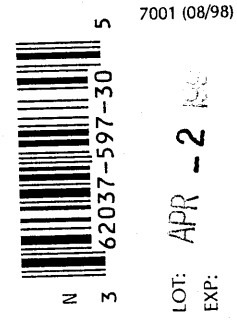
WARNING: KEEP OUT OF REACH OF CHILDREN.
PHARMACIST: Dispense in tight, light-resistant container as defined in USP.
Store at controlled room temperature, 15°-30°C (59°-86°F).
Avoid excessive humidity.
120 mg
30 CAPSULES
Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314


7001 (08/98)
N 3 62037-597-30 5
LOT: APR - 2
EXP:


NDC 62037-597-30
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
30 CAPSULES
Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314


7001 (08/98)
N 3 62037-597-30 5
LOT: APR - 2
EXP:

OR15

NDC 62037-598-30

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

Andrx PHARMACEUTICALS, INC.

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 (08/98)

N 3 62037-598-30 2

LOT: APR -2
EXP:

NDC 62037-598-30

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

Andrx PHARMACEUTICALS, INC.

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 (08/98)

N 3 62037-598-30 2

LOT: APR -2
EXP:

NDC 62037-598-30

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

Andrx PHARMACEUTICALS, INC.

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 (08/98)

N 3 62037-598-30 2

LOT: APR -2
EXP:

NDC 62037-598-30

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

Andrx PHARMACEUTICALS, INC.

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 (08/98)

N 3 62037-598-30 2

LOT: APR -2
EXP:

ORIG

7009 (08/98)

NDC 62037-599-30

Andrx PHARMACEUTICALS, INC.

ONCE DAILY

CartiaXT™

(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

N 3 62037-599-30 9

LOT: APR -2
EXP:

7009 (08/98)

NDC 62037-599-30

Andrx PHARMACEUTICALS, INC.

ONCE DAILY

CartiaXT™

(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

N 3 62037-599-30 9

LOT: APR -2
EXP:

7009 (08/98)

NDC 62037-599-30

Andrx PHARMACEUTICALS, INC.

ONCE DAILY

CartiaXT™

(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

N 3 62037-599-30 9

LOT: APR -2
EXP:

7009 (08/98)

NDC 62037-599-30

Andrx PHARMACEUTICALS, INC.

ONCE DAILY

CartiaXT™

(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

N 3 62037-599-30 9

LOT: APR -2
EXP:

NDC 62037-599-05

7011 (08/98)

Andrx
PHARMACEUTICALS, INC.

ONCE DAILY
CartiaXT™
(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

500 CAPSULES

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

N 3 62037-599-05 7

LOT:

EXP:

NDC 62037-600-05

7015 (08/98)

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: -2

EXP:

290000

NDC 62037-597-90

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
90 CAPSULES

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

N 3 62037-597-90 9

7002 (08/98)

LOT:
EXP: JUN 8 1999

390000

NDC 62037-597-10

ONCE DAILY

CartiaXT™

(diltiazem HCl extended-release capsules, USP)

ONCE-A-DAY DOSAGE

Andrx PHARMACEUTICALS, INC.

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

1000 CAPSULES

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

7004 (08/98)

N 3 62037-597-10 7

LOT:

EXP:

NDC 62037-598-90

ONCE DAILY

CartiaXT™

(diltiazem HCl extended-release capsules, USP)

ONCE-A-DAY DOSAGE

Andrx PHARMACEUTICALS, INC.

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
90 CAPSULES

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

N 3 62037-598-90 6

APPROVED
JUN - 8 1999

LOT:
EXP:

7006 (08/98)

590065

NDC 62037-598-10

ONCE DAILY

CartiaXT™

(diltiazem HCl extended-release capsules, USP)

ONCE-A-DAY DOSAGE

Andrx PHARMACEUTICALS, INC.

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

1000 CAPSULES

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

7008(08/98)

N 3 62037-598-10 4

LOT:

EXP:

990000

NDC 62037-599-90

ONCE DAILY

CartiaXT™

(diltiazem HCl extended-release capsules, USP)

ONCE-A-DAY DOSAGE

240 mg

90 CAPSULES

Andrx PHARMACEUTICALS, INC.

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.

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

7010 (08/98)

N 3 62037-599-90 3

APPROVED JUN 98

LOT:

EXP:

NDC 62037-599-10

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.

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

1000 CAPSULES

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

7012 (08/98)

N 3 62037-599-10 1

LOT:

EXP:

000067

890000

NDC 62037-600-90

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

90 CAPSULES

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

N 3 62037-600-90 6

7014 (08/98)

LOT:

EXP: JUN - 8 1999

690000

NDC 62037-600-10

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

1000 CAPSULES

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

Andrx PHARMACEUTICALS, INC.

7016 (08/98)

N 3 62037-600-10 4

LOT:

EXP:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-752/S-001 to S-018

CHEMISTRY REVIEW(S)

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Chemistry Division II - Branch VI
Abbreviated New Drug Supplemental Application Review

ANDA 74-752/S-001, S-002, S-003

NAME AND ADDRESS OF APPLICANT:
Andrx Pharmaceutics, Inc.
4001 S.W. 47th Avenue
Fort Lauderdale, FL 33314

PURPOSE OF AMENDMENT/SUPPLEMENT

S-001 - Packaging Addition: To provide for the addition of 90 count container/closure systems, 1000 count container closure systems, and changes in container sizes for the 120 mg x 30 capsule, 240 mg x 30 capsule, and 240 mg x 500 capsule packaging.

S-002 - Packaging Revision: To provide for a change in the

S-003 - Packaging Revision: To provide for a change in the

S-007 - Labeling Revision

DATE(S) OF SUBMISSION(S)
Supplement submission - August 18, 1998.
Amendment - April 23, 1999.

PHARMACOLOGICAL CATEGORY	TRADE NAME	NONPROPRIETARY NAME
Calcium Channel Blocker	Cartia-XT	Diltiazem Hydrochloride

DOSAGE FORM	POTENCY	RX OR OTC
Extended release capsule	120 mg, 180 mg 240 mg, 300 mg	Rx

SAMPLES
N/A

RELATED IND/NDA/DMF
DMF # [redacted]
DMF # [redacted]
DMF # [redacted]
DMF # [redacted]
DMF # [redacted]
DMF # [redacted]

DMF # [redacted]
DMF # [redacted]
DMF # [redacted]

STERILIZATION
N/A

LABELING
Labeling was submitted as requested in the 3/23/99 letter showing the new proposed container/closure systems.

Labeling was found to be satisfactory per A. Vezza, 5/5/99.

The HOW SUPPLIED section of the package insert included all proposed container/closure systems.

BIOEQUIVALENCY STATUS
N/A

ESTABLISHMENT INSPECTION
N/A

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS
No change.

PACKAGING
The firm indicated that they proposed the addition of a larger package size (1000 count) and changes to the [redacted] Comparison of the proposed changes to the currently approved container/closure systems showed the following:

APPEARS THIS WAY
ON ORIGINAL

Approved container/closure systems

	120 mg	180 mg	240 mg	300 mg
30 count	bottle,	bottle	bottle	bottle
500 count				

All caps are

Proposed container/closure systems

	120 mg	180 mg	240 mg	300 mg
30 count	bottle,	bottle	bottle	bottle
90 count	bottle	bottle	bottle	bottle
500 count	bottle	bottle	bottle	bottle
1000 count				

All caps are

In addition to the proposed changes, comparison will show that the firm has also included an size of 90 count and changes to the container size used for the 120 mg x 30, 240 mg x 30 and 240 mg x 500. All of these changes except the 120 mg x 30 are bracketed by the original container/closure systems.

APPEARS THIS WAY
ON ORIGINAL

In support of the proposed changes, the firm submitted the following information regarding the proposed container/closure systems. Note that several of the container/closure systems have been previously approved in the original application.

1. Specifications and drawings for all bottles and caps.

2. USP <661> and <671> testing results for all container/closure systems except the [redacted] bottles.

3. Specifications, testing results, and 21 CFR certification for the [redacted]

4. Specifications, testing results, and USP 23 certification for the [redacted]

In support of the new container/closure systems, the firm packaged drug product in the smallest (30 count) and largest (1000 count) systems and placed them on accelerated stability. Packaging records were submitted for 120 mg Lot #597H001, 180 mg Lot #598H001, 240 mg Lot #599H001, and 300 mg Lot #600H001, along with blank packaging records for all container/closure sizes for all dosage levels.

1. **The firm submitted USP <661> and <671> testing results for the 120 cc and 150 cc container/closure systems demonstrating conformance to requirements as requested.**

STABILITY

[redacted]

APPEARS THIS WAY
ON ORIGINAL

[redacted]

REMARKS AND CONCLUSION
The supplemental applications may be Approved.

RECALLS	Reviewer
N/A	Glen Jon Smith

ORDER OF REVIEW:
The application submission(s) covered by this review was taken in the date order of receipt Yes____
No__X____

If no, explain reason(s) below. Expedited Review - Minor Amendment

cc: ANDA 74-752
Division File
Field Copy

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Chemistry Division II - Branch VI
Abbreviated New Drug Supplemental Application Review

ANDA 74-752/S-001, S-002, S-003

NAME AND ADDRESS OF APPLICANT:
Andrx Pharmaceutics, Inc.
4001 S.W. 47th Avenue
Fort Lauderdale, FL 33314

PURPOSE OF AMENDMENT/SUPPLEMENT

S-001 - Packaging Addition: To provide for the addition of 90 count container/closure systems, 1000 count container closure systems, and changes in container sizes for the 120 mg x 30 capsule, 240 mg x 30 capsule, and 240 mg x 500 capsule packaging.

S-002 - Packaging Revision: To provide for a change in the [redacted]

S-003 - Packaging Revision: To provide for a change in the [redacted]

DATE(S) OF SUBMISSION(S)
Supplement submission - August 18, 1998.

PHARMACOLOGICAL CATEGORY	TRADE NAME	NONPROPRIETARY NAME
Calcium Channel Blocker	Cartia-XT	Diltiazem Hydrochloride

DOSAGE FORM	POTENCY	RX OR OTC
Extended release capsule	120 mg, 180 mg 240 mg, 300 mg	Rx

SAMPLES	RELATED IND/NDA/DMF	STERILIZATION
N/A	DMF # [redacted]	N/A
	DMF # [redacted]	
	DMF # [redacted]	
	DMF # [redacted]	
	DMF # [redacted]	
	DMF # [redacted]	

DMF #
DMF #
DMF #

LABELING

The firm has added 90 count and 1000 count container/closure systems with no labeling submission. Since the 1000 count requires prior approval supplement, package and container labels as well as revised package inserts must be submitted.

BIOEQUIVALENCY STATUS

N/A

ESTABLISHMENT INSPECTION

N/A

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS

No change.

PACKAGING

The firm indicated that they proposed the addition of a larger package size (1000 count) and changes to the Comparison of the proposed changes to the currently approved container/closure systems showed the following:

Approved container/closure systems

	120 mg	180 mg	240 mg	300 mg
30 count	bottle,	bottle	bottle	bottle
500 count				

All caps are

Proposed container/closure systems

	120 mg	180 mg	240 mg	300 mg
30 count	bottle,	bottle	bottle	bottle
90 count	bottle	bottle	bottle	bottle

500 count	bottle	bottle	bottle	bottle
1000 count				

All caps are [redacted].

In addition to the proposed changes, comparison will show that the firm has also included an [redacted], size of 90 count and changes to the container size used for the 120 mg x 30, 240 mg x 30 and 240 mg x 500. All of these changes except the 120 mg x 30 are bracketed by the original container/closure systems.

In support of the proposed changes, the firm submitted the following information regarding the proposed container/closure systems. Note that several of the container/closure systems have been previously approved in the original application.

1. Specifications and drawings for all bottles and caps.

2. USP <661> and <671> testing results for all container/closure systems except the [redacted] bottles.

   The firm should submit USP <661> and <671> testing results for the 120 cc and 150 cc container/closure systems.

3. Specifications, testing results, and 21 CFR certification for the [redacted]

4. Specifications, testing results, and USP 23 certification for the [redacted]

In support of the new container/closure systems, the firm packaged drug product in the smallest (30 count) and largest (1000 count) systems and placed them on accelerated stability. Packaging records were submitted for 120 mg Lot #597H001, 180 mg Lot #598H001, 240 mg Lot #599H001, and 300 mg Lot #600H001, along with blank packaging records for all container/closure sizes for all dosage levels.

STABILITY

[redacted]

REMARKS AND CONCLUSION
The supplemental applications should be considered Not Approvable - Minor Amendment.

RECALLS	Reviewer
N/A	Glen Jon Smith

ORDER OF REVIEW:
The application submission(s) covered by this review was taken in the date order of receipt Yes X
No_____

If no, explain reason(s) below.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Chemistry Division II - Branch VI
Abbreviated New Drug Supplemental Application Review

ANDA 74-752/S-004, S-006

NAME AND ADDRESS OF APPLICANT:
Andrx Pharmaceutics, Inc.
4001 S.W. 47th Avenue
Fort Lauderdale, FL 33314

PURPOSE OF AMENDMENT/SUPPLEMENT
S-004 - Formulation Change:

[redacted]

S-006 - Label Revision.

DATE(S) OF SUBMISSION(S)
Supplement submission - September 11, 1998.
Amendment - December 22, 1998.
Amendment - January 14, 1999.
New Correspondence - January 29, 1999.
New Correspondence - February 23, 1999.
New Correspondence - March 26, 1999.
Amendment - April 14, 1999.
Amendment - May 20, 1999.

PHARMACOLOGICAL CATEGORY	TRADE NAME	NONPROPRIETARY NAME
Calcium Channel Blocker	Cartia-XT	Diltiazem Hydrochloride

DOSAGE FORM	POTENCY	RX OR OTC
Extended release capsule	120 mg, 180 mg 240 mg, 300 mg	Rx

SAMPLES	RELATED IND/NDA/DMF	STERILIZATION
N/A	N/A	N/A

LABELING

Labeling was submitted as requested in the 4/2/99 letter showing Magnesium Stearate as an inactive ingredient in the DESCRIPTION section of the package insert.

Labeling was found to be satisfactory per A. Vezza, 4/27/99.

BIOEQUIVALENCY STATUS

The firm submitted an *in vivo* bioequivalence study conducted using the revised formulation Lot #600R003B, 300 mg/capsule, comparing it to Cardizem CD® 300 mg/capsule, Lot #8P70935.

The firm requested a waiver of *in vivo* bioequivalence testing requirements for the 120 mg, 180 mg, and 240 mg product. Comparative dissolution data was submitted.

The Division of Bioequivalence has found the 300 mg capsules Lot #600R003B to be bioequivalent to Cardizem CD® 300 mg capsules Lot #P70935 per S. Pradhan, 1/7/99.

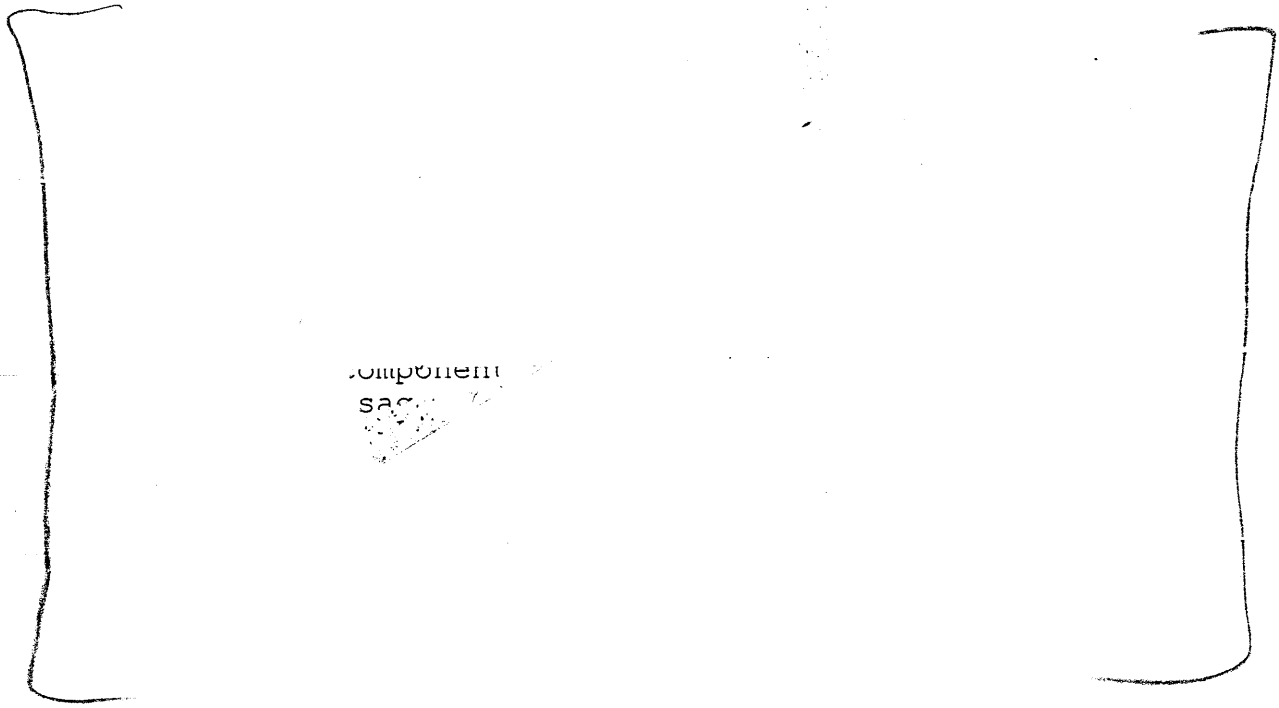
A waiver of *in vivo* bioequivalence studies for the 120 mg, 180 mg, and 240 mg capsules was granted per S. Pradhan, 1/7/99.

In vitro dissolution testing results were found to be acceptable per S. Pradhan, 1/7/99.

ESTABLISHMENT INSPECTION

N/A

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS



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PACKAGING
N/A

STABILITY
See above.

REMARKS AND CONCLUSION
The firm submitted certification on March 26, 1999 (New Correspondence, Paragraph IV Certification received by the innovator firm February 5 and 8, 1999) indicating that the 45 day waiting period has expired. No actions have been taken against the firm as a result of the Paragraph IV Certification submitted to the Agency on January 29, 1999 and received by the innovator, February 5 and 8, 1999.

The supplemental application may be Approved.

RECALLS
N/A

Reviewer
Glen Jon Smith

ORDER OF REVIEW:

The application submission(s) covered by this review was taken in the date order of receipt Yes_____

No X

If no, explain reason(s) below. Expedited Review - Minor Amendment

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Chemistry Division II - Branch VI
Abbreviated New Drug Supplemental Application Review

ANDA 74-752/S-004

NAME AND ADDRESS OF APPLICANT:
Andrx Pharmaceutics, Inc.
4001 S.W. 47th Avenue
Fort Lauderdale, FL 33314

PURPOSE OF AMENDMENT/SUPPLEMENT
S-004 - Formulation Change:

[redacted]

DATE(S) OF SUBMISSION(S)
Supplement submission - September 11, 1998.
Amendment - December 22, 1998.
Amendment - January 14, 1999.
New Correspondence - February 23, 1999.

PHARMACOLOGICAL CATEGORY	TRADE NAME	NONPROPRIETARY NAME
Calcium Channel Blocker	Cartia-XT	Diltiazem Hydrochloride

DOSAGE FORM	POTENCY	RX OR OTC
Extended release capsule	120 mg, 180 mg 240 mg, 300 mg	Rx

SAMPLES	RELATED IND/NDA/DMF	STERILIZATION
N/A	N/A	N/A

LABELING
The firm failed to submit a revised package insert indicating the addition of magnesium stearate as an inactive ingredient.

BIOEQUIVALENCY STATUS
The firm submitted an *in vivo* bioequivalence study conducted using the revised formulation Lot #600R003B, 300 mg/capsule, comparing it to Cardizem CD® 300 mg/capsule, Lot #8P70935.

The firm requested a waiver of *in vivo* bioequivalence testing requirements for the 120 mg, 180 mg, and 240 mg product. Comparative dissolution data was submitted.

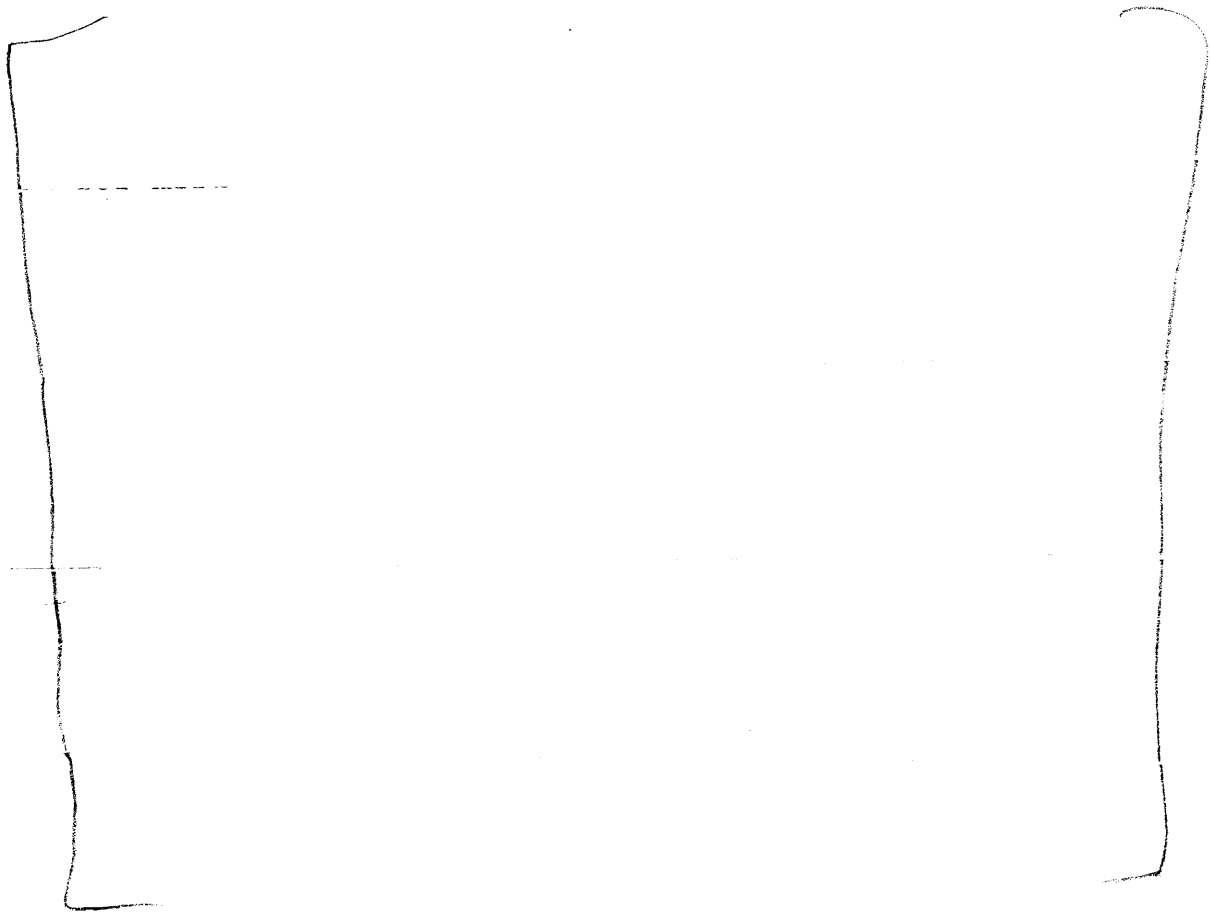
The Division of Bioequivalence has found the 300 mg capsules Lot #600R003B to be bioequivalent to Cardizem CD® 300 mg capsules Lot #P70935 per S. Pradhan, 1/7/99.

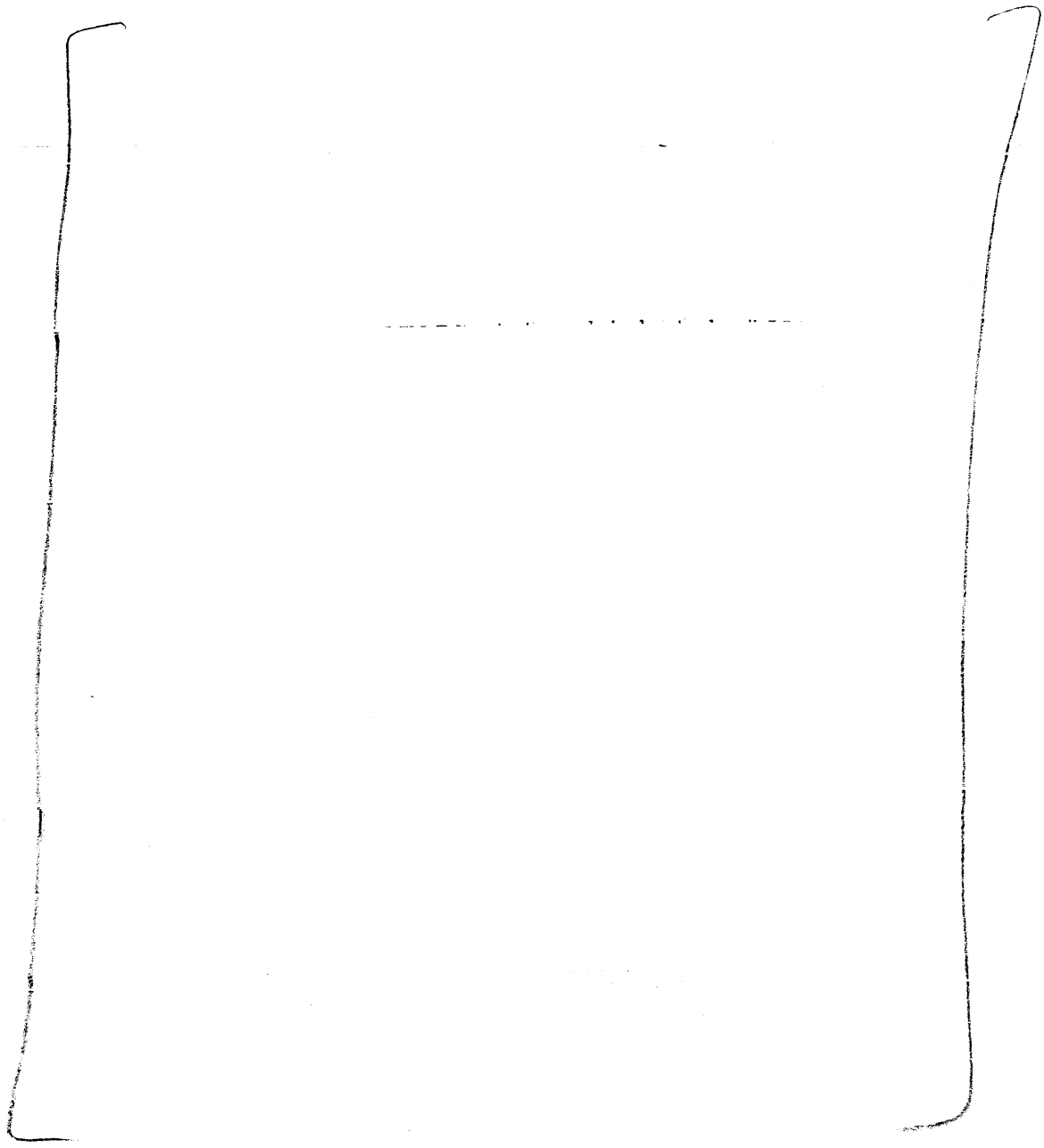
A waiver of *in vivo* bioequivalence studies for the 120 mg, 180 mg, and 240 mg capsules was granted per S. Pradhan, 1/7/99.

In vitro dissolution testing results were found to be acceptable per S. Pradhan, 1/7/99.

ESTABLISHMENT INSPECTION
N/A

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS





PACKAGING
N/A

STABILITY
See above.

REMARKS AND CONCLUSION
Note that litigation between the innovator and the firm has not been resolved. The firm sent additional notices of noninfringement to the innovator as a result of this supplement.

The supplemental application should be considered Not Approvable - Minor Amendment.

RECALLS	Reviewer
N/A	Glen Jon Smith

ORDER OF REVIEW:
The application submission(s) covered by this review was taken in the date order of receipt Yes X
No_____

If no, explain reason(s) below.

cc: ANDA 74-752
Division File
Field Copy

Endorsements:

HFD-647/GJSmith/3.12.99. /S/ - 3/30/99

HFD-647/UVenkataram/3.19.99 /S/ 4/1/99

74752S04.RGS/V:\FIRMSAM\ANDRX\LTRS&REV\74752S04.RGS

F/T by gp/3.30.99

TYPE OF LETTER: NOT APPROVABLE - MINOR AMENDMENT

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Supplemental Application Review

✓ANDA 74-752/S-008, S-009

NAME AND ADDRESS OF APPLICANT
Andrx Pharmaceuticals, Inc.
Attention: Diane Servello
4001 SW 47th Avenue
Fort Lauderdale, FL 33314

PURPOSE OF AMENDMENT/SUPPLEMENT
S-008, S-009: [redacted]

DATE(S) OF SUBMISSION(S)
June 24, 1999

January 27, 2000 - minor amendment

PHARMACOLOGICAL CATEGORY	TRADE NAME
Anti-hypertensive	N/A

NONPROPRIETARY NAME
Diltiazem Hydrochloride Extended-Release Capsules, USP

DOSAGE FORM	POTENCY
Capsules/Oral	120 mg, 180 mg, 240 mg, and 300 mg

RX OR OTC
Rx

SAMPLES	RELATED IND/NDA/DMF
N/A	DMF # [redacted]
	DMF # [redacted]

STERILIZATION
N/A

LABELING
No changes

BIOEQUIVALENCY STATUS
Dissolution profiles of the 300 mg capsules manufactured using the [redacted] Diltiazem, lot #600R010, and the [redacted] Diltiazem, lot

#600R011 were compared to that of the ANDA biobatch lot #600R003. The applicant states all three lots were manufactured using the

ESTABLISHMENT INSPECTION

An acceptable EIR was issued by the Office of Compliance for the following facility, 07/12/99:

An acceptable EIR was issued by the Office of Compliance for the following facility on 11/22/99 by E. Egas.

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Supplemental Application Review

✓ **ANDA** 74-752/S-010

NAME AND ADDRESS OF APPLICANT
Andrx Pharmaceuticals, Inc.
Attention: Diane Servello
4001 SW 47th Avenue
Fort Lauderdale, FL 33314

PURPOSE OF AMENDMENT/SUPPLEMENT
S-010:

DATE(S) OF SUBMISSION(S)
September 17, 1999

PHARMACOLOGICAL CATEGORY
Anti-hypertensive

TRADE NAME
Cartia-XT™

NONPROPRIETARY NAME
Diltiazem Hydrochloride Extended-release Capsules, USP

DOSAGE FORM
Capsules/Oral

POTENCY
120 mg, 180 mg, 240 mg, and 300 mg

RX OR OTC
Rx

SAMPLES
N/A

RELATED IND/NDA/DMF
N/A

STERILIZATION
N/A

LABELING
No changes

BIOEQUIVALENCY STATUS
N/A

ESTABLISHMENT INSPECTION
N/A

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cc: ANDA 74-752/S-010
Division File
Field Copy

Endorsements:

HFD-647/B.M.Azarm/02/22/00, 02/25/00 (revised)
HFD-647/U.Venkataram/3/6/0^ /S/ /S/ 03/17/00

v:\firmsam\andrx\ltrs&rev\74752s10.r1f 3/20/00
F/T by/ms/3-16-00

NOT APPROVABLE - MINOR

APPEARS THIS WAY
ON ORIGINAL

ANDA 74-752/S-011 (120 mg, 180 mg, 240 mg and 300 mg)
74-852/S-004 (120 mg, 180 mg and 240 mg)

NAME AND ADDRESS OF APPLICANT:
Andrx Pharmaceuticals, Inc.
Attention: Diane Servello
4001 SW 47th Avenue
Fort Lauderdale, FL 33314

PURPOSE OF AMENDMENT/SUPPLEMENT
S-011, S-004:

DATE(S) OF SUBMISSION(S)
02/28/00

PHARMACOLOGICAL CATEGORY	TRADE NAME
Anti-hypertensive	Cartia XT (74-752) Diltia XT (74-852)

NONPROPRIETARY NAME
Diltiazem Hydrochloride Extended-release Capsules, USP

DOSAGE FORM
Capsules/Oral

POTENCY	RX OR OTC
120 mg, 180 mg, 240 mg & 300 mg (74-752) 120 mg, 180 mg & 240 mg (74-852)	RX

SAMPLES	RELATED IND/NDA/DMF	STERILIZATION
N/A	N/A	N/A

LABELING
No changes

BIOEQUIVALENCY STATUS
N/A

ESTABLISHMENT INSPECTION
N/A

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS

Redacted 3

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ANDA 74-752/S-012

NAME AND ADDRESS OF APPLICANT:
Andrx Pharmaceuticals, Inc.
Attention: Diane Servello
4001 SW 47th Avenue
Fort Lauderdale, FL 33314

PURPOSE OF AMENDMENT/SUPPLEMENT
S-012: To provide for an additional in-process dissolution test for Diltiazem HCl Extended-release

DATE(S) OF SUBMISSION(S)
July 19, 2000

PHARMACOLOGICAL CATEGORY
1. hypertension
2. chronic stable angina due to coronary artery spasm

TRADE NAME
Cartia XT

NONPROPRIETARY NAME
Diltiazem Extended-release Capsules, USP

DOSAGE FORM
Capsules/Oral

POTENCY	RX OR OTC
120 mg, 180 mg, 240 mg, & 300 mg	RX

SAMPLES	RELATED IND/NDA/DMF	STERILIZATION
N/A	N/A	N/A

LABELING
No changes

BIOEQUIVALENCY STATUS
N/A

ESTABLISHMENT INSPECTION
N/A

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STABILITY
N/A

REMARKS AND CONCLUSION
The supplemental application may be approved.

RECALLS

Reviewer	Date Completed
Bita Mirzai-Azarm	12/27/00

ORDER OF REVIEW:
The application submission(s) covered by this review was taken in the date order of receipt Yes X
No_____

If no, explain reason(s) below.

✓ANDA 74-752/S-013

NAME AND ADDRESS OF APPLICANT:
Andrx Pharmaceuticals, Inc.
Attention: Diane Servello
4001 SW 47th Avenue
Fort Lauderdale, FL 33314

PURPOSE OF AMENDMENT/SUPPLEMENT
S-013: To provide for an improvement to the [redacted] process for Diltiazem HCl Extended-release [redacted]

DATE(S) OF SUBMISSION(S)
July 28, 2000

PHARMACOLOGICAL CATEGORY
1. hypertension
2. chronic stable angina due to coronary artery spasm

TRADE NAME
Cartia XT

NONPROPRIETARY NAME
Diltiazem Extended-release Capsules, USP

DOSAGE FORM
Capsules/Oral

POTENCY	RX OR OTC
120 mg, 180 mg, 240 mg, & 300 mg	RX

SAMPLES	RELATED IND/NDA/DMF	STERILIZATION
N/A	N/A	N/A

LABELING
No changes

BIOEQUIVALENCY STATUS
N/A

ESTABLISHMENT INSPECTION
N/A

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STABILITY
See above.

REMARKS AND CONCLUSION
The supplemental application may be approved.

RECALLS

Reviewer	Date Completed
Bita Mirzai-Azarm	12/27/00

ORDER OF REVIEW:
The application submission(s) covered by this review was taken in the date order of receipt Yes__X___
No_____

If no, explain reason(s) below.

APPEARS THIS WAY
ON ORIGINAL

ANDA 74-752/S-014

NAME AND ADDRESS OF APPLICANT:
Andrx Pharmaceuticals, Inc.
Attention: Diane Servello
4955 Orange Drive
Fort Lauderdale, FL 33314

PURPOSE OF AMENDMENT/SUPPLEMENT
S-014: To [redacted] that exceed the [redacted] dissolution limit at the 12-hour time point.

DATE(S) OF SUBMISSION(S)
June 13, 2001

PHARMACOLOGICAL CATEGORY
1. treatment of hypertension
2. management of chronic stable angina due to coronary artery spasm

TRADE NAME
Cartia XT

NONPROPRIETARY NAME
Diltiazem Hydrochloride Extended-Release Capsules, USP

DOSAGE FORM
Capsules/Oral

POTENCY	RX OR OTC
120 mg, 180 mg, 240 mg, & 300 mg	RX

SAMPLES	RELATED IND/NDA/DMF	STERILIZATION
N/A	N/A	N/A

LABELING
No changes

BIOEQUIVALENCY STATUS
N/A

ESTABLISHMENT INSPECTION
N/A

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS

[redacted]

Redacted 6

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RECALLS

Reviewer	Date Completed
Bita Mirzai-Azarm	11/26/01

ORDER OF REVIEW:

The application submission(s) covered by this review was taken in the date order of receipt Yes_____

No X

If no, explain reason(s) below.

Previous supplements were not available.

APPEARS THIS WAY
ON ORIGINAL

ANDA 74-752/S-015

NAME AND ADDRESS OF APPLICANT:
Andrx Pharmaceuticals, Inc.
Attention: Diane Servello
4955 Orange Drive
Fort Lauderdale, FL 33314

PURPOSE OF AMENDMENT/SUPPLEMENT
S-015: To provide for a revision of the in-process dissolution specifications for Diltiazem HCl

DATE(S) OF SUBMISSION(S)
August 21, 2001

PHARMACOLOGICAL CATEGORY
1. treatment of hypertension
2. management of chronic stable angina due to coronary artery spasm

TRADE NAME
Cartia XT

NONPROPRIETARY NAME
Diltiazem Hydrochloride Extended-Release Capsules, USP

DOSAGE FORM
Capsules/Oral

POTENCY	RX OR OTC
120 mg, 180 mg, 240 mg, & 300 mg	RX

SAMPLES	RELATED IND/NDA/DMF	STERILIZATION
N/A	N/A	N/A

LABELING
No changes

BIOEQUIVALENCY STATUS
N/A

ESTABLISHMENT INSPECTION
N/A

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ANDA 74-752/S-016

NAME AND ADDRESS OF APPLICANT:
Andrx Pharmaceuticals, Inc.
Attention: Diane Servello
4955 Orange Drive
Fort Lauderdale, FL 33314

PURPOSE OF AMENDMENT/SUPPLEMENT
S-016: Addition of [redacted]

DATE(S) OF SUBMISSION(S)
June 4, 2002

PHARMACOLOGICAL CATEGORY
1. hypertension
2. chronic stable angina due to coronary artery spasm

TRADE NAME
Cartia XT

NONPROPRIETARY NAME
Diltiazem Extended-release Capsules, USP

DOSAGE FORM
Capsules/Oral

POTENCY	RX OR OTC
120 mg, 180 mg, 240 mg, & 300 mg	RX

SAMPLES	RELATED IND/NDA/DMF	STERILIZATION
N/A	N/A	N/A

LABELING
No changes

BIOEQUIVALENCY STATUS
N/A

ESTABLISHMENT INSPECTION
Acceptable on June 10, 2002

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS
N/A

PACKAGING
The applicant proposed to add the following site [redacted]

[redacted]

[redacted]

[redacted]

Packaging of the drug product will be conducted using equipment of the same design and operating principle as those approved in the original application. The applicant enclosed a written stability commitment which states that Andrx Pharmaceuticals commits to placing the first production batch of each strength of the drug product in the smallest and largest container/closure system, and annual batches thereafter, on long-term stability studies using the approved protocol in the application.

STABILITY
N/A

REMARKS AND CONCLUSION
The supplemental application may be approved.

RECALLS

Reviewer	Date Completed
Bita Mirzai-Azarm	10/07/02

ORDER OF REVIEW:
The application submission(s) covered by this review was taken in the date order of receipt Yes X
No_____

If no, explain reason(s) below.

APPEARS THIS WAY
ON ORIGINAL

ANDA See the appendix for the list of ANDAs (Global)

NAME AND ADDRESS OF APPLICANT:
Andrx Pharmaceuticals, Inc.
Attention: Janet Vaughn
4955 Orange Drive
Fort Lauderdale, FL 33314

PURPOSE OF AMENDMENT/SUPPLEMENT
Addition of [redacted]

DATE(S) OF SUBMISSION(S)
June 24, 2002

PHARMACOLOGICAL CATEGORY
See the appendix

TRADE NAME	NONPROPRIETARY NAME	
See the appendix	See the appendix	
DOSAGE FORM	**POTENCY**	**RX OR OTC**
See the appendix	See the appendix	RX
SAMPLES	**RELATED IND/NDA/DMF**	**STERILIZATION**
N/A	N/A	N/A

LABELING
N/A

BIOEQUIVALENCY STATUS
N/A

ESTABLISHMENT INSPECTION
Acceptable on July 3, 2002 by J.D. Ambrogio

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS
No change

PACKAGING
The applicant proposed to add the following site as [redacted]

Packaging of the drug product will be conducted using equipment of the same design and operating principle as those approved in the original application.

STABILITY

The applicant commits to placing the first production batch of each strength of the drug product in the smallest and largest container/closure system and annual batches thereafter, on long-term stability studies using the approved protocol in the application and to submitting the resulting data in annual reports.

REMARKS AND CONCLUSION

The supplemental applications may be approved.

RECALLS

Reviewer	Date Completed
Bita Mirzai-Azarm	12/23/02

ORDER OF REVIEW:

The application submission(s) covered by this review was taken in the date order of receipt Yes__X___
No_____

If no, explain reason(s) below.

APPEARS THIS WAY
ON ORIGINAL

ANDA 74-752/S-018

NAME AND ADDRESS OF APPLICANT:
Andrx Pharmaceuticals, LLC
Attention: Janet Vaughn
4955 Orange Drive
Fort Lauderdale, FL 33314

PURPOSE OF AMENDMENT/SUPPLEMENT
S-018:

DATE(S) OF SUBMISSION(S)
June 30, 2003
October 24, 2003 – Telephone Amendment

PHARMACOLOGICAL CATEGORY
1. Treatment of hypertension
2. Management of chronic stable angina due to coronary artery spasm

TRADE NAME	NONPROPRIETARY NAME	
Cartia XT	Diltiazem Hydrchloride Extended-release Capsules, USP	
DOSAGE FORM	POTENCY	RX OR OTC
ER Capsules/Oral	120 mg, 180 mg, 240 mg & 300 mg	RX
SAMPLES	RELATED IND/NDA/DMF	STERILIZATION
N/A	N/A	N/A

LABELING
No changes

BIOEQUIVALENCY STATUS
N/A

ESTABLISHMENT INSPECTION
N/A

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS
In summary, Cartia XT is manufactured as follows:

[redacted]

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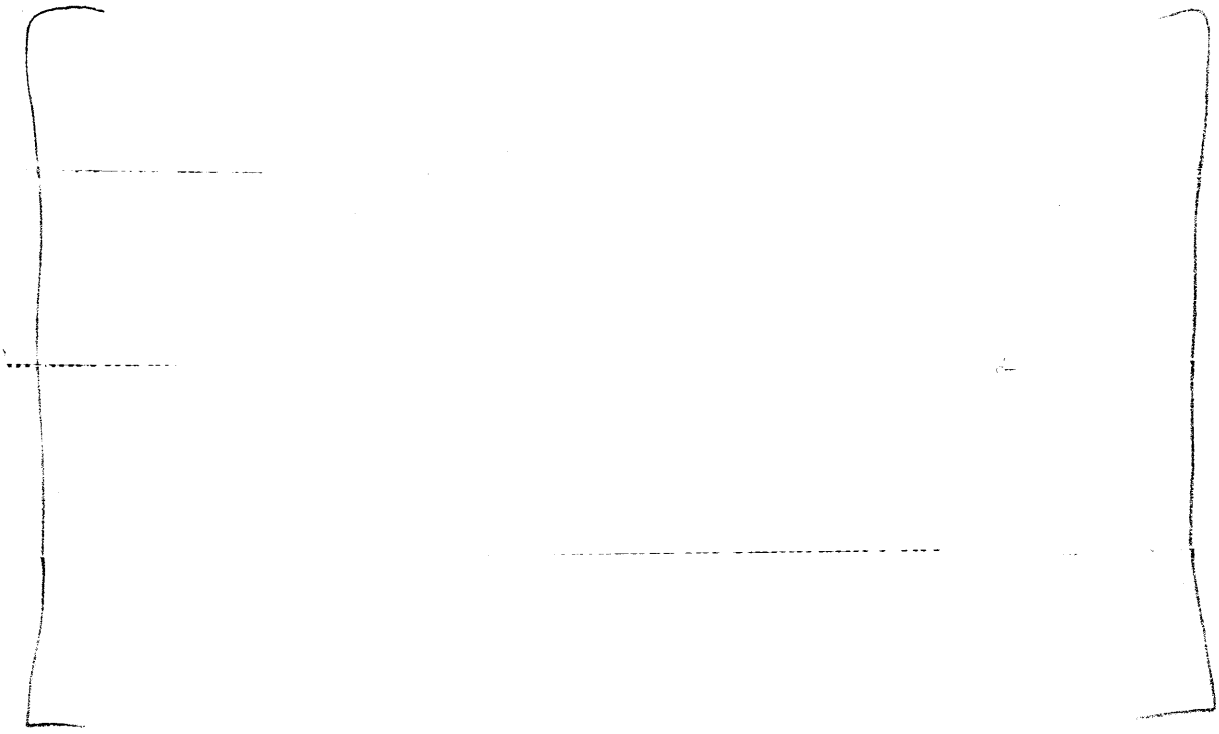

PACKAGING
N/A

STABILITY
N/A

REMARKS AND CONCLUSION
The supplemental application may be approved.

RECALLS

Reviewer	Date Completed
Bita Mirzai-Azarm	10/14/03

ORDER OF REVIEW:
The application submission(s) covered by this review was taken in the date order of receipt
Yes X No

If no, explain reason(s) below.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-752/S-001 to S-018

BIOEQUIVALENCE REVIEW

Diltiazem Hydrochloride ER Capsules
120 mg, 180 mg, 240 mg & 300 mg
ANDA # 74-752 / SC 4
Reviewer: Sikta Pradhan
WORD/X:\Pradhan\74752SSW.998

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 [redacted] Diltiazem HCl Extended-release [redacted] and Diltiazem HCl Extended-release [redacted]

In this supplement Andrx Pharmaceuticals, Inc. informed the Agency that the firm wants [redacted] In addition, the firm is also requesting a change (tightened specification) in the dissolution specification in 0.1N HCl at 18 hours for the new [redacted] from NLT [redacted] to NLT [redacted] (see II. Dissolution Specifications). However, there is no change to the dissolution specifications in pH 7.5 buffer. The firm has further stated that there will be no change to the dissolution specifications for, a) the [redacted] 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 [redacted] of diltiazem from the [redacted] and [redacted] of diltizem from the [redacted]

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

Ingredient	Diltiazen,%LC	Diltiazem %w/w (Theoretical)	Amount (mg)
[redacted]	0	0	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Total			[redacted]

In order to enhance the quality of the product, the firm has proposed a small change in the compositions of [redacted]

Proposed Change in [redacted]

	ANDA Biobatch (%)	Validation Batches* (%)	Proposed Change (%)
[redacted]	[redacted]	[redacted]	[redacted]
Talc, USD	[redacted]	[redacted]	[redacted]
Mg Stearate	--------	---------	[redacted]
Acetyl tributyl citrate(ATBC)	[redacted]	[redacted]	[redacted]
Polysorbate 80	[redacted]	[redacted]	[redacted]
Subtotal [redacted]	[redacted]	[redacted]	[redacted]
Diltiazem Active [redacted]	[redacted]	[redacted]	[redacted]
Total	100.0	[redacted]	

commercial scale.(Validation Batch).
The proposed change replaces [redacted] talc from the Validation Batch with [redacted] magnesium stearate in the [redacted] formulation. There is no change to the [redacted]

II. DISSOLUTION SPECIFICATIONS

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

Medium	0.1N HCl		PH 7.5*, Paddles @75 rpm	
	Time, hr.	Specifications	Time, hr.	Specifications
Diltiazem HCl ER Once-a-Day Capsules	2	NMT [redacted] (paddle @ 75 rpm)	2 12 18 24	Between [redacted] and [redacted] Between [redacted] and [redacted] NLT [redacted] NLT [redacted]
[redacted]	18	NLT [redacted] (paddle @ 100 rpm)	6 12 21	NMT [redacted] NMT [redacted] NLT [redacted]

- * pH 7.5 phosphate buffer

Proposed Dissolution Specification:

The proposed dissolution specification for the new [redacted] in 0.1N HCl at 18 hours is NLT [redacted].
There is no change to the dissolution specifications in pH 7.5 buffer.
There is also no change to the dissolution specifications for the [redacted] or the finished product.

Firm's Rationales in Support of Proposed Specification Change for [redacted] and Proposed Component and Composition Change for [redacted]

1. As the gastric emptying time for the [redacted] is relatively short, i.e. 0.5 hr. (fast) to 2 hr. (fed), most of the time the [redacted] are in the intestinal region. Therefore, the dissolution in 0.1N HCl (gastric condition) is only relevent up to the 2 hr. time point, and consequently, the specification for [redacted] in 0.1N HCl at 18 hr.has no physiological meaning. After gastric emptying, the dissolution in the pH 7.5 buffer becomes more relevant. Hence, the proposed

dissolution specification, NLT [redacted] in 0.1N HCl at 18 hours, for the new [redacted] 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 [redacted] during the [redacted] and are therefore, [redacted] 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: [redacted]
& Analytical Facilities: [redacted]
Clinical Director: [redacted]
Analytical Director: [redacted]
Project No.: 98090 (approved by [redacted]
Pharmacokinetic and statistical Analysis: [redacted]

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 [redacted] capsules, 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 240 mL 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

[ ]

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

[ ]

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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 80 - 125%.

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:

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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: 0.1N HCl; Vol.: 900mL;
Medium#2:.Buffer pH 7.5 (SIF) vol.: 900 mL
Reference Drug: Cardizem
Assay Methodology:
Specifications: 2 hr NMT in 0.1N HCl
2 hr in SIF
12 hr in SIF
18 hr NLT
24 hr NLT

II. Results of In Vitro Dissolution Testing in 0.1N HCl:

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 0.1N HCl:						
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	[redacted]	13.6	3	[redacted]	11.3
12						
18						
24						
V. Results of In Vitro Dissolution Testing in Buffer pH 7.5 (SIF):						
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	[redacted]	5.6	38	[redacted]	2.1
12	42	[redacted]	2.9	43	[redacted]	2.0
18	83	[redacted]	2.3	85	[redacted]	2.1
24	92	[redacted]	2.0	94	[redacted]	1.5
VI. Results of In Vitro Dissolution Testing in 0.1N HCl:						
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	[redacted]	12.8	3	[redacted]	16.5
12						
18						
24						
VII. Results of In Vitro Dissolution Testing in Buffer pH 7.5 (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	[redacted]	2.2	40	[redacted]	1.8
12	44	[redacted]	1.9	43	[redacted]	3.0
18	85	[redacted]	2.4	85	[redacted]	2.2
24	97	[redacted]	1.5	92	[redacted]	2.3

VIII. Results of In Vitro Dissolution Testing in 0.1N HCl:						
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	[redacted]	19.6	3	[redacted]	13.9
12						
18						
24						
IX. Results of In Vitro Dissolution Testing in Buffer pH 7.5 (SIF):						
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	[redacted]	2.3	41	[redacted]	2.6
12	46	[redacted]	1.8	44	[redacted]	3.7
18	90	[redacted]	2.4	84	[redacted]	3.1
24	99	[redacted]	2.8	93	[redacted]	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 [redacted]

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 [redacted] is justifiable.

3. The firm's rationale for Proposed Component and Composition Change for [redacted] 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 900 mL of 0.1N HCl for 2 hours at 37^{0}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	0.1N HCl	Time	SIF
2 hr	NMT [redacted]	2 hr	[redacted]
		12 hr	[redacted]
		18 hr	NLT [redacted]
		24 hr	NLT [redacted]

4. Hence, the current supplement is acceptable.

/S/

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

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Concur: ---------- /S/ Date: 1/11/99
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

cc: ANDA # 74752SSW (original, duplicate), HAD-652 (Huang, Pradhan), HAD-650 (Director), Drug File, Division File

Draft:SP/12-28-98//**WORD**/X:\Pradhan\74752SSW.998

CC: ANDA# 74-752/SC4
ANDA DUPLICATE
DIVISION FILE
BIO DRUG FILE
FIELD COPY

ENDORSEMENTS: (Final with Dates)
HFD-652/ S. Pradhan /S/
HFD-650/ Y. Huang /S/ 1/7/99
HFD-617/ L. Sanchez /S/
HFD-650/ D. Conner /S/ 1/11/99

Printed in final on 01/07/99
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Supplemental Application on — Submission date: 09-11-98
Biostudy (fasting) on 300 mg capsules STF 300mg AC
~~Dissolution waiver on 240 mg cap.~~
~~Dissolution waiver on 180 mg cap.~~
~~Dissolution waiver on 120 mg cap.~~

Amendment to ~~Biostudy (fasting) on 300 mg cap.~~ — Submission date: 12-22-98
Amendment to Dissolution waiver on 240 mg cap. (DIW)
Dissolution waiver on 180 mg cap. (DIW)
Dissolution waiver on 120 mg (DIW)

Supplement Application. Acceptable

Figure 1 Linear Plot of Mean Plasma Diltiazem Concentrations *vs* Time

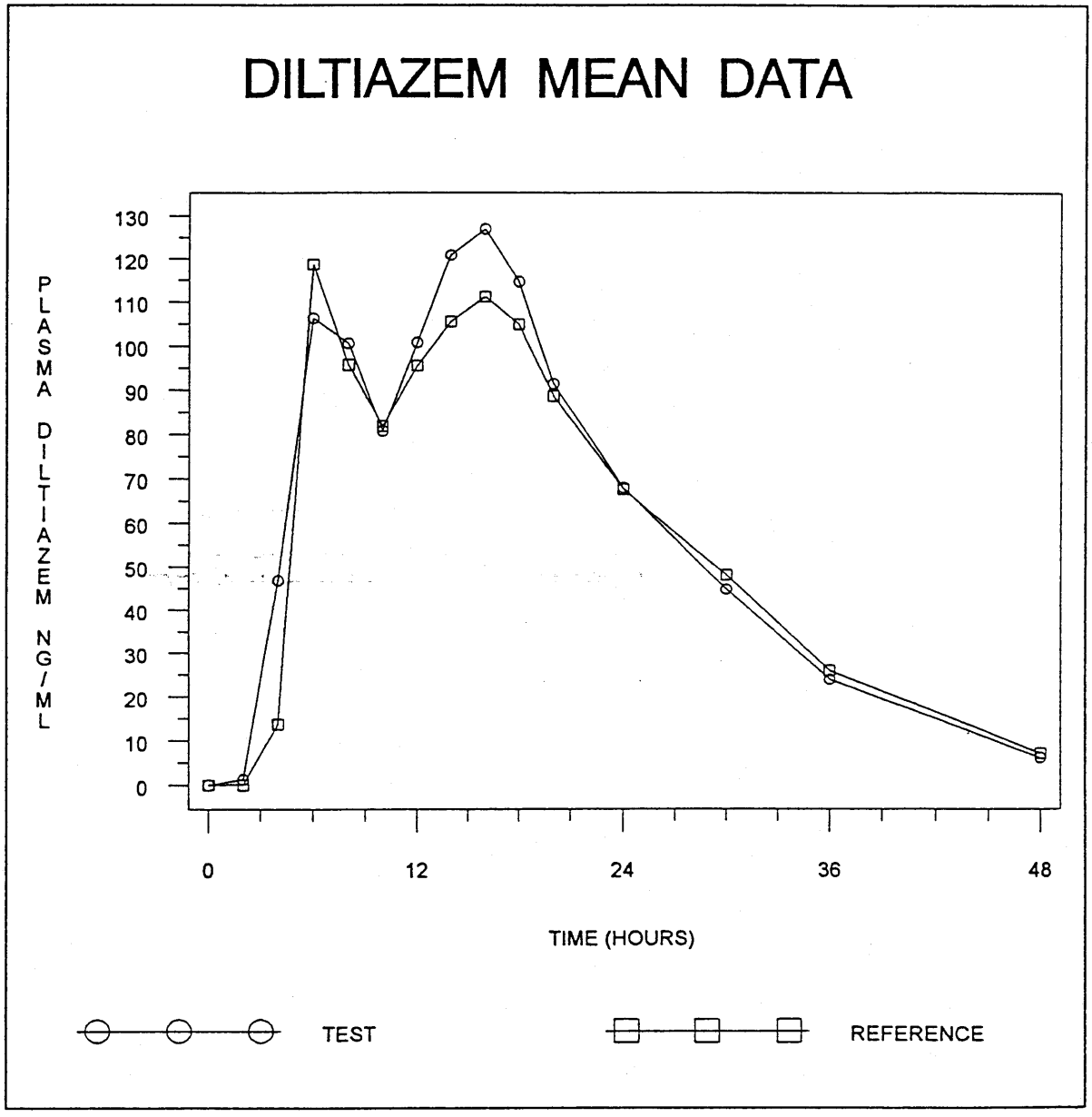

Figure 2 Linear Plot of Mean Plasma Desmethyldiltiazem Concentrations *vs* Time

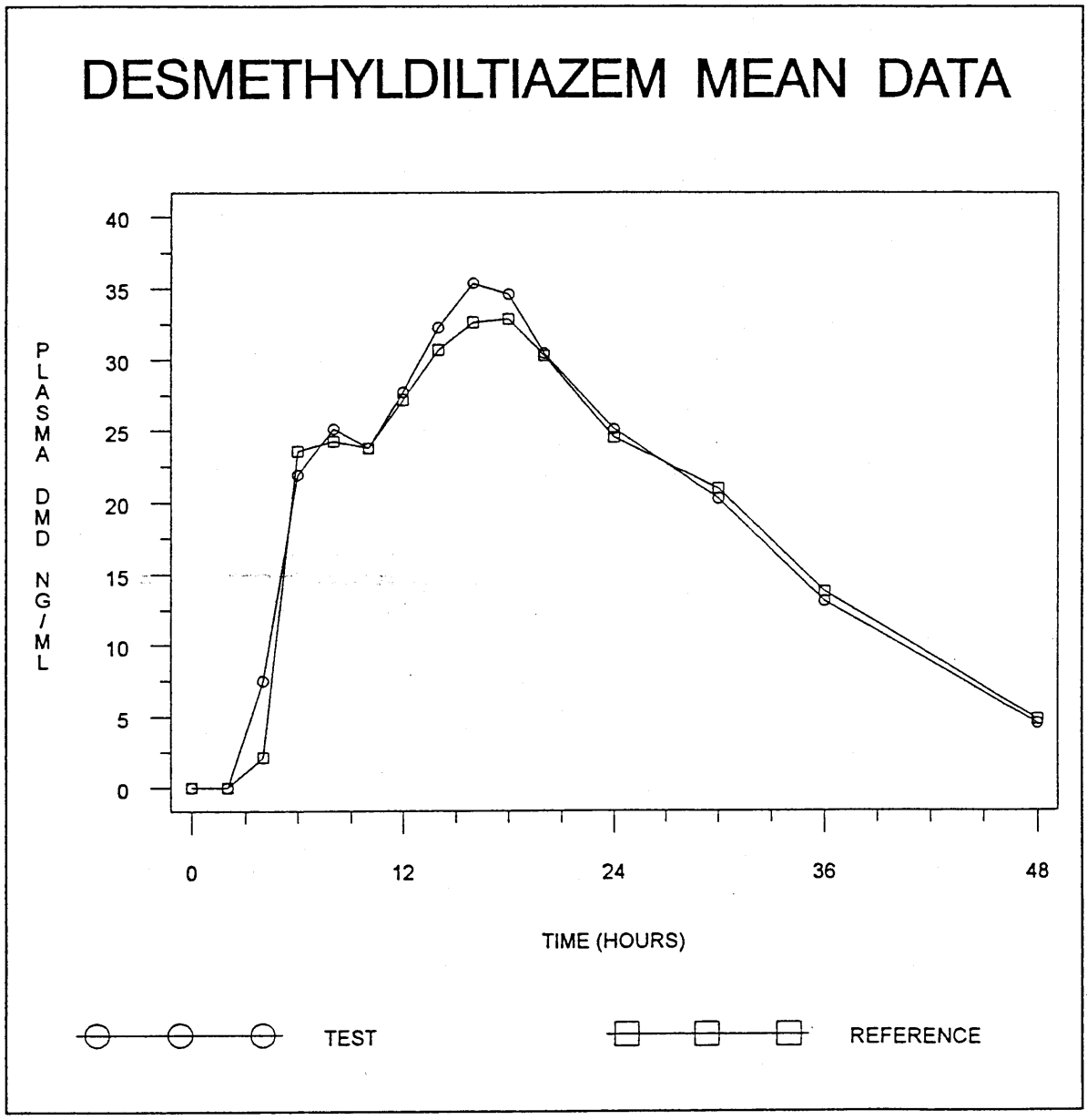

Figure 3 Linear Plot of Mean Plasma Desacetyldiltiazem Concentrations *vs* Time

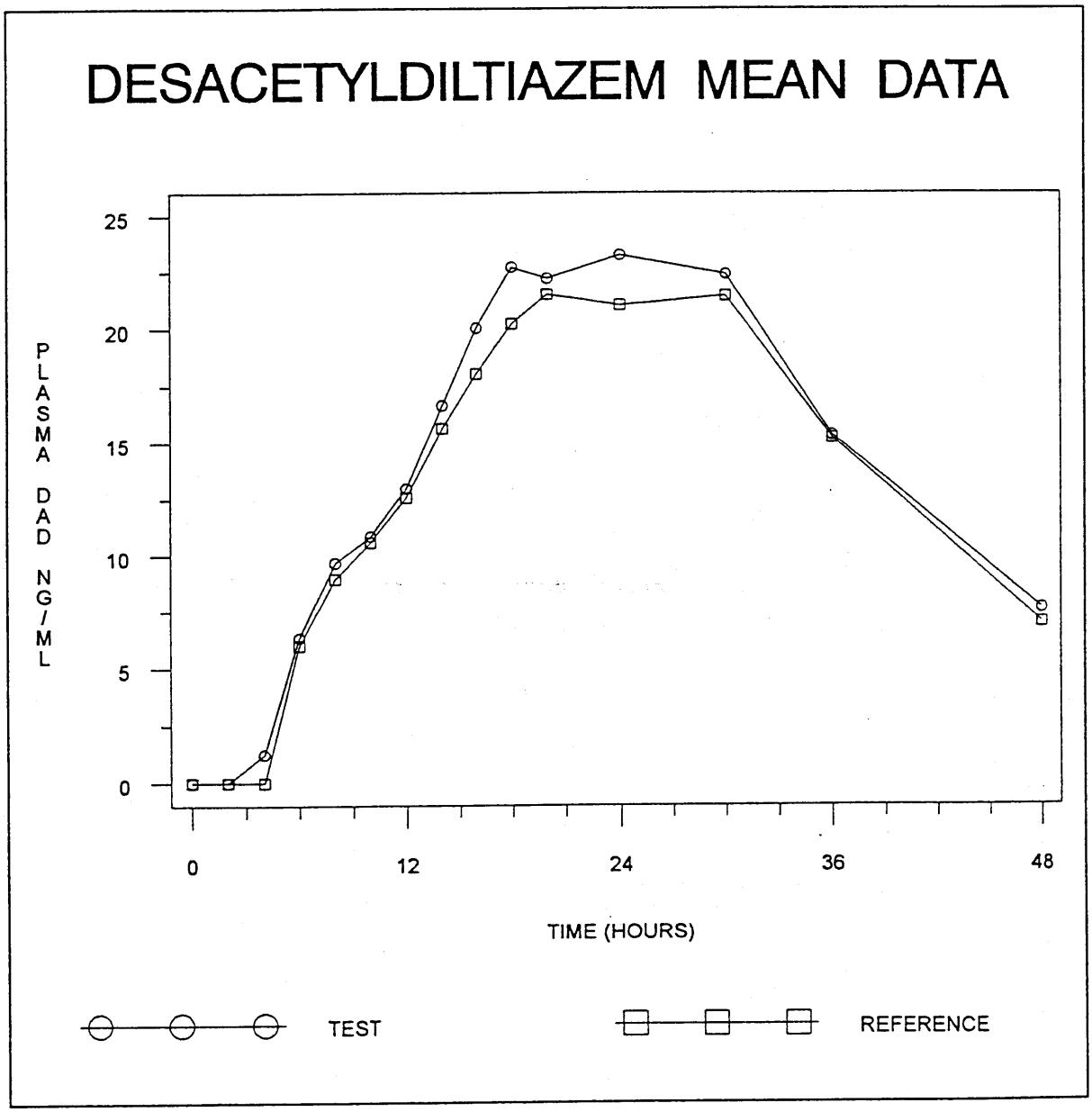

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Table 11

Spreadsheet of Calculation for the [redacted] 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
1	[redacted]											
2												
3												
4												
5												
6												
7												
8												
9												
10												
11												
12												
Average	39.08333	43.91667	85.83333	96.5					40.5	44	86.75	93.58333
Minimum	[redacted]											
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 [redacted] 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	
1	[redacted]										
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
Average	37.66667	42	83.25	91.91667			38.16667	42.5	84.91667	94.08333	
Minimum	[redacted]										
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										

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Table 13

Spreadsheet of Calculation for the [redacted]				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	
1	[redacted]										
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
Average	40.58333	44	84.66667	97.33333			40.5	43.16667	85.41667	91.75	
Minimum	[redacted]										
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										

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Table 14

Spreadsheet of Calculation for the [redacted] 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	[redacted]											
2	[redacted]											
3	[redacted]											
4	[redacted]											
5	[redacted]											
6	[redacted]											
7	[redacted]											
8	[redacted]											
9	[redacted]											
10	[redacted]											
11	[redacted]											
12	[redacted]											
Average	39.41667	46	89.41667	98.66667				41.33333	44	83.75	93.25	
Minimum	[redacted]											
Maximum	[redacted]											
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											

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-752/S-001 to S-018

ADMINISTRATIVE DOCUMENTS

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **ANDA 74752/016**
Stamp: **05-JUN-2002** Regulatory Due:
Applicant: **ANDRX PHARMS**
4001 SOUTH WEST 47TH AVE
FORT LAUDERDALE, FL 33314

Priority:
Org Code: **600**
Action Goal:
District Goal: **05-NOV-2002**
Brand Name:
Established Name: **DILTIAZEM HYDROCHLORIDE**
Generic Name:
Dosage Form: **EXC (EXTENDED RELEASE CAPSUL)**
Strength: **120, 180, 240, 300 MG**

FDA Contacts:
S. SHEPPERSON (HFD-617) **301-827-5849 , Project Manager**
B. MIRZAI AZARM (HFD-647) **301-827-5849 , Review Chemist**
U. VENKATARAM (HFD-647) **301-827-5849 , Team Leader**

Overall Recommendation:

ACCEPTABLE on 10-JUN-2002 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: [redacted]

DMF No:
AADA No:

Profile: **CTR** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **10-JUN-2002**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: [redacted]

APPEARS THIS WAY
ON ORIGINAL

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **ANDA 74752/017**
Stamp: **26-JUN-2002** Regulatory Due:
Applicant: **ANDRX PHARMS**
4001 SOUTH WEST 47TH AVE
FORT LAUDERDALE, FL 33314

Priority: Org Code: **600**
Action Goal: District Goal: **26-NOV-2002**
Brand Name:
Established Name: **DILTIAZEM HYDROCHLORIDE**
Generic Name:
Dosage Form: **EXC (EXTENDED RELEASE CAPSUL**
Strength: **120, 180, 240, 300 MG**

FDA Contacts: **S. SHEPPERSON (HFD-617)** **301-827-5849 , Project Manager**
B. MIRZAI AZARM (HFD-647) **301-827-5849 , Review Chemist**
U. VENKATARAM (HFD-647) **301-827-5849 , Team Leader**

Overall Recommendation:

ACCEPTABLE on 03-JUL-2002 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: [redacted]
DMF No:
AADA No:

Profile: **CTR** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **03-JUL-2002**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: [redacted]

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING # 1

SUPPLEMENT

FPL - Container Labels and Insert Labeling

DATE OF REVIEW: April 30, 1999

ANDA #: 74-752/S-007

NAME OF FIRM: Andrx Pharmaceuticals, Inc.

NAME OF DRUG: Diltiazem Extended-release Capsules USP, 120 mg, 180 mg, 240 mg, 300 mg

DATE OF SUBMISSION: April 23, 1999

COMMENTS:

Regarding the Labeling Revision:

Container: 90s and 1000s

1. Relocate "Rx only" to the main panel.

2. Revise the storage temperature recommendations as follows:

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

These revisions may be done in an annual report provided that the changes are described in full.

RECOMMENDATIONS:

1. Inform the firm of the above comments if there are to be chemistry comments.

2. Request the firm revise their container labels, then prepare and submit final print.

FOR THE RECORD:

1. Review based on the labeling of Cardizem CD, revised 7/95; approved 4/2/96.

2. This combined chemistry/labeling submission is for the addition of two new container sizes, 90s and 1000s.

REVIEW OF PROFESSIONAL LABELING # 1

SUPPLEMENT

FPL - Insert Labeling

DATE OF REVIEW: April 21, 1999

ANDA #: 74-752/S-006

NAME OF FIRM: Andrx Pharmaceuticals, Inc.

NAME OF DRUG: Diltiazem Hydrochloride Extended-release Capsules, 120 mg, 180 mg, 240 mg and 300 mg

DATE OF SUBMISSION: April 14, 1999

COMMENTS:

From a labeling standpoint the insert labeling has been satisfactorily revised to reflect the addition of magnesium stearate to the listing of inactive ingredients in the DESCRIPTION section.

RECOMMENDATIONS:

Inform the firm of the above comments.

NOTE TO CHEMIST:

Firm still labeled that USP release test is pending. See DESCRIPTION section.

FOR THE RECORD:

1. Review based on the labeling of Cardizem CD, revised 7/95; approved 4/2/96.

2. [redacted]

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pages of trade secret and/or confidential commercial information

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pages of trade secret and/or confidential commercial information

Telephone Conversation Memorandum

ANDA: 74-752/S-009

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

FIRM: Andrx Pharmaceuticals, Inc.

SUPPL AMENDMENT
SCC 009/AM

PERSONS INVOLVED: Jackie Davis, Andrx
Tim Ames, FDA

PHONE NUMBER: 954-581-7500

DATE: April 26, 2000

Background:

Firm called to request evaluation of this supplement for approval since no deficiencies pertained to this drug substance manufacturer. After checking the CMC review, it was apparent that in fact this supplement could be approved. I informed the firm that I would request an approval be issued.

Timothy W. Ames, R.Ph., M.P.H.
Project Manager, Div Chem II, Team 8, OGD

/S/

cc: ANDA 74-752
Division file (1)

File: V:\firmsam\andrx\telecons\74752tc1.doc

APPEARS THIS WAY
ON ORIGINAL

Request for approval of S-009: ANDA 74-752/Diltiazem Hydrochloride ER Capsules/Andrx Pharmaceuticals, Inc.

Date of letter: April 3, 2000

The firm requested that S-009 [redacted] be approved. This request was based on the fact that our February 15, 2000 deficiency letter contained no deficiencies pertaining to S-009.

The request is granted.

Bita Mirzai-Azarm
Review Chemist

/S/ 5/10/00

/S/ 5/24/00

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APPEARS THIS WAY
ON ORIGINAL

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pages of trade secret and/or confidential commercial information

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Andrx Pharmaceuticals, Inc.	**April 3, 2000**
TELEPHONE NO. *(Include Area Code)*	FACSIMILE (FAX) Number *(Include Area Code)*
(954) 581-7500	**(954) 587-1054**

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
4001 SW 47th Avenue **Fort Lauderdale, FL 33314**	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) **74-752**

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)	PROPRIETARY NAME (*trade name*) IF ANY
Diltiazem Hydrochloride Extended-Release Capsules, USP	**Cartia XT**

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*)	CODE NAME (*If any*)
1,5 benzothiazepin-4(5H)one, 3-(acetyloxy)-5-[2-(4-methoxyphenyl)-, monohydrochloride, (+)-cis-	

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Capsule	**120 mg, 180 mg, 240 mg, & 300 mg**	**Oral**

(PROPOSED) INDICATION(S) FOR USE:
(1) For the treatment of hypertension
(2) For the management of chronic stable angina due to coronary artery spasm

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☐ NEW DRUG APPLICATION (21 CFR 314.50) ☒ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug	Holder of Approved Application
Cardizem CD	**Carderm**

TYPE OF SUBMISSION
(check one) ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☒ CHEMISTRY, MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

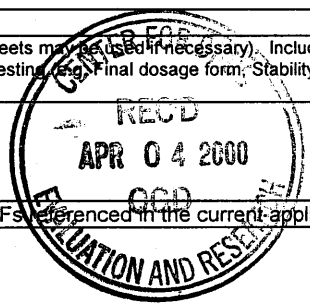
REASON FOR SUBMISSION
Amendment to Supplement

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED **N/A**	THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., final dosage form, Stability testing) conducted at this site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.



Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
X	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	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. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
X	17. Field copy certification (21 CFR 314.5 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. 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.
The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.
Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Diane Servello	**Diane Servello** **Director, Regulatory Affairs**	**April 3, 2000**

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
4001 SW 47th Avenue **Ft. Lauderdale, FL 33314**	**(954) 327-4412**

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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ON ORIGINAL

ATTACHMENT 1

Redacted 1

pages of trade secret and/or confidential commercial information

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **ANDA 74752/008**
Priority:
Org Code: **600**
Stamp: **25-JUN-1999** Regulatory Due:
Action Goal:
District Goal: **25-NOV-1999**
Applicant: **ANDRX PHARMS**
4001 SOUTH WEST 47TH AVE
FORT LAUDERDALE, FL 33314
Brand Name:
Established Name: **DILTIAZEM HYDROCHLORIDE**
Generic Name:
Dosage Form: **EXC (EXTENDED RELEASE CAPSUL**
Strength: **120, 180, 240, 300 MG**

FDA Contacts: **B. MIRZAI AZARM (HFD-647)** **301-827-5849 , Review Chemist**

Overall Recommendation:

ACCEPTABLE on 22-NOV-1999 by M. EGAS (HFD-322) 301-594-0095

Establishment: [redacted]
DMF No:
AADA No:

Profile: **CSN**
OAI Status: **NONE**
Responsibilities: [redacted]
Last Milestone: **OC RECOMMENDATION**
Milestone Date **22-NOV-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

APPEARS THIS WAY
ON ORIGINAL

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **ANDA 74752/009**
Stamp: **25-JUN-1999** Regulatory Due:
Applicant: **ANDRX PHARMS**
4001 SOUTH WEST 47TH AVE
FORT LAUDERDALE, FL 33314

Priority:
Org Code: **600**
Action Goal:
District Goal: **25-NOV-1999**
Brand Name:
Established Name: **DILTIAZEM HYDROCHLORIDE**
Generic Name:
Dosage Form: **EXC (EXTENDED RELEASE CAPSUL**
Strength: **120, 180, 240, 300 MG**

FDA Contacts: **B. MIRZAI AZARM (HFD-647)** **301-827-5849 , Review Chemist**

Overall Recommendation:

ACCEPTABLE on 12-JUL-1999 by M. EGAS (HFD-322) 301-594-0095

Establishment: [redacted]

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **12-JUL-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: [redacted]

APPEARS THIS WAY
ON ORIGINAL

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **ANDA 74752/008**
Stamp: **25-JUN-1999** Regulatory Due:
Applicant: **ANDRX PHARMS**
4001 SOUTH WEST 47TH AVE
FORT LAUDERDALE, FL 33314

Priority:
Org Code: **600**
Action Goal:
District Goal: **25-NOV-1999**
Brand Name:
Established Name: **DILTIAZEM HYDROCHLORIDE**
Generic Name:
Dosage Form: **EXC (EXTENDED RELEASE CAPSUL**
Strength: **120, 180, 240, 300 MG**

FDA Contacts: **B. MIRZAI AZARM (HFD-647)** **301-827-5849 , Review Chemist**

Overall Recommendation:

Establishment: [redacted]
DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **INSPECTION PERFORMED**
Milestone Date **01-NOV-1999**

Responsibilities: [redacted]

APPEARS THIS WAY
ON ORIGINAL

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **ANDA 74752/008**
Stamp: **25-JUN-1999** Regulatory Due:
Applicant: **ANDRX PHARMS**
4001 SOUTH WEST 47TH AVE
FORT LAUDERDALE, FL 33314

Priority: Org Code: **600**
Action Goal: District Goal: **25-NOV-1999**
Brand Name:
Established Name: **DILTIAZEM HYDROCHLORIDE**
Generic Name:
Dosage Form: **EXC (EXTENDED RELEASE CAPSULI**
Strength: **120, 180, 240, 300 MG**

FDA Contacts: **B. MIRZAI AZARM (HFD-647)** **301-827-5849 , Review Chemist**

Overall Recommendation:

Establishment: [redacted]

DMF No:
ANADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC**
Milestone Date: **09-JUL-1999**

Responsibilities: [redacted]

APPEARS THIS WAY
ON ORIGINAL

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **ANDA 74752/009**
Stamp: **25-JUN-1999** Regulatory Due:
Applicant: **ANDRX PHARMS**
4001 SOUTH WEST 47TH AVE
FORT LAUDERDALE, FL 33314

Priority: Org Code: **630**
Action Goal: District Goal: **25-NOV-1999**
Brand Name:
Established Name: **DILTIAZEM HYDROCHLORIDE**
Generic Name:
Dosage Form: **EXC (EXTENDED RELEASE CAPSUL**
Strength: **120, 180, 240, 300 MG**

FDA Contacts: **B. MIRZAI AZARM (HFD-647)** **301-827-5849 , Review Chemist**

Overall Recommendation:

Establishment [redacted]

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC**
Milestone Date: **09-JUL-1999**

Responsibilities: [redacted]

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Andrx Pharmaceuticals, Inc.	**November 20, 2000**
TELEPHONE NO. *(Include Area Code)*	FACSIMILE (FAX) Number *(Include Area Code)*
(954) 581-7500	**(954) 587-1054**

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
4001 SW 47th Avenue **Fort Lauderdale, FL 33314**	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) **74-752**

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)	PROPRIETARY NAME (*trade name*) IF ANY
Diltiazem Hydrochloride Extended-Release Capsules, USP	**Cartia XT**

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*)	CODE NAME (*If any*)
1,5 benzothiazepin-4(5H)one, 3-(acetyloxy)-5-[2-(4-methoxyphenyl)-, monohydrochloride, (+)-cis-	

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Capsule	**120 mg, 180 mg, 240 mg, & 300 mg**	**Oral**

(PROPOSED) INDICATION(S) FOR USE:

(1) For the treatment of hypertension

(2) For the management of chronic stable angina due to coronary artery spasm

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☐ NEW DRUG APPLICATION (21 CFR 314.50) ☒ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug	Holder of Approved Application
Cardizem CD	**Carderm**

TYPE OF SUBMISSION
(check one) ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION

☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT

☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY, MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION
Withdrawal of Supplemental Application

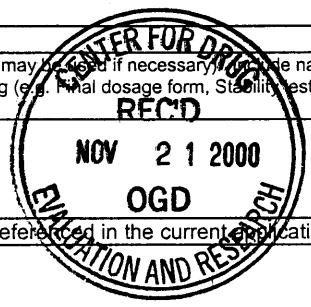
PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED **N/A**

THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary) to include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at this site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.



Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
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	8. Clinical data section (e.g. 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	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. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.5 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. 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.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Diane I Servello for	**Diane Servello** **Director, Regulatory Affairs**	**November 20, 2000**

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
4001 SW 47th Avenue **Ft. Lauderdale, FL 33314**	**(954) 327-4412**

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DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Andrx Pharmaceuticals, Inc.	**August 21, 2001**
TELEPHONE NO. *(Include Area Code)*	FACSIMILE (FAX) Number *(Include Area Code)*
(954) 581-7500	**(954) 587-1054**

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
4955 Orange Drive **Fort Lauderdale, FL 33314**	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) **74-752**

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)	PROPRIETARY NAME (*trade name*) IF ANY
Diltiazem Hydrochloride Extended-Release Capsules, USP	**Cartia XT**

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*)	CODE NAME (*If any*)
1,5 benzothiazepin-4(5H)one, 3-(acetyloxy)-5-[2-(4-methoxyphenyl)-, monohydrochloride, (+)-cis-	**N/A**

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Capsule	**120 mg, 180 mg, 240 mg, & 300 mg**	**Oral**

(PROPOSED) INDICATION(S) FOR USE:
(1) For the treatment of hypertension
(2) For the management of chronic stable angina due to coronary artery spasm

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☐ NEW DRUG APPLICATION (21 CFR 314.50) ☒ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug	Holder of Approved Application
Cardizem CD	**Carderm**

TYPE OF SUBMISSION
(check one) ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☒ CHEMISTRY, MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION
Supplement – Changes being Effected in 30 Days

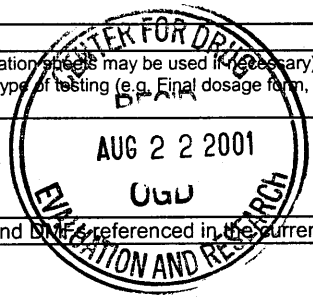
PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at this site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

No Changes



Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

No Changes

This application contains the following items: *(Check all that apply)*		
	1.	Index
	2.	Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3.	Summary (21 CFR 314.50 (c))
	4.	Chemistry section
X		A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
		B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
		C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5.	Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6.	Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7.	Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8.	Clinical data section (e.g. 314.50 (d) (5), 21 CFR 601.2)
	9.	Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10.	Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11.	Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12.	Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
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	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.	Establishment description (21 CFR Part 600, if applicable)
	16.	Debarment certification (FD&C Act 306 (k)(1))
	17.	Field copy certification (21 CFR 314.5 (k) (3))
	18.	User Fee Cover Sheet (Form FDA 3397)
	19.	OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

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2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. 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.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	**Diane Servello** **Director, Regulatory Affairs**	**August 21, 2001**

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
4955 Orange Drive **Ft. Lauderdale, FL 33314**	**(954) 585-1412**

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DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-752/S-001 to S-018

CORRESPONDENCE

Andrx
PHARMACEUTICALS
LLC

ANDA # 74-752
Cartia XT ™ Capsules 120mg, 180mg, 240mg, and 300mg

June 30, 2003

Gary Buehler
Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA NO. 74-752 SEF NO. SOS-018
NDA SUPPL FOR Control Rev.

Re: Prior Approval Supplement

Dear Mr. Buehler:

Please refer to Andrx Pharmaceuticals abbreviated new drug application for the above referenced product. Pursuant to 21 CFR 314.70(b), Andrx herewith submits a Prior Approval Supplement to provide for a

In support of the proposed change, we have evaluated lots of the drug product manufactured between January 2001 and February 2003. A report describing the results of this evaluation is enclosed. As the report indicates, trend analysis of various Quality Control tests performed during this period has shown that under normal circumstances, these tests will consistently meet the required specifications. In addition, some tests are performed by production and hence redundantly performed by the . Based on the results of our evaluation, we are requesting a of the following tests:

A form 356H immediately follows this cover letter. Andrx Pharmaceuticals certifies that a true copy of this supplement has been sent to the Florida District Office as a Field Copy.

Should you have any questions concerning this submission or if additional information is required, please do not hesitate to contact the undersigned at (954) 358-6125 *(Tel.)* or (954) 358-6350*(Fax)*.

Sincerely,

Janet Vaughn
Assoc. Director, Regulatory Affairs

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JUN 30 2003
OGD/CDER

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Andrx™
PHARMACEUTICALS INC.

74852-009 ✓
75604-0023? ✓
75347-002 ✓
74752-017 ✓
75961-005 ✓
75270-003 ✓

ANDA # 74-752
Cartia XT ™ Capsules 120mg, 180mg, 240mg, and 300mg

June 24, 2002

Gary Buehler
Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA NO. 74752 REF NO. SCD-017AT
NDA SUPPL FOR
/S/
EER submitted 7/2/02
A Shepperson

Re: Supplement - Changes Being Effected in 30 Days

Dear Mr. Buehler:

Please refer to Andrx Pharmaceuticals' abbreviated new drug application for Cartia XT™ Capsules , ANDA 74-752. Pursuant to 21 CFR § 314.70, Andrx herewith submits a Changes Being Effected in 30 Days Supplement providing for the addition of [redacted]. This change has no potential to adversely affect the identity, strength, quality, purity, or potency of the drug product as it may relate to its safety or effectiveness. Andrx anticipates making this change effective on **July 24, 2002**.

Packaging of each strength of the drug product is currently performed at Andrx's Fort Lauderdale facility. We are [redacted]

[redacted] has a current and satisfactory cGMP compliance profile with the FDA for the type of [redacted] being proposed. In this regard, they have provided the following documents:

1. Written certification stating that [redacted] is in compliance with current Good Manufacturing Practices (GMP)
2. Debarment Certification
3. Last FDA Establishment Inspection Report (EIR) – Summary of Findings

[redacted] of the drug product will be conducted using equipment of the same design and operating principle as those approved in the original application. The [redacted] records will include the same components (container(s)/closure(s)) as those currently being used for the drug product, except for administrative information and the location of the facility.

This supplement also includes a written stability commitment which states that Andrx Pharmaceuticals commits to placing the first production batch of each strength of the drug product in the smallest and largest container/closure system, and annual batches thereafter, on long-term stability studies using the approved

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protocol in the application and to submitting the resulting data in annual reports.

A form 356H immediately follows this cover letter. Andrx Pharmaceuticals, Inc. certifies that a true copy of this supplement has been sent to the Florida District Office as a Field Copy.

Should you have any questions concerning this submission or if additional information is required, please do not hesitate to contact Janet Vaughn at (954) 358-6125 *(Tel.)* or (954) 358-6350*(Fax)*.

Sincerely,

Diane Servello
Senior Director Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Andrx™
PHARMACEUTICALS INC.

EER submitted 6/10/02 1st

ANDA # 74-752
Cartia XT ™ Capsules 120mg, 180mg, 240mg, and 300mg

June 4, 2002

NDA NO. 74 752 REF. NO. SCD 016/AT
NDA SUPPL. FOP

Gary Buehler
Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Supplement - Changes Being Effected in 30 Days
Alternate Packaging Site

Dear Mr. Buehler:

Please refer to Andrx Pharmaceuticals' abbreviated new drug application for Cartia XT ™ Capsules, ANDA 74-752. Pursuant to 21 CFR § 314.70, Andrx herewith submits a Changes Being Effected in 30 Days Supplement providing for the addition of [redacted] This change has no potential to adversely affect the identity, strength, quality, purity, or potency of the drug product as it may relate to its safety or effectiveness. Andrx anticipates making this change effective on **July 5, 2002.**

Packaging of each strength of the drug product is currently performed at Andrx's Fort Lauderdale facility. We are [redacted]

[redacted] has a current and satisfactory cGMP compliance profile with the FDA for the type of [redacted]. In this regard, they have provided the following documents:

1. Written certification stating that [redacted] in compliance with current Good Manufacturing Practices (GMP)
2. Debarment Certification
3. Last FDA Establishment Inspection Report (EIR) – Summary of Findings

[redacted], of the drug product will be conducted using equipment of the same design and operating principle as those approved in the original application. The [redacted] records will include the same components (container(s)/closure(s)) as those currently being used for the drug product, except for administrative information and the location of the facility.

This supplement also includes a written stability commitment which states that Andrx Pharmaceuticals commits to placing the first production batch of each strength of the drug product in the smallest and largest container/closure system, and annual batches thereafter, on long-term stability [redacted] the approved

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protocol in the application and to submitting the resulting data in annual reports.

A form 356H immediately follows this cover letter. Andrx Pharmaceuticals, Inc. certifies that a true copy of this supplement has been sent to the Florida District Office as a Field Copy.

Should you have any questions concerning this submission or if additional information is required, please do not hesitate to contact Janet Vaughn at (954) 358-6125 *(Tel.)* or (954) 358-6350*(Fax)*.

Sincerely,

Diane Servello
Senior Director Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

ANDA 74-752/S-015

OCT 11 2001

Andrx Pharmaceuticals, Inc.
Attention: Diane Servello
4955 Orange Drive
Fort Lauderdale, Florida 33314

Dear Madam:

This refers to your supplemental new drug application dated August 21, 2001, submitted pursuant to 21 CFR 314.70, for Diltiazem Extended-release Capsules USP, 120 mg, 180 mg, 240 mg and 300 mg.

You requested review as a "Supplement - Changes Being Effected in 30 Days." The supplemental application provides for a revision of the in-process dissolution specifications.

Reference is also made to the September 10, 2001, telephone message from Bonnie McNeal of this Administration informing you that the proposed change should not be initiated. The change is **not**, in our opinion, the kind permitted by regulation to be put in effect in advance of approval of a supplement.

This letter notifies you that an approved supplement is required for the proposed change and that the supplement is under review. Please do not implement the proposed change.

Sincerely yours,

/S/

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

Andrx
PHARMACEUTICALS, INC.

Mirzai - Azarm

does not qualify per VIII.B.1 of guidance
09/05/01.

August 21, 2001

Gary Buehler
Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

74752 505 015
FOR COMPLE FOR Control Revision
AT

CENTER FOR DRUG
AUG 2 2 2001
OGD
EVALUATION AND RESEARCH

RE: **ANDA 74-752; Cartia XT (Diltiazem HCl Extended-release Capsules USP)**
Supplement – Changes Being Effected in 30 Days

Dear Mr. Buehler:

Please refer to Andrx Pharmaceuticals, Inc's. ("Andrx") abbreviated new drug application for the above referenced product. Pursuant to 21 CFR 314.70(c) and in accordance with Section 506A of the Act, Andrx herewith submits a Changes Being Effected in 30 Days Supplement to provide for a revision of the in-process dissolution specifications for Diltiazem HCl : ——— , one of the process intermediates for the drug product. For the reasons stated in this supplement, Andrx considers this change to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product. Andrx anticipates making this change effective on September 28, 2001.

Andrx's Diltiazem Hydrochloride ER Capsules contain two types of Diltiazem HCl ER ——— in a potency ratio of ——— have a ———

During the early development of this product, Andrx established in-process dissolution specifications for both the ——— to assure that the finished capsules meet the finished product dissolution specifications. The current dissolution specifications for the ——— and the finished capsules are presented in Table 1 below along with the proposed changes to the current — dissolution specifications:

Table 1

Dissolution Specifications for ——— and the Finished Product				
0.05M Phosphate Buffer, pH 7.5	**Proposed** —	**Current** —	—	**Capsules**
—	NLT —	NLT —	-	-
2 hours	NLT —	NL —	-	—
6 hours	-	-	NMT —	-
12 hours	-	-	NMT —	—
18 hours	-	-	-	NLT —
21 hours	-	-	NLT —	-
24 hours	-	-	—	NLT —
0.1 N HCl				
2 hours	NMT —	NMT —	-	NMT —
18 hours			NLT —	-

* Regulatory specification. For patent purposes an internal specification of NLT — is used.

As shown in Table 1, the current dissolution specifications for [redacted] in phosphate buffer are NLT [redacted], released at both [redacted] and 2 hours. The specification for the [redacted] time interval was established at the time of the ANDA submission with limited manufacturing history with this product. The specification for the two hour time interval was added through a "Changes Being Effected" supplement dated July 19, 2000 (S-012), to provide a time interval corresponding to the finished product dissolution testing, thus providing a more meaningful quality control test.

The dissolution specifications for [redacted], are used for in-process control purposes, and have a minimal affect on the finished product dissolution. The first dissolution test interval for the finished product is 2 hours in phosphate buffer, which requires that [redacted] of the capsule's label claim be released. Based on this finished product specification, [redacted] which represent [redacted] of the capsule's label claim, having a dissolution rate as low as [redacted] at two hours time interval could still meet the finished product specification.

We acknowledge that a change of the magnitude of [redacted], from the current specification of NLT [redacted] to NLT [redacted], is unrealistic; therefore, a more modest change has been proposed. A [redacted] specification of NLT [redacted] is being proposed for the [redacted] while keeping the 2-hour specification of NLT [redacted] As can be seen from Table 1, the revised [redacted] dissolution specifications should not affect the dissolution profile of the finished product. The revised [redacted] specification is presented in Exhibit 1.

To demonstrate that this specification change does not affect the performance of the finished product, two research lots of finished product (one lot each of the highest and lowest dosage strengths) were manufactured using [redacted], with one hour dissolution values below the current specification of NLT [redacted], lots 021B177 (average [redacted] dissolution = [redacted]) and 021B170 (average [redacted] dissolution = [redacted]) were used to manufacture Diltiazem HCl ER Capsules 120 mg and 300 mg, lots 597R011 and 600R015, respectively. Both finished capsule lots met all product performance criteria. The dissolution results for the two lots of finished product are presented in Table 2 below and are compared to the average results for all finished product lots manufactured this year with [redacted] that complied with the current specifications.

Table 2

Dissolution Results for Diltiazem ER Capsules Using [redacted], Outside Current Dissolution Specifications				
Specification	**Average of 120 mg lots for 2001**	**120 mg Lot 597R011**	**Average of 300 mg lots for 2001**	**300 mg Lot 600R015**
2 hour PO4 [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 hour PO4 [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] hour PO4 NLT [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 hour PO4 NLT [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 hour HCl NMT [redacted]	[redacted]	[redacted]	[redacted]	[redacted]

This comparison demonstrates that [redacted], meeting the revised dissolution specifications have no impact on the dissolution results of the finished capsule lots. Therefore, this change would have a minimal potential to have an adverse effect on the identity, strength, quality, purity or potency of the drug product as it relates to the safety and effectiveness of the product.

Executed batch records for the two finished capsule lots and the [redacted] lots are provided in Exhibit 2. Certificates of Analysis for both finished capsule lots and the in-process test results for the [redacted] used in these lots are provided in Exhibit 3.

The two exhibit lots of finished product (lots 597R011 and 600R015) have been packaged in the largest and smallest market packages and placed on accelerated and room temperature stability. Andrx Pharmaceuticals makes a commitment to monitor these lots and report the results in upcoming annual reports. A signed stability commitment is provided in Exhibit 4.

A form 356H immediately follows this cover letter. Andrx Pharmaceuticals, Inc. certifies that a true copy of this supplement has been sent to the Florida District Office as a Field Copy.

Should you have any questions concerning this submission or if additional information is required, please do not hesitate to contact Sam Swetland at (954) 581-1634 *(Tel.)* or (954) 585-1848 *(Fax)*.

Sincerely,

Diane Servello
Director Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Andrx
PHARMACEUTICALS, INC.

July 28, 2000

NDA NO. 74-752 REF. NO. SCR-013
NDA SUPPL FOR MANUFACTURE REVISION / AT
meets VII.C.1.a of guidance
/S/ 08/25/00

Gary Buehler, Acting Director
Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: ANDA 74-752; Diltiazem HCl Extended-Release Capsules,
120 mg, 180 mg, 240 mg, and 300 mg

SPECIAL SUPPLEMENT – CHANGES BEING EFFECTED – 30 DAYS

Dear Mr. Buehler:

Pursuant to 21 CFR 314.70(c), Andrx Pharmaceuticals, Inc. ("Andrx") is herewith submitting a **Special Supplement –Changes Being Effected, - 30 days** providing for an improvement to the [redacted] process for "Diltiazem HCl Extended-release [redacted]. Andrx plans to implement this change on August 28, 2000.

As described in our ANDA, Andrx's manufacturing process for "Diltiazem HCl Extended-release [redacted] Product Code 021 consists of [redacted] 'Diltiazem HCl [redacted]" with a [redacted]

[redacted]

on page 8 of 19 for the proposed in-process LOD determination. The revised

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JUL 31 2000
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4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

2. [redacted]

3. [redacted]

4. Comparative dissolution profiles on twelve individual capsules will be conducted on each strength of the product (120 mg, 180 mg, 240 mg and 300 mg), comparing batches made with the currently approved Master Batch Record with batches made with the revision to the [redacted] process described in this supplement. The similarity factor (f_2) described in the SUPAC guidances will be calculated for the dissolution profiles. This information will be included in our next annual report.

Andrx Pharmaceuticals, Inc. certifies that a true copy of this supplement was sent to the Florida District Office as a Field Copy.

Should you have any questions concerning this submission, please contact the undersigned at (954) 327-4412 (telephone) or (954) 587-1054 (fax).

Sincerely,

Diane Servello

Diane Servello
Director of Regulatory Affairs

Andrx
PHARMACEUTICALS, INC.

July 19, 2000

NDA NO. _____ REF. NO. SCS 012
FROM Control Rm / AT

Gary Buehler, Acting Director
Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: ANDA 74-752; Diltiazem HCl Extended-Release Capsules,
120 mg, 180 mg, 240 mg, and 300 mg

SPECIAL SUPPLEMENT – CHANGES BEING EFFECTED – 30 DAYS

Dear Mr. Buehler:

Pursuant to 21 CFR 314.70(c), Andrx Pharmaceuticals, Inc. ("Andrx") is herewith submitting a **Special Supplement –Changes Being Effected,** providing for an additional in-process dissolution test for "Diltiazem HCl Extended-release [redacted]. Andrx, plans to implement this change on August 18, 2000.

As described in our ANDA, Andrx's formulation for this product contains a fixed-ratio of [redacted] "Diltiazem HCl Extended-release [redacted]. The following table describes the in-process and finished product dissolution testing that is currently approved for this product:

Dissolution Test	In-process dissolution testing for [redacted]	In-process dissolution testing for [redacted]	Finished product dissolution testing
0.1N HCl; paddles @ 75 rpm	[redacted]	----	2 hours
0.05M phosphate buffer; pH 7.5, paddles @ 75 rpm	[redacted]	[redacted]	2, 12, 18 and 24 hours
0.1N HCl; paddles @ 100 rpm	----	[redacted]	----

REC'D
JUL 20 2000
OGD
EVALUATION AND RESEARCH

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reflective of the intended finished product dissolution characteristics, and therefore a more appropriate quality control test.

Please note that the same specification of "Not less than — " will be applied to both the — and 2-hour in-process dissolution tests in 0.05M phosphate buffer for the — Andrx would prefer to replace the — time interval with the new 2-hour interval, however this represents the deletion of a specification. A supplement for the deletion of the — test will be submitted at a later date. In the meantime, we will continue to test the at the — time interval, in addition to the new 2-hour time interval.

In support of this change, we have enclosed the following:

Exhibit 1: Revised specifications for "Diltiazem HCl Extended-release — (Code #021) and "Diltiazem HCl Extended-release — (Code 024).

Andrx Pharmaceuticals, Inc. certifies that a true copy of this supplement was sent to the Florida District Office as a Field Copy.

Should you have any questions concerning this submission, please contact the undersigned at (954) 327-4412 (telephone) or (954) 587-1054 (fax).

Sincerely,

Diane Servello
Director of Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Status
AM rated
To CMC Reviewer for
review
/S/

Andrx
PHARMACEUTICALS, INC.

June 16, 2000

SUPPL AMENDEMENT
SCC 008 AM

Mr. Gary Buehler, Acting Director
Office of Generic Drugs, CDER, FDA
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

RE: **ANDA 74-752; Diltiazem Hydrochloride Extended-release Capsules**
Minor Amendment to Supplemental Application (S-008)

Dear Mr. Buehler:

Reference is made to our supplemental application dated June 24, 1999, providing for the use of [redacted] Reference is also made to your "not approvable" letter dated April 14, 2000 (copy attached).

Pursuant to 21 CFR §314.120, Andrx Pharmaceuticals, Inc. ("Andrx") is herewith submitting a minor amendment to our supplemental application, by providing a complete response to the deficiency listed in your April 14, 2000 letter as follows:

Chemistry Deficiencies

The referenced DMF [redacted] remains deficient and the DMF holder is being notified. Please do not amend these supplements until the DMF deficiencies have been addressed.

Response

[redacted] has informed Andrx that a response to the FDA's April 21, 2000 deficiency letter for DMF [redacted] was submitted to the agency on June 14, 2000 (Exhibit 1).

Andrx Pharmaceuticals, Inc. certifies that a Field Copy of this amendment was forwarded to the FDA's Florida District Office. The Field Copy contained a true copy of the information contained in this amendment.

Please contact the undersigned at (954) 327-4412 (phone) or (954) 587-1054 (facsimile) if you require any additional information.

Sincerely,

Diane Servello

Diane Servello
Director of Regulatory Affairs

CENTER FOR DRUG
REC'D
JUN 19 2000
OGD
EVALUATION

NW 6-22-00

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

ANDA 74-752/S-008, S-009

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

APR 14 2000

Dear Diane Servello:

This is in reference to your supplemental new drug applications dated June 24, 1999, submitted under 505 (j), of the Federal Food, Drug and Cosmetic Act, regarding your abbreviated new drug application for Diltiazem Hydrochloride Extended-release Capsules USP, 120 mg, 180 mg, 240 mg, and 300 mg.

Reference is also made to your amendment dated January 27, and April 3, 2000.

The supplemental applications submitted as "Prior Approval Supplements", provide for the [redacted].

The supplemental applications are deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

Chemistry Deficiencies

The referenced DMF #[redacted] remains deficient and the DMF holder is being notified. Please do not amend these supplements until the DMF deficiencies have been addressed.

The file on these supplemental applications is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw these supplemental applications. 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. The responses to this letter will be considered as MINOR amendments and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving these supplemental applications, you may request an opportunity for a hearing.

Sincerely yours,

/S/ for

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

APPEARS THIS WAY
ON ORIGINAL

AM noted to CMC Review for review. /S/ 7/2000

Andrx
PHARMACEUTICALS, INC.

NDA SUPPL AMENDMENT
SCC-008
SCC-009
AM

April 3, 2000

Mr. Gary Buehler, Acting Director
Office of Generic Drugs, CDER, FDA
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 74-752; Diltiazem Hydrochloride Extended-release Capsules
Minor Amendment to Supplemental Application (S-008/S-009)

Dear Mr. Buehler:

Reference is made to our supplemental application dated June 24, 1999, providing for the [redacted] for the above mentioned drug product. Reference is also made to the FDA's not approvable letter dated February 15, 2000 (see attached).

Pursuant to 21 CFR §314.120, Andrx Pharmaceuticals, Inc. ("Andrx") is herewith submitting a minor amendment to our supplemental application, by providing complete responses to each of the deficiencies listed in the February 15, 2000 letter as follows:

Chemistry Deficiencies

1. **The referenced DMF [redacted] remains deficient and the DMF holder is being notified. Please do not amend these supplements until the DMF deficiencies have been responded to.**

   Response

   [redacted] has informed Andrx that a response to the FDA's February 24, 2000 deficiency letter for DMF # [redacted] was submitted to the agency on March 28, 2000 (Attachment 1).

Andrx is requesting that [redacted], be approved upon receipt of this minor amendment. This request is based on the fact that your February 15, 2000 letter contained no deficiencies pertaining to [redacted] and therefore is eligible for approval immediately.

Andrx Pharmaceuticals, Inc. certifies that a Field Copy of this amendment was forwarded to the FDA's Florida District Office. The Field Copy contained a true copy of the information contained in this amendment.

Please contact Janet Vaughn, Regulatory Affairs Manager, at (954) 327-3265 (phone) or (954) 587-1054 (facsimile) if you require any additional information.

Sincerely,

Diane Servello
Director of Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
APR 0 4 2000
OGD

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Andrx
PHARMACEUTICALS, INC.

ANDA 74-752
Diltiazem HCl Extended-release Capsules USP (CD)
120 mg, 180 mg, 240 mg and 300 mg

NDA NO. _____ REF NO. SCS0.11
NDA SUBMITTED FOR Comment Rec'd

February 28, 2000

Douglas L. Sporn
Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: Prior Approval Supplements

Dear Mr. Sporn:

Please refer to Andrx Pharmaceuticals abbreviated new drug application for Diltiazem Hydrochloride Extended-release Capsules, ANDA 74-752. Pursuant to 21 CFR 314.70(b), we are submitting a prior approval supplemental application to [redacted] the drug product.

In accordance with the approved release specifications, [redacted]. Every lot of each container tested to date has consistently met the required release specification.

Based on the accumulated test data, and in keeping with common industry practice, we are requesting a [redacted]. This change will not affect the characteristics of identity, strength, quality and purity of the drug product. The containers will continue to be provided by the same vendors that have proven their ability to consistently provide containers of optimal quality.

The following is a list of the containers that would be affected by the proposed change:

[redacted]

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
FEB 29 2000
OGD

These containers are used to package the drug product as follows:

[redacted]

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120 mg

[redacted]

180 mg

[redacted]

240 mg

[redacted]

300 mg

[redacted]

This supplemental application contains revised release specifications for the above containers that reflect the [redacted] Please note however, that a change from the container [redacted] for the 90 count of the 300 mg strength of the drug product, was reported in the last annual report, reporting period July 9, 1998 to July 8, 1999. A release specification for [redacted] is not included in this submission as the specification [redacted] was included in the annual report (page 000380) and is currently effective for this code.

A Form 356h immediately follows this cover letter. Andrx Pharmaceuticals, Inc. certifies that a true copy of this supplement has been sent to the Florida District Office as a Field Copy.

Should you have any questions concerning this submission or if additional information is required, please do not hesitate to contact Janet Vaughn at (954) 327-3265 *(Tel.)* or (954) 587-1054 *(Fax)*.

Sincerely,

Diane Servello

Diane Servello
Director Regulatory Affairs

Andrx
PHARMACEUTICALS, INC.

February 28, 2000

Douglas D. Tolen
Director, Florida District Office
Food and Drug Administration
555 Winderley Place
Suite 200
Maitland, FL 32751

RE: FIELD COPY - ANDA 74-752; Diltiazem HCl Extended-Release Capsules, 120 mg, 180 mg, 240 mg & 300 mg - SUPPLEMENT [§ 314.70(b)]

Dear Mr. Tolen:

Andrx Pharmaceuticals Inc. submitted a supplement to the above referenced ANDA on February 28, 2000, providing for [redacted]. Pursuant to 21 CFR 314.94(d)(5), we are providing your office with a Field Copy of this supplement. We certify that this is a true copy of the supplement submitted to the Office of Generic Drugs.

Should you have any questions or comments concerning this submission, please contact Janet Vaughn at (954) 327-3265 (telephone) or (954) 587-1054 (facsimile).

Sincerely,

Diane Servello
Director Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

ANDA 74-752/S-008, S-009

Andrx pharmaceutical, Inc.
Attention: Diane Servello
4001 SW 47th Avenue
Fort Lauderdale, FL 33314

FEB 15 2000

Dear Diane Servello:

This is in reference to your supplemental new drug applications dated June 24, 1999, submitted under 505 (j), of the Federal Food, Drug and Cosmetic Act, regarding your abbreviated new drug application for Diltiazem Hydrochloride Extended-release Capsules USP, 120 mg, 180 mg, 240 mg, and 300 mg.

Reference is also made to your amendment dated January 27, 2000.

The supplemental applications submitted as "Prior Approval Supplements", provide for the

The supplemental applications are deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

Chemistry Deficiencies

The referenced DMF # ____ remains deficient and the DMF holder is being notified. Please do not amend these supplements until the DMF deficiencies have been responded to.

The file on these supplemental applications is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw these supplemental applications. 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. The responses to this letter will be considered as MINOR amendments and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving these supplemental applications, you may request an opportunity for a hearing.

Sincerely yours,

/s/

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

APPEARS THIS WAY
ON ORIGINAL

ANDA 74-752/S-008, S-009

Andrx pharmaceutical, Inc.
Attention: Diane Servello
4001 SW 47th Avenue
Fort Lauderdale, FL 33314

FEB 15

Dear Diane Servello:

This is in reference to your supplemental new drug applications dated June 24, 1999, submitted under 505 (j), of the Federal Food, Drug and Cosmetic Act, regarding your abbreviated new drug application for Diltiazem Hydrochloride Extended-release Capsules USP, 120 mg, 180 mg, 240 mg, and 300 mg.

Reference is also made to your amendment dated January 27, 2000.

The supplemental applications submitted as "Prior Approval Supplements", provide for the

The supplemental applications are deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

Chemistry Deficiencies

The referenced DMF # remains deficient and the DMF holder is being notified. Please do not amend these supplements until the DMF deficiencies have been responded to.

The file on these supplemental applications is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw these supplemental applications. 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. The responses to this letter will be considered as MINOR amendments and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving these supplemental applications, you may request an opportunity for a hearing.

Sincerely yours,

/S/

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

APPEARS THIS WAY
ON ORIGINAL

Andrx
PHARMACEUTICALS, INC.

January 27, 2000

NDA SUPPL AMENDMENT
SCC-008 AM
SCC-009 AM

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

RE: ANDA 74-752; Diltiazem Hydrochloride Extended-release Capsules
Minor Amendment to Supplemental Application (S-008/S-009)

Dear Mr. Sporn:

Reference is made to our supplemental application dated June 24, 1999, providing for the [redacted] for the above mentioned drug product. Reference is also made to the FDA's not approvable letter dated December 9, 1999 (Attachment 1).

Pursuant to 21 CFR §314.120, Andrx Pharmaceutical, Inc. is herewith submitting a minor amendment to our supplemental application, by providing complete responses to each of the deficiencies listed in the December 9th letter as follows:

Chemistry Deficiencies

1. **The referenced DMF [redacted] is deficient and the DMF holder has been notified.**

[redacted]

In addition, we acknowledge that a satisfactory compliance evaluation for the firms referenced in the application is required for approval.

Andrx Pharmaceuticals, Inc. certifies that a Field Copy of this amendment was forwarded to the FDA's Florida District Office. The Field Copy contained a true copy of the information contained in this amendment.

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JAN 28 2000
OGD

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-581-1061

Please contact Janet Vaughn, Regulatory Affairs Manager, at (954) 327-3265 (phone) or (954) 587-1054 (facsimile) if you require any additional information.

Sincerely,

Diane Servello
Director of Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

ATTACHMENT I

ANDA 74-752/S-008, S-009

Andrx pharmaceutical, Inc.
Attention: Diane Servello
4001 SW 47th Avenue
Fort Lauderdale, FL 33314

DEC 9 1999

Dear Diane Servello:

This is in reference to your supplemental new drug applications dated June 24, 1999, submitted under 505 (j), of the Federal Food, Drug and Cosmetic Act, regarding your abbreviated new drug application for Diltiazem Hydrochloride Extended-release Capsules USP, 120 mg, 180 mg, 240 mg, and 300 mg.

The supplemental applications submitted as "Prior Approval Supplements", provide for the [redacted]

The supplemental applications are deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

Chemistry Deficiencies

1. The referenced DMF # [redacted] is deficient and the DMF holder has been notified.

2. Please provide [redacted] data for lot 9807012 and lot 9807011.

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

A satisfactory compliance evaluation for the firms referenced in the application is required for approval. Our request for an evaluation of [redacted] from the Office of Compliance is pending.

The file on these supplemental applications is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw these supplemental applications. 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. The responses to this letter will be considered as MINOR amendments and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving these supplemental applications, you may request an opportunity for a hearing.

Sincerely yours,

/S/

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

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

ANDA 74-752/S-008, S-009

Andrx pharmaceutical, Inc.
Attention: Diane Servello
4001 SW 47th Avenue
Fort Lauderdale, FL 33314

DEC 9 1999

Dear Diane Servello:

This is in reference to your supplemental new drug applications dated June 24, 1999, submitted under 505 (j), of the Federal Food, Drug and Cosmetic Act, regarding your abbreviated new drug application for Diltiazem Hydrochloride Extended-release Capsules USP, 120 mg, 180 mg, 240 mg, and 300 mg.

The supplemental applications submitted as "Prior Approval Supplements", provide for the [redacted]

The supplemental applications are deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

Chemistry Deficiencies

1. The referenced DMF # [redacted] is deficient and the DMF holder has been notified.

2. Please provide [redacted] data for lot 9807012 and lot 9807011.

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

A satisfactory compliance evaluation for the firms referenced in the application is required for approval. Our request for an evaluation of [redacted] from the Office of Compliance is pending.

The file on these supplemental applications is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw these supplemental applications. 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. The responses to this letter will be considered as MINOR amendments and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving these supplemental applications, you may request an opportunity for a hearing.

Sincerely yours,

/S/

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

APPEARS THIS WAY
ON ORIGINAL

ATTACHMENT 2

APPEARS THIS WAY
ON ORIGINAL

Andrx
PHARMACEUTICALS, INC.

NDA NO. 74752 REF. NO. SCC008
NDA SUPPL FOR [redacted]

June 24, 1999

NDA NO. 74752 REF. NO. SCC009
NDA SUPPL FOR [redacted]

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

RE: ANDA 74-752; Diltiazem HCl Extended-Release Capsules,
120 mg, 180 mg, 240 mg, and 300 mg - **SUPPLEMENT [§ 314.70(b)(2)(ii)]**

Dear Mr. Sporn:

Pursuant to 21 CFR 314.70(b)(2)(ii), Andrx Pharmaceuticals, Inc. is herewith submitting a supplement providing for [redacted] Diltiazem Hydrochloride USP [redacted]

The [redacted] are as follows:

[redacted]

Andrx Pharmaceuticals, Inc. certifies that a true copy of this supplement was sent to the Florida District Office as a Field Copy.

Should you have any questions concerning this submission, please contact the undersigned at (954) 327-4412 (telephone) or (954) 587-1054 (fax).

Sincerely,

Diane Servello
Director of Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUN 25 1999
OGD

6/28/99

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

Andrx
PHARMACEUTICALS, INC.

May 20, 1999

NDA SUPP AMEND
SC004 AM
SL006 AM

Douglas L. Sporn, Director
Office of Generic Drugs, CDER, FDA
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

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

MINOR AMENDMENT TO SUPPLEMENT S-004, S-006

Dear Mr. Sporn:

In accordance with 21 CFR 314.120, Andrx Pharmaceuticals, Inc. is herewith submitting a minor amendment to the above referenced supplemental application.

This amendment is being submitted in response to a Not Approvable letter dated May 19, 1999. Complete responses to the chemistry deficiencies are provided.

Andrx Pharmaceuticals, Inc. certifies that true copies of the technical sections contained in this amendment were sent to the Florida District Office as a Field Copy.

Should you have any questions concerning this submission, please contact the undersigned at (954) 327-4412 (telephone) or (954) 587-1054 (fax).

Sincerely,

Diane Servello
Director of Regulatory Affairs

CENTER FOR DRUG
REC'D
MAY 2 1 1999
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ANDA 74-752/S-004, S-006

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

MAY 19 1999

Dear Sir:

This is in reference to your supplemental new drug applications dated September 11, 1998, submitted pursuant to 21 CFR 314.70, regarding your abbreviated new drug application for Cartia-XT (Diltiazem Hydrochloride Extended-release Capsules, USP); 120 mg, 180 mg, 240 mg and 300 mg.

Reference is also made to your amendment dated April 14, 1999.

The supplemental applications provide for:

S-004: Formulation Change -

[redacted]

S-006: Labeling Revision.

The supplemental application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

[redacted]

1. Revised stability protocols indicating that at least the smallest and largest container/closure system will be tested for each strength of drug product.

2. Stability data accrued to date for each strength of drug product.

The file on these supplemental applications is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw these supplemental applications. 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. The response to this letter will be considered a MINOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this supplemental application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ for

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

APPEARS THIS WAY
ON ORIGINAL

Andrx
PHARMACEUTICALS, INC.

Labeling review drafted 4/30/99 /s/

NDA SUPPL AMENDMENT
S-001, 002, 003 /AM

April 23, 1999

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

NDA NO. _____ REF NO. SL007
NDA SUPPL FOR Label review

RE: ANDA 74-752; Diltiazem Extended-Release Capsules USP 120 mg, 180 mg, 240 mg and 300 mg

MINOR AMENDMENT TO SUPPLEMENT S-001, S-002 AND S-003

Dear Mr. Sporn:

We refer to your letter dated March 23, 1999 (copy attached) describing chemistry and labeling deficiencies in the above-mentioned supplemental applications submitted on August 18, 1998. Pursuant to 21 CFR 314.120, we are herewith submitting a MINOR amendment responding to all the listed deficiencies.

In this regard, we are enclosing the following:

A. CHEMISTRY DEFICIENCIES:

Comment 1: *Please submit USP <661> and <671> testing results for the 120 cc and 150 cc container/closure systems.*

Response: Testing results per USP <661> and <671> for the 120 cc and 150 cc container/closure systems are enclosed under Tab 1.

Comment 2: [redacted]

Response: [redacted]

APR 26 1999

GENERIC DRUGS

/s/ 4-30-99

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

B. LABELING DEFICIENCIES:

Comment: *You have added 90 count and 1000 count container/closure systems with no labeling submission. Please submit labeling for the new packages and containers as well as package inserts with all necessary revisions.*

Response: We have prepared final printed container labels for the 90 count and 1000 count containers, as well as package inserts with the necessary revisions. Please see Tab 3 for the following information:

i) Side-by-side labeling for the package insert, annotated to describe the changes from the latest approved package insert. Please note that since the container labels are for new package sizes rather than revisions to previous labels, a side-by-side comparison has not been prepared for the container labels.

ii) Final printed container labels are enclosed as follows:
- 120 mg strength (90 count)
- 120 mg strength (1000 count)
- 180 mg strength (90 count)

- 180 mg strength (1000 count)
- 240 mg strength (90 count)
- 240 mg strength (1000 count)
- 300 mg strength (90 count)
- 300 mg strength (1000 count)

iii) Final printed package outsert labeling. Please note that the blue-inked outserts are for submission purposes only and that the outserts for commercial distribution will be printed in black ink.

Twelve copies of final printed labeling have been provided - one set in the archival copy, one set in the review copy, and ten sets separately bound in a black, labeled binder.

Andrx Pharmaceuticals, Inc. certifies that true copies of the technical sections contained in this amendment were sent to the Florida District Office as a Field Copy.

Should you have any questions concerning this submission, please contact the undersigned at (954) 327-4412 (telephone) or (954) 587-1054 (fax).

Sincerely,

Diane Servello

Diane Servello
Director of Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Andrx
PHARMACEUTICALS, INC.

NDA NO. 74-752 REF. NO. SL-006
NDA SUPPL FOR Labeling Rev

labeling review drafted 4/21/99

April 14, 1999

NDA SUPP AMEND
SCS 004
AM

Douglas L. Sporn, Director
Office of Generic Drugs, CDER, FDA
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

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

MINOR AMENDMENT TO SUPPLEMENT S-004

Dear Mr. Sporn:

In accordance with 21 CFR 314.120, Andrx Pharmaceuticals, Inc. is herewith submitting a minor amendment to the above referenced supplemental application.

This amendment is being submitted in response to a Not Approvable letter dated April 2, 1999. Complete responses to the chemistry and labeling deficiencies are provided.

Andrx Pharmaceuticals, Inc. certifies that true copies of the technical sections contained in this amendment were sent to the Florida District Office as a Field Copy.

Should you have any questions concerning this submission, please contact the undersigned at (954) 327-4412 (telephone) or (954) 587-1054 (fax).

Sincerely,

Diane Servello
Director of Regulatory Affairs

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APR 15 1999
GENERIC DRUGS

4-15-99

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

ANDA 74-752/S-004

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

APR 2 1999

Dear Sir:

This is in reference to your supplemental new drug application dated September 11, 1998, submitted pursuant to 21 CFR 314.70, regarding your abbreviated new drug application 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 December 22, 1998 and January 14, 1999.

The supplemental application provides for the

[redacted]

The supplemental application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies:

1. [redacted]

2. [redacted]

B. Labeling Deficiencies:

Please submit a revised package insert indicating the addition of magnesium stearate as an inactive ingredient.

The file on this supplemental application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw this supplemental application. 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. The response to this letter will be considered a MINOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this supplemental application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ for

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

APPEARS THIS WAY
ON ORIGINAL

ANDA 74-752/S-001, S-002, S-003

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

23

Dear Sir:

This is in reference to your supplemental new drug applications dated August 18, 1998, submitted pursuant to 21 CFR 314.70, regarding your abbreviated new drug application for Cartia-XT (Diltiazem Hydrochloride Extended-release Capsules USP, 120 mg, 180 mg, 240 mg and 300 mg).

The supplemental applications provide for:

S-001: Packaging Addition - the addition of 90 count container/closure systems, 1000 count container closure systems, and changes in container sizes for the 120 mg x 30 capsule, 240 mg x 30 capsule, and 240 mg x 500 capsule packaging.

S-002: Packaging Revision - a change in the [redacted]

S-003 - Packaging Revision - a change in the [redacted]

The supplemental applications are deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies:

1. Please submit USP <661> and <671> testing results for the 120 cc and 150 cc container/closure systems.

2. [redacted]

stability test results. Please explain this discrepancy.

B. Labeling Deficiencies:

You have added 90 count and 1000 count container/closure systems with no labeling submission. Please submit labeling for the new packages and containers as well as package inserts with all necessary revisions.

The file on these supplemental applications is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw these supplemental applications. 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. The responses to this letter will be considered a MINOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this supplemental application, you may request an opportunity for a hearing.

Sincerely yours,

/S/

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

NAI
Horsenberg
proof of US mail
to patent or application
hold - see #1/29/99
correspondence
(S) 1/26/14

Andrx
PHARMACEUTICALS INC.

February 23, 1999

NEW CORRESP
N C

Mr. Douglas Sporn
Director, Office of Generic Drugs (HFD-600)
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 74-752: Cartia XT (Diltiazem Hydrochloride Extended-release Tablets USP), 120 mg, 180 mg, 240 mg & 300 mg
PATENT AMENDMENT

Dear Mr. Sporn:

Andrx is amending its September 11, 1998 supplemental application to ANDA 74-752 (S-004) to provide documentation of notification/receipt of notification under 21 CFR 314.95(a).

In accordance with 21 CFR 314.95(b), Andrx Pharmaceuticals, Inc. certifies that:

(i) notices of certification of noninfringement of a patent have been provided by U.S. registered mail, return receipt requested, to the patent owners (Carderm Capital and Elan Corp.) and the NDA holder (Carderm Capital), and

(ii) the notices met the content requirements under section 314.95(c).

In accordance with section 314.95(e), copies of the return receipt postcards are provided as documentation of receipt of the notices.

This amendment consists of one volume. An archival copy and a review copy are provided. Should you have any questions or comments regarding this submission, please contact the undersigned at (954) 321-5229 (Tel.) or (954) 587-1054 (Fax).

Sincerely,

JDavis

Jacqueline Davis
Regulatory Affairs Manager

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FEB 24 1999
GENERIC DRUGS

Nadine 2-25-99

Andrx

PHARMACEUTICALS INC.

NAI Paragraph IV OK for supplement for new strengths 120mg, 300mg still waiting for the proof notification (as stated) /S/ 2/10/99

January 29, 1999

NEW CORRESP

NC to SC-004

Document Control Room
Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: ANDA #74-752: Cartia-XT (Diltiazem Hydrochloride Extended Release Capsules USP) 120 mg, 180 mg, 240 mg & 300 mg (Once-A-Day Dosage)
<u>AMENDMENT TO SUPPLEMENT S-004</u>

Dear Sir or Madam:

Andrx Pharmaceuticals, Inc. is hereby amending its prior approval supplement, S-004, submitted on September 11, 1998, to provide a Paragraph IV Certification (enclosed herewith). As discussed with Mr. Peter Rickman, Branch Chief, Regulatory Support Branch, Andrx does not believe this Paragraph IV Certification is legally required. Despite this belief, Andrx is submitting the enclosed certification based upon the following representations and understandings:

1. As the FDA procedures do not provide for a notice of acceptance of filing of a supplement, which is the event that triggers the notice to the parties having an interest in the referenced product, Andrx is authorized to immediately forward the detailed explanation of its Paragraph IV Certification to Hoechst Marion Roussel, Inc. and Carderm Capital Ltd. Appropriate proof of their receipt of such notification will be forwarded to your office in due course; and

2. The Andrx supplement has been assigned ANDA #74-752, the same ANDA number as our application that was approved on July 9, 1998, and thus, such application and this supplement remain fully entitled to the 180-day period of marketing exclusivity accorded to Andrx pursuant to Section 355(j)(5)(B)(iv). Accordingly, our application will not delay or prevent the approval of our supplement and the period of exclusivity will not commence until such time as either of the events specified in the foregoing section has been satisfied.

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/S/ 2-4-99

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

We thank you for your consideration of this matter. Please contact me at 954-321-5214 (telephone) or 954-792-1034 (facsimile) if you have any questions or concerns with respect to the foregoing.

Sincerely,

Scott Lodin
Vice President and General Counsel

SL:aal
Enclosure

cc: Chih-Ming J. Chen, Ph.D.
James Costigan, Esq.
Jacqueline Davis
Eugene Pfeifer, Esq.

[illegible] MAY
ON ORIGINAL

Andrx
PHARMACEUTICALS INC.

January 14, 1999

NDA SUPPL AMENDMENT
S004AC

Document Control Room
Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA #74-752: Cartia-XT (Diltiazem Hydrochloride Extended-Release Capsules USP) 120 mg, 180 mg, 240 mg, & 300 mg (Once-A-Day Dosage)

AMENDMENT TO SUPPLEMENT S-004

Dear Sir/Madam:

Andrx Pharmaceuticals is amending its prior approval supplement, S-004, submitted on September 11, 1998, to provide updated stability data. Supplement S-004 provides for a change in

This amendment provides additional stability data in support of this change.

The information provided includes stability protocols for the 120 and 300 mg strengths, a stability commitment, and three months accelerated and long term stability data for three lots each of the 120 and 300 mg strengths. The stability data also includes six months long term data for the 300 mg biobatch, Lot #600R003.

This amendment consists of one volume. An archival copy and a chemistry review copy are provided.

In accordance with 21 CFR 314.96(b), Andrx Pharmaceuticals certifies that a field copy of this amendment has been sent to the Florida District Office.

Should you have any questions concerning this submission, please contact the undersigned at (954) 321-5229 (tel.) or (954) 587-1054 (fax).

Sincerely,

Jacqueline Davis
Regulatory Affairs Manager

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JAN 19 1999
GENERIC DRUGS

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

Andrx
PHARMACEUTICALS INC.

VIA Facsimile

NDA SUPP AMEND
SC-004
AC

December 22, 1998

Document Control Room
Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: **ANDA #74-752: Cartia-XT (Diltiazem Hydrochloride Extended-Release Capsules USP) 120 mg, 180 mg, 240 mg, & 300 mg (Once-A-Day Dosage)**

TELEPHONE BIOEQUIVALENCY AMENDMENT

Dear Sir/Madam:

Andrx Pharmaceuticals is amending its prior approval supplement submitted on September 11, 1998, to provide the additional information requested by telephone on December 11,1998. This amendment provides the following:

(i) dissolution profiles for the 120 mg, 180 mg, 240 mg, and 300 mg strengths (Attachment A)
(ii) comparative dissolution data for the new formation vs. the old formulation for all strengths (Attachment B)
(iii) a request for waiver for the lower strengths (Attachment C)
(iv) formulation data (comparison of the formulation for the proposed product vs. the previously approved product) for all strengths (Attachment D)

In addition, please note the following responses:

- the lot size of the 300 mg biobatch (Lot #600R003A) is [redacted] capsules)
- the potency of Lot #600R003A is [redacted] (see certificate of analysis on page 46 of original supplement)
- the potency of the reference product (Lot #P70395) is [redacted]

Should you have any questions concerning this submission, please contact the undersigned at (954) 321-5229 (tel.) or (954) 587-1054 (fax).

Sincerely,

Jacqueline Davis
Regulatory Affairs Manager

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GENERIC DRUGS

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

Redacted 7

pages of trade secret and/or confidential commercial information

Andrx
PHARMACEUTICALS, INC.

Approval Letter drafted 3/3/99

October 23, 1998

FPL

NDA NO. _____ REF NO. SL-005
NDA SUPPL FOR Labeling Rev

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: Cartia XT (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** container labels for each package size of each strength for an original abbreviated new drug application ("ANDA") for Cartia XT (Diltiazem Hydrochloride Extended-release Capsules, USP) 120 mg, 180 mg, 240 mg and 300 mg (Once-a-day Dosage) dated September 22, 1995. This ANDA received approval on July 9, 1998.

On June 25, 1998, prior to approval, the final container labelling was submitted for this ANDA. What was submitted at that time were color printer's proofs which had been generated by the vendor using a color lazer printer. The labels provided with this submission are the final printed container labels which is the reason the submission is being made.

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

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
OCT 26 1998
GENERIC DRUGS

Thank you for your prompt handling of this amendment.

Sincerely,

David A. Gardner

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

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confidential

commercial

information

BIOAVAILABILITY

Andrx
PHARMACEUTICALS, INC.

September 11, 1998

NDA NO. 74752 REF NO. SC-004
NDA SUPPL FOR Control Rev. SC-004 4X

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

SUPPLEMENT - EXPEDITED REVIEW

Re: **ANDA 74-752: Cartia-XT (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 a Prior Approval Supplement to ANDA 74-752, Cartia-XT (Diltiazem Hydrochloride Extended-release Capsules, USP) 120 mg, 180 mg, 240 mg & 300 mg (Once-a-day Dosage). This ANDA was approved on July 9, 1998. The supplement is being submitted based on 21 CFR §314.70(b)(2)(i).

[redacted]

Andrx hereby requests an **expedited review** of the supplement. While the supplement represents only a minor modification of the formulation for Andrx' approved product, the resulting change in the Cartia XT dissolution specification, when approved by FDA, will be presented to the Court in our pending patent litigation concerning that product. As the FDA is aware, Andrx has not commenced the marketing of Cartia XT due to the pendency of that litigation and Andrx believes that this change will allow that Court to more easily makes its determination with respect to an important issue in that litigation.

Andrx is providing two copies of this Prior Approval Supplement to the Office of Generic Drugs, an Archival Copy, a Chemistry Review Copy and a Pharmacokinetic Review Copy which contains a randomized, two-way crossover, single dose, fasting bioequivalence study - protocol No. 98090. [**Note:** The four (4) volumes containing the bioequivalence study - volumes 4 through 7 - have been numbered separately beginning with 1 through 2146.]

This also certifies that, concurrent with the filing of this supplement, a true copy of the supplement 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. (Note: A copy of the bioequivalence study was not submitted to the local district office.)

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SEP 15 1998
GENERIC DRUGS

9/15/98

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7560 • 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 supplement.

Sincerely,

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

APPEARS THIS WAY
ON ORIGINAL

NDA NO. ____ REF. NO 5C001
NDA SUPPL FOR Package Add

NDA NO. ____ REF. NO. 5C002
NDA SUPPL FOR Manufacturing

Andrx
PHARMACEUTICALS, INC.

August 18, 1998

NDA NO. ____ REF. NO. 5C003
NDA SUPPL FOR Control Rev

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

PRIOR APPROVAL SUPPLEMENT

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

Dear Director Sporn:

Andrx Pharmaceuticals, Inc. ("Andrx"), today submits a Prior Approval Supplement to ANDA 74-752, Cartia-XT (Diltiazem Hydrochloride Extended-release Capsules, USP) 120 mg, 180 mg, 240 mg & 300 mg (Once-a-day Dosage). The supplement is being submitted based on 21 CFR §314.70(b)(2)(vii). The following changes are being submitted in this supplement:

(1) addition of a larger package size - 1000 count bottle;
(2) change in the [redacted]
(3) change in the [redacted]

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

This also certifies that, concurrent with the filing of this supplement, a true copy of the supplement 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. 47th Avenue
Ft. Lauderdale, FL 33314

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AUG 19 1998
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If you need to telephone or send a facsimile, my numbers are (954) 581-7500 and (954) 327-5389 (FAX).

Thank you for the prompt handling of this supplement.

Sincerely,

David A. Gardner

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

APPEARS THIS WAY
ON ORIGINAL