

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 75124

Trade Name Diltiazem Hydrochloride Extended-release
Capsules USP 120mg, 180mg and 240mg

Generic Name Diltiazem Hydrochloride Extended-release
Capsules USP 120mg, 180mg and 240mg

Sponsor Mylan Pharmaceuticals, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 75124

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75124

APPROVAL LETTER

ANDA 75-124

MAR 18 1998

Mylan Pharmaceuticals Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26505-2730

Dear Sir:

This is in reference to your abbreviated new drug application dated April 29, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Diltiazem Hydrochloride Extended-release Capsules USP, 120 mg, 180 mg, and 240 mg.

Reference is also made to your amendments dated July 15, September 9, October 6 and November 26, 1997; and January 23, and February 25, 1998.

The listed drug product referenced in your application is subject to periods of patent protection which expire on December 9, 2006 (Patent No. 4,839,177) and June 6, 2012 (Patent No. 5,422,123), 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 Diltiazem Hydrochloride Extended-release Capsules, USP will not infringe on the patents and that the patents are otherwise invalid. You informed us that the patent holder, Jagotec AG and JAGO Research AG, initiated a patent infringement action pertaining only to the 240 mg formulation against you in the United States District Court for the Southern District of New York (Civil Action No. 97 CIV 7015). You have also notified us that the above entitled action against Mylan Pharmaceuticals, Inc. was dismissed by the plaintiffs without prejudice.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Diltiazem Hydrochloride Extended-release Capsules USP, 120 mg, 180 mg, and 240 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug

(Dilacor XR Extended-release Capsules, 120 mg, 180 mg and 240 mg, respectively, of Rhone-Poulenc Rorer Pharmaceuticals, Inc.).

Your "interim" dissolution testing should be incorporated into the stability and quality control program using the same method as proposed in your application. The "interim" dissolution test(s) and tolerances are:

The dissolution testing should be conducted in 900 mL of water at 37 degrees C using USP 23 Apparatus 2 (Paddle) at 100 rpm. The test product should meet the following tentative dissolution specifications:

Limits:	1 hour	between
	4 hours	between
	10 hours	between
	15 hours	Not less than

The "interim" dissolution test and tolerances should be finalized by submitting dissolution data for the first three production size batches in a supplemental application. The supplemental application should be submitted under 21 CFR 314.70(c)(1) when there are no revisions to the interim specifications or when the final specifications are tighter than the interim specifications. In all other instances, the supplement should be submitted under 21 CFR 314.70(b)(2)(ii).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

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

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

3/18/98

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER **75124** _____

FINAL PRINTED LABELING

DILTIAZEM HCl ER CAPSULES,
USP 120mg, 180mg and 240mg

ANDA 75-124

MAR 62

Each extended-release capsule contains:
Diltiazem Hydrochloride, USP 120 mg

120 mg

N 0378-5220-01 5



NDC 0378-5220-01

MYLAN®

CAPSULES, USP

100 CAPSULES

CAUTION: Federal law prohibits dispensing without prescription.

Dispense in a light, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

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

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

Usual Dosage: See accompanying prescribing information.

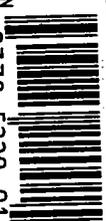
Mylan Pharmaceuticals Inc.
Bergantown, WV 26046

RMS220A

Each extended-release capsule contains:
Diltiazem Hydrochloride, USP 120 mg

120 mg

N 0378-5220-01 5



NDC 0378-5220-01

MYLAN®

CAPSULES, USP

100 CAPSULES

CAUTION: Federal law prohibits dispensing without prescription.

Dispense in a light, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

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

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

Usual Dosage: See accompanying prescribing information.

Mylan Pharmaceuticals Inc.
Bergantown, WV 26046

RMS220A

Each extended-release capsule contains:
Diltiazem Hydrochloride, USP 120 mg

120 mg

N 0378-5220-01 5



NDC 0378-5220-01

MYLAN®

CAPSULES, USP

100 CAPSULES

CAUTION: Federal law prohibits dispensing without prescription.

Dispense in a light, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

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

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

Usual Dosage: See accompanying prescribing information.

Mylan Pharmaceuticals Inc.
Bergantown, WV 26046

RMS220A

DILTIAZEM HCl ER CAPSULES,
USP 120mg, 180mg and 240mg

ANDA 75-124

Each extended-release capsule contains:
Diltiazem Hydrochloride, USP 240 mg

N 0378-5340-05 8

240 mg

NDC 0378-5340-05

MYLAN®

**DILTIAZEM
HYDROCHLORIDE
EXTENDED-RELEASE
CAPSULES, USP
(Once-a-Day Dosage)
240 mg**

500 CAPSULES

CAUTION: Federal law prohibits dispensing without prescription. Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure. Keep container tightly closed. Keep this and all medication out of the reach of children.

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

Usual Dosage: See accompanying prescribing information.

This is a bulk container and not intended for dispensing for household use.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM5340B

Each extended-release capsule contains:
Diltiazem Hydrochloride, USP 240 mg

N 0378-5340-05 8

240 mg

NDC 0378-5340-05

MYLAN®

**DILTIAZEM
HYDROCHLORIDE
EXTENDED-RELEASE
CAPSULES, USP
(Once-a-Day Dosage)
240 mg**

500 CAPSULES

CAUTION: Federal law prohibits dispensing without prescription. Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure. Keep container tightly closed. Keep this and all medication out of the reach of children.

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

Usual Dosage: See accompanying prescribing information.

This is a bulk container and not intended for dispensing for household use.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM5340B

Each extended-release capsule contains:
Diltiazem Hydrochloride, USP 240 mg

N 0378-5340-05 8

240 mg

NDC 0378-5340-05

MYLAN®

**DILTIAZEM
HYDROCHLORIDE
EXTENDED-RELEASE
CAPSULES, USP
(Once-a-Day Dosage)
240 mg**

500 CAPSULES

CAUTION: Federal law prohibits dispensing without prescription. Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure. Keep container tightly closed. Keep this and all medication out of the reach of children.

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

Usual Dosage: See accompanying prescribing information.

This is a bulk container and not intended for dispensing for household use.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM5340B

DILTIAZEM HCl ER CAPSULES,
USP 120mg, 180mg and 240mg

ANDA 75-124

Each extended-release capsule contains:
Diltiazem Hydrochloride, USP 240 mg

N 0378-5340-01 0

240 mg

MDC 0378-5340-01

MYLAN®

DILTIAZEM HYDROCHLORIDE EXTENDED-RELEASE CAPSULES, USP
(Once-a-Day Dosage)
240 mg

100 CAPSULES

CAUTION: Federal law prohibits dispensing without prescription.
Dispense in a light, light-resistant container as defined in the USP using a child-resistant closure.
Keep container tightly closed.
Keep this and all medication out of the reach of children.
STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).
Usual Dosage: See accompanying prescribing information.
This is a bulk container and not intended for dispensing for household use.
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RMS340A

Each extended-release capsule contains:
Diltiazem Hydrochloride, USP 240 mg

N 0378-5340-01 0

240 mg

MDC 0378-5340-01

MYLAN®

DILTIAZEM HYDROCHLORIDE EXTENDED-RELEASE CAPSULES, USP
(Once-a-Day Dosage)
240 mg

100 CAPSULES

CAUTION: Federal law prohibits dispensing without prescription.
Dispense in a light, light-resistant container as defined in the USP using a child-resistant closure.
Keep container tightly closed.
Keep this and all medication out of the reach of children.
STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).
Usual Dosage: See accompanying prescribing information.
This is a bulk container and not intended for dispensing for household use.
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RMS340A

Each extended-release capsule contains:
Diltiazem Hydrochloride, USP 240 mg

N 0378-5340-01 0

240 mg

MDC 0378-5340-01

MYLAN®

DILTIAZEM HYDROCHLORIDE EXTENDED-RELEASE CAPSULES, USP
(Once-a-Day Dosage)
240 mg

100 CAPSULES

CAUTION: Federal law prohibits dispensing without prescription.
Dispense in a light, light-resistant container as defined in the USP using a child-resistant closure.
Keep container tightly closed.
Keep this and all medication out of the reach of children.
STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).
Usual Dosage: See accompanying prescribing information.
This is a bulk container and not intended for dispensing for household use.
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RMS340A

DILTIAZEM HCl ER CAPSULES,
USP 120mg, 180mg and 240mg

ANDA 75-124

Each extended-release
capsule contains:
Diltiazem
Hydrochloride, USP 180 mg



180 mg

NDC 0378-5280-05

MYLAN®

**DILTIAZEM
HYDROCHLORIDE
EXTENDED-RELEASE
CAPSULES, USP**
(Once-a-Day Dosage)
180 mg

500 CAPSULES

CAUTION: Federal law prohibits dispensing without prescription. Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure. Keep container tightly closed. Keep this and all medication out of the reach of children.

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

Usual Dosage: See accompanying prescribing information.

This is a bulk container and not intended for dispensing for household use.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RMS280B

Each extended-release
capsule contains:
Diltiazem
Hydrochloride, USP 180 mg



180 mg

NDC 0378-5280-05

MYLAN®

**DILTIAZEM
HYDROCHLORIDE
EXTENDED-RELEASE
CAPSULES, USP**
(Once-a-Day Dosage)
180 mg

500 CAPSULES

CAUTION: Federal law prohibits dispensing without prescription. Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure. Keep container tightly closed. Keep this and all medication out of the reach of children.

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

Usual Dosage: See accompanying prescribing information.

This is a bulk container and not intended for dispensing for household use.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RMS280B

Each extended-release
capsule contains:
Diltiazem
Hydrochloride, USP 180 mg



180 mg

NDC 0378-5280-05

MYLAN®

**DILTIAZEM
HYDROCHLORIDE
EXTENDED-RELEASE
CAPSULES, USP**
(Once-a-Day Dosage)
180 mg

500 CAPSULES

CAUTION: Federal law prohibits dispensing without prescription. Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure. Keep container tightly closed. Keep this and all medication out of the reach of children.

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

Usual Dosage: See accompanying prescribing information.

This is a bulk container and not intended for dispensing for household use.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RMS280B

DILTIAZEM HCl ER CAPSULES,
USP 120mg, 180mg and 240mg

ANDA 75-124

MAR 60

Each extended-release capsule contains:
Diltiazem Hydrochloride, USP 180 mg



NDC 0378-5280-01
MYLAN®
DILTIAZEM HYDROCHLORIDE EXTENDED-RELEASE CAPSULES, USP (Once-a-Day Dosage) 180 mg
100 CAPSULES

CAUTION: Federal law prohibits dispensing without prescription.
Dispense in a light, light-resistant container as defined in the USP using a child-resistant closure.
Keep container tightly closed.
Keep this and all medication out of the reach of children.
STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).
Usual Dosage: See accompanying prescribing information.
Mylan Pharmaceuticals Inc. Kenilworth, NJ 07033

RMS280A

Each extended-release capsule contains:
Diltiazem Hydrochloride, USP 180 mg



NDC 0378-5280-01
MYLAN®
DILTIAZEM HYDROCHLORIDE EXTENDED-RELEASE CAPSULES, USP (Once-a-Day Dosage) 180 mg
100 CAPSULES

CAUTION: Federal law prohibits dispensing without prescription.
Dispense in a light, light-resistant container as defined in the USP using a child-resistant closure.
Keep container tightly closed.
Keep this and all medication out of the reach of children.
STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).
Usual Dosage: See accompanying prescribing information.
Mylan Pharmaceuticals Inc. Kenilworth, NJ 07033

RMS280A

Each extended-release capsule contains:
Diltiazem Hydrochloride, USP 180 mg



NDC 0378-5280-01
MYLAN®
DILTIAZEM HYDROCHLORIDE EXTENDED-RELEASE CAPSULES, USP (Once-a-Day Dosage) 180 mg
100 CAPSULES

CAUTION: Federal law prohibits dispensing without prescription.
Dispense in a light, light-resistant container as defined in the USP using a child-resistant closure.
Keep container tightly closed.
Keep this and all medication out of the reach of children.
STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).
Usual Dosage: See accompanying prescribing information.
Mylan Pharmaceuticals Inc. Kenilworth, NJ 07033

RMS280A

MYLAN PHARMACEUTICALS INC.

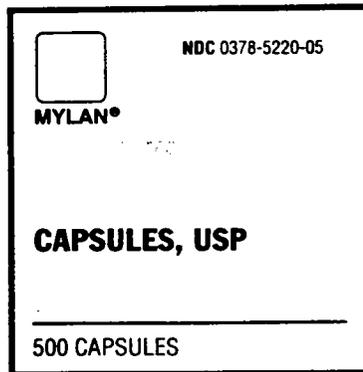
DILTIAZEM HCl ER CAPSULES,
USP 120mg, 180mg and 240mg

ANDA 75-124

Each extended-release capsule contains:
Diltiazem Hydrochloride, USP 120 mg

N
3 0378-5220-05 3

120 mg



CAUTION: Federal law prohibits dispensing without prescription. Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure. Keep container tightly closed. Keep this and all medication out of the reach of children.

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

Usual Dosage: See accompanying prescribing information.

This is a bulk container and not intended for dispensing for household use.

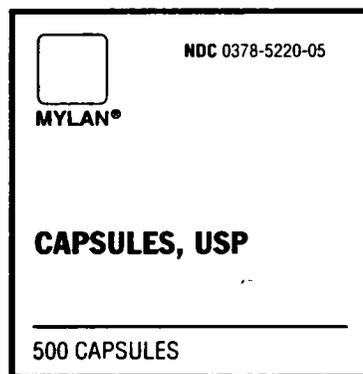
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RMS220B

Each extended-release capsule contains:
Diltiazem Hydrochloride, USP 120 mg

N
3 0378-5220-05 3

120 mg



CAUTION: Federal law prohibits dispensing without prescription. Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure. Keep container tightly closed. Keep this and all medication out of the reach of children.

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

Usual Dosage: See accompanying prescribing information.

This is a bulk container and not intended for dispensing for household use.

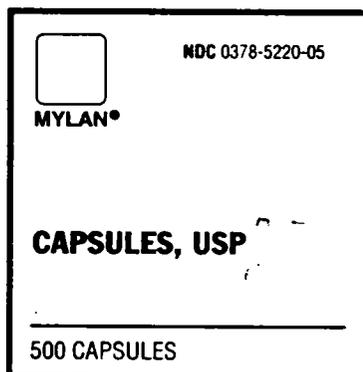
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RMS220B

Each extended-release capsule contains:
Diltiazem Hydrochloride, USP 120 mg

N
3 0378-5220-05 3

120 mg



CAUTION: Federal law prohibits dispensing without prescription. Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure. Keep container tightly closed. Keep this and all medication out of the reach of children.

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

Usual Dosage: See accompanying prescribing information.

This is a bulk container and not intended for dispensing for household use.

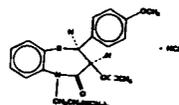
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RMS220B



**DILTIAZEM
HYDROCHLORIDE
EXTENDED-RELEASE
CAPSULES, USP**
(Once-a-Day Dosage)
120 mg, 180 mg
and 240 mg

DESCRIPTION: Diltiazem 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-. Its molecular formula is $C_{27}H_{30}N_2O_4$ HCl and its molecular weight is 450.59. Its structural formula is as follows:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol and chloroform.

Diltiazem Hydrochloride Extended-release Capsules (Once-a-Day Dosage), for oral administration, contain multiple units of diltiazem hydrochloride extended-release 60 mg, resulfing in the 120 mg, 180 mg or 240 mg dosage strengths allowing for the controlled release of diltiazem hydrochloride over a 24-hour period. In addition, each capsule contains the following inactive ingredients: ammonium hydroxide, colloidal silicon dioxide, dibutyl sebacate, D&C Yellow #10 aluminum lake, ethylcellulose, FD&C Red #40 aluminum lake, FD&C Blue #1 aluminum lake, FD&C #2 aluminum lake, gelatin, hydroxypropyl methylcellulose, magnesium stearate, maltodextrin, microcrystalline cellulose, n-butyl alcohol, oleic acid, pharmaceutical grade, polyethylene glycol, polyethylene glycol, SD-3A alcohol, sodium lauryl sulfate, synthetic black iron oxide and titanium dioxide. In addition, the 120 mg strength contains D&C Red #1 aluminum lake and the 180 mg strength contains D&C Red #28 aluminum lake.

Diltiazem Hydrochloride Extended-release Capsules, USP (Once-a-Day Dosage) 120 mg, 180 mg and 240 mg meet USP Drug Release Test 2.

CLINICAL PHARMACOLOGY: The therapeutic benefits of diltiazem are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

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

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

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

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential.

most USP Drug Release Test 2.
CLINICAL PHARMACOLOGY: The therapeutic benefits of diltiazem are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

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

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

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

In animal studies, diltiazem interferes with the slow channel (slowly activating) current in excitable tissues. 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 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 AV 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. In exercise tolerance studies in patients with ischemic heart disease, diltiazem reduces the double product (HR x SBP) for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect. Cardiac output, ejection fraction and left ventricular end diastolic pressure have not been affected. Such data have no predictive value with respect to effects in patients with poor ventricular function. Increased heart failure has, however, been reported in occasional patients with pre-existing impairment of ventricular function. There are as yet few data on the interaction of diltiazem with digitalis glycosides in patients with poor ventricular function. Resting heart rate is usually slightly reduced by diltiazem.

Diltiazem hydrochloride extended-release capsules produce antihypertensive effects both in the supine and standing positions. Postural hypotension is infrequently noted upon suddenly assuming an upright position. Diltiazem decreases vascular resistance, increases cardiac output (by increasing stroke volume), and produces a slight decrease or no change in heart rate. No reflex tachycardia is associated with the chronic antihypertensive effects.

During dynamic exercise, increases in diastolic pressure are inhibited while maximum achievable systolic pressure is usually reduced. Heart rate at maximum exercise does not change or is slightly reduced.

Diltiazem antagonizes the renal and peripheral effects of angiotensin II. An increased activity of the renin-angiotensin-aldosterone axis has been observed. Chronic therapy with diltiazem produces no change or an increase in plasma catecholamines. Hypertensive animal models respond to diltiazem with reductions in blood pressure and increased urinary output and natriuresis without a change in the urinary sodium/potassium ratio. In man, treatment natriuresis and kaliuresis have been reported, but only in high intravenous doses of 0.5 mg/kg of body weight.

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

In two short-term, double-blind, placebo-controlled studies, 303 hypertensive patients were treated with once-daily diltiazem hydrochloride extended-release capsules in doses of up to 540 mg. There were no instances of greater than first-degree atrioventricular block, and the maximum increase in the PR interval was .80 seconds. No patients were prematurely discontinued from the medication due to symptoms related to prolongation of the PR interval.

Pharmacodynamics: In one short-term, double-blind, placebo-controlled study, diltiazem hydrochloride extended-release capsules (once-a-day dosage) 120, 240, 360 and 480 mg/day demonstrated a dose-related antihypertensive response among patients with mild to moderate hypertension. Statistically significant decreases in trough mean supine diastolic blood pressure were seen through

In two short-term, double-blind, placebo-controlled studies, 303 hypertensive patients were treated with once-daily diltiazem hydrochloride extended-release capsules in doses of up to 540 mg. There were no instances of greater than first-degree atrioventricular block, and the maximum increase in the PR interval was .38 seconds. No patients were prematurely discontinued from the study due to symptoms related to prolongation of the PR interval.

Pharmacodynamics: In one short-term, double-blind, placebo-controlled study, diltiazem hydrochloride extended-release capsules (once-a-day dosage) 120, 240, 360 and 480 mg/day demonstrated a dose-related antihypertensive response among patients with mild to moderate hypertension. Statistically significant decreases in trough mean supine diastolic blood pressure were seen through four weeks of treatment: 120 mg/day (-5.1 mmHg); 240 mg/day (-4.9 mmHg); 360 mg/day (-4.5 mmHg); and 480 mg/day (-10.6 mmHg). Statistically significant decreases in trough mean supine systolic blood pressure were also seen through four weeks of treatment: 120 mg/day (-2.6 mmHg); 240 mg/day (-4.5 mmHg); 360 mg/day (-4.8 mmHg); and 480 mg/day (-10.5 mmHg). The proportion of ambulatory patients exhibiting a therapeutic response (supine diastolic blood pressure <90 mmHg or decrease >10 mmHg) was greater as the dose increased: 31%, 42%, 46%, and 69% with the 120, 240, 360 and 480 mg/day diltiazem groups, respectively. Similar findings were observed for standing systolic and diastolic blood pressures. The trough (24 hours after a dose) antihypertensive effect of diltiazem hydrochloride extended-release capsules (once-a-day dosage) remained more than one-half of the response seen at peak (3-5 hours after administration).

Significant reductions of mean supine blood pressure (at trough) in patients with mild to moderate hypertension were also seen in a short-term, double-blind, dose-escalation, placebo-controlled study after 2 weeks of once-daily diltiazem hydrochloride extended-release capsules 180 mg/day (diastolic: -6.1 mmHg; systolic: -4.7 mmHg) and again, 2 weeks after escalation to 360 mg/day (diastolic: -9.3 mmHg; systolic: -7.2 mmHg). However, a further increase in dose to 540 mg/day for 2 weeks provided only a minimal further increase in the antihypertensive effect (diastolic: -10.2 mmHg; systolic: -6.7 mmHg).

Diltiazem hydrochloride extended-release capsules (once-a-day dosage), given at 120 mg, 240 mg, and 480 mg/day, in a randomized, multicenter, double-blind, placebo-controlled, parallel-group, dose-ranging study, in 189 patients with chronic angina, demonstrated a dose-related increase in exercise time by Exercise Tolerance Test (ETT) and a reduction in rates of anginal attacks (based on individual patient diaries). The response was dose-related, with the Bruce protocol, measured at trough exercise periods, for placebo, 120 mg, 240 mg, and 480 mg, was 20, 37, 49, and 56 seconds, respectively.

Pharmacokinetics And Metabolism:

Diltiazem is well absorbed from the gastrointestinal tract, and is subject to an extensive first-pass effect. When given as an immediate-release oral formulation, the absolute bioavailability (compared to intravenous administration) of diltiazem is approximately 40%. Diltiazem undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. 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, phenytoin, propranolol, salicylic acid, or warfarin. The plasma elimination half-life of diltiazem is approximately 3.0 to 4.5 hours. Decarboxy-diltiazem, the major metabolite of diltiazem, which is also present in the plasma at concentrations of 16% to 20% of the parent drug, is approximately 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of diltiazem appear to be in the range of 40-200 ng/mL. There is a departure from linearity when dose strengths are increased. The half-life is slightly increased with dose.

A study that compared patients with normal hepatic function to patients with cirrhosis found an increase in half-life and a 65% increase in bioavailability in the hepatically impaired patients. Patients with severely impaired renal function showed no difference in the pharmacokinetic profile of diltiazem compared to patients with normal renal function.

Diltiazem hydrochloride extended-release capsules (once-a-day dosage) contain a controlled-release tablet formulation designed to release diltiazem over a 24-hour period. Controlled absorption of diltiazem begins within 1 hour, with maximum plasma concentrations being achieved 4 to 6 hours after administration. The apparent steady-state half-life of diltiazem following once-daily administration of diltiazem hydrochloride extended-release capsules ranges from 5 to 10 hours. This prediction of half-life is attributed to con-

of plasma diiazem is also present in the plasma at concentrations of 10% to 20% of the parent drug, is approximately 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of diltiazem appear to be in the range of 40-200 ng/ml. There is a decrease in plasma diiazem 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. Patients with severely impaired renal function showed no difference in the pharmacokinetic profile of diltiazem compared to patients with normal renal function.

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The absolute bioavailability of diltiazem from a single dose of diltiazem hydrochloride extended-release capsules (compared to intravenous administration) is 41% (±14). This value was similar to the 40% systemic availability reported following administration of an immediate-release diltiazem hydrochloride formulation.

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 AUC of 2.3 fold. When the dose is increased from 240 mg to 360 mg, AUC increases 1.6 fold and when increased from 240 mg to 480 mg, AUC increases 2.4 fold.

In-vivo release of diltiazem occurs throughout the gastrointestinal tract, with controlled release still occurring for up to 24 hours after administration, as determined by radio-labeled methods. As the once-daily dose of diltiazem hydrochloride extended-release capsules was increased, departures from linearity were noted. These were disproportionate increases in area under the curve for doses from 120 mg to 480 mg.

The presence of food did not affect the ability of diltiazem hydrochloride extended-release capsules to maintain a controlled release of drug and did not impact its sustained release properties over 24 hours after administration. However, simultaneous administration of diltiazem hydrochloride extended-release capsules with a high-fat breakfast resulted in increases in AUC of 13% and 19%, and in C_{max} by 37% and 51% respectively.

INDICATIONS AND USAGE: Diltiazem Hydrochloride Extended-release Capsules (Once-a-Day Dosage) are indicated for the treatment of hypertension. Diltiazem hydrochloride may be used alone or in combination with other antihypertensive medications, such as diuretics.

Diltiazem hydrochloride extended-release capsules (once-a-day dosage) are indicated for the management of chronic stable angina.

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

WARNINGS: **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 (22 of 10,119 patients, or 0.2%). 41% of these 22 patients were receiving concomitant beta-adrenergic antagonist versus 17% of the total group. 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 60 mg dose of diltiazem.

Congestive Heart Failure: Although diltiazem has a negative inotropic effect in randomized 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 of 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 pre-existing impairment of ventricular function. Experience with the use of diltiazem in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

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

Acute Hepatic Injury: Mild elevations of serum transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been ob-

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 mmHg systolic); (4) patients who have demonstrated hypersensitivity to the drug; and (5) patients with acute myocardial infarction and pulmonary congestion as documented by X-ray on admission.

Warnings: **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 (22 of 10,119 patients, or 0.2%). 41% of these 22 patients were receiving concomitant beta-adrenergic receptor antagonists versus 17% of the total group. Concomitant use of diltiazem with beta-blockers or digitals may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 3 minutes) after a single 60 mg dose of diltiazem. **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 of 24% ± 5%) showed improvement in indices of ventricular function without significant decrease in contractile function (dP/dt). Worsening of congestive heart failure has been reported in patients with pre-existing impairment of ventricular function. Experience with the use of diltiazem in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

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

Acute Hepatic Injury: Mild elevations of serum 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 alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur only after therapy initiation (1 to 6 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to diltiazem is uncertain in some cases, but probable in some others (see PRECAUTIONS).

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

Dermatological events (see ADVERSE REACTIONS) may be transient and may disappear despite continued use of diltiazem. However, skin eruptions progressing to *Stevens-Johnson* and/or *ery-*

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Having symptoms have also been infrequently reported. Should a dermatologic reaction occur, the drug should be discontinued.

Although diltiazem hydrochloride extended-release capsules (once-a-day dosage) utilize a slowly erodible matrix, caution should still be used in patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been no reports of obstructive symptoms in patients with known strictures in association with the ingestion of diltiazem hydrochloride extended-release capsules (once-a-day dosage).

Instructions For Patients: Diltiazem hydrochloride extended-release capsules (once-a-day dosage) should be taken on an empty stomach. Patients should be cautioned that the diltiazem hydrochloride extended-release capsules (once-a-day dosage) should not be opened, chewed or crushed, and should be swallowed whole.

Drug Interactions: Due to the potential for additive effects, caution and careful titration are warranted in patients receiving diltiazem concomitantly with any agents known to affect cardiac contractility or/and 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. Co-administration 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 such as cyclosporine, may require adjustment when starting or stopping concomitantly administered diltiazem to maintain optimum therapeutic blood levels. Concomitant administration of diltiazem with carbamazepine has been reported to result in elevated plasma levels of carbamazepine, resulting in toxicity in some cases.

Beta-Blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of diltiazem and beta-blockers is usually well-tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities. Administration of diltiazem concomitantly with propranolol in four normal volunteers resulted in increased propranolol levels in all subjects and the bioavailability of propranolol was increased approximately 50%. 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 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digoxin: Administration of diltiazem with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing diltiazem therapy in such patients (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 channel blockers should be titrated carefully.

Contraception, Menstruation, Impairment Of Fertility: A 24-month study in rats and an 18-month study in mice showed no evidence of contraceptive effect. There was also no mutagenic response *in-vitro* or *in-vivo* in bacteria. No evidence of impaired fertility was observed in male or female rats at oral doses of up to 100 mg/kg/day.

Pregnancy: Fetal/Teratogenic Effects - Pregnancy Category C: Reproduction studies have been conducted in mice, rats and rabbits. Administration of doses ranging from 4 to 6 times (depending on species) the upper limit of the optimum dosage range in clinical trials (480 mg q.d. or 8 mg/kg q.d. for a 60 kg patient) has resulted in embryo and fetal lethality. These studies have revealed, in one species or another, a propensity to cause abnormalities of the skeleton, heart, retina and tongue. Also observed were reductions in early individual pup weights and pup survival, prolonged delivery and increased incidence of stillbirths.

There are no well-controlled studies in pregnant women; therefore, use diltiazem in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Diltiazem is excreted in human milk. One report suggests that

Use in children should be titrated carefully.

Cardiomyopathy, Mitral Regurgitation, Impairment of Fertility: A 24-month study in rats and an 18-month study in mice showed an absence of cardiomyopathy. There was also no mitogenic response *in-vitro* or *in-vivo* in mammalian cell assays or *in-vitro* in bacteria. No evidence of impaired fertility was observed in male or female rats at oral doses of up to 160 mg/kg/day.

Pregnancy: Reproductive Effects - Pregnancy Category C: Reproduction studies have been conducted in mice, rats and rabbits. Administration of doses ranging from 4 to 6 times (depending on species) the upper limit of the optimum dosage range in clinical trials (400 mg q.d. or 8 mg/kg q.d. for a 60 kg patient) has resulted in embryo and fetal lethality. These studies have revealed, in one species or another, a propensity to cause abnormalities of the skeleton, heart, ribs and tongue. Also observed were reductions in early individual pup weights and pup survival, prolonged delivery and increased incidence of stillbirths.

There are no well-controlled studies in pregnant women; therefore, use diltiazem in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of diltiazem 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 to diltiazem hydrochloride have been rare in studies with other formulations, as well as with diltiazem hydrochloride extended-release capsules (once-a-day dosage). It should be recognized, however, that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

Hypertension: The most common adverse events (frequency $\geq 1\%$) in placebo-controlled, clinical hypertension studies with diltiazem hydrochloride extended-release capsules (once-a-day dosage) using daily doses up to 540 mg are listed in the table below with placebo-treated patients included for comparison.

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

Adverse Events (COSTART Term)	Diltiazem HCl	
	Extended-release Capsules (Once-a-Day Dosage)* n=303 # pts (%)	Placebo n=87 # pts (%)
rhinitis	29 (9.6)	7 (8.0)
headache	27 (8.9)	12 (13.8)
pharyngitis	17 (5.6)	4 (4.6)
constipation	11 (3.6)	2 (2.3)
cough increase	9 (3.0)	2 (2.3)
flu syndrome	7 (2.3)	1 (1.1)
edema, peripheral	7 (2.3)	0 (0.0)
myalgia	7 (2.3)	0 (0.0)
diarrhea	6 (2.0)	0 (0.0)
vomiting	6 (2.0)	0 (0.0)
sinusitis	6 (2.0)	1 (1.1)
asthenia	5 (1.7)	0 (0.0)
pain, back	5 (1.7)	2 (2.3)
nausea	5 (1.7)	1 (1.1)
dyspepsia	4 (1.3)	0 (0.0)
vasodilatation	4 (1.3)	0 (0.0)
injury, accidental	4 (1.3)	0 (0.0)
pain, abdominal	3 (1.0)	0 (0.0)
arthrosis	3 (1.0)	0 (0.0)
insomnia	3 (1.0)	0 (0.0)
dyspnea	3 (1.0)	0 (0.0)
cash	3 (1.0)	1 (1.1)
hematuria	3 (1.0)	0 (0.0)

* Adverse events occurring in 1% or more of patients receiving diltiazem hydrochloride extended-release capsules (once-a-day dosage).

Angina: The most common adverse events (frequency $\geq 1\%$) in a placebo-controlled, short-term (2 week) clinical angina study with diltiazem hydrochloride extended-release capsules (once-a-day dosage) are listed in the table below with placebo-treated patients included for comparison. In this trial, following a placebo phase, patients were randomly assigned to once-daily doses of either 120, 240 or 480 mg of diltiazem hydrochloride extended-release capsules (once-a-day dosage).

MOST COMMON ADVERSE EVENTS IN A DOUBLE-BLIND, PLACEBO-CONTROLLED SHORT-TERM ANGINA TRIAL

Adverse Events (COSTART Term)	Diltiazem HCl	
	Extended-release Capsules (Once-a-Day Dosage)* n=139 # pts (%)	Placebo n=50 # pts (%)
asthenia	5 (3.6)	2 (4.0)
headache	4 (2.9)	3 (6.0)
pain, back	4 (2.9)	1 (2.0)
rhinitis	4 (2.9)	1 (2.0)
constipation	3 (2.2)	1 (2.0)
nausea	3 (2.2)	0 (0.0)
edema, peripheral	3 (2.2)	1 (2.0)
dizziness	3 (2.2)	0 (0.0)
cough, increased	3 (2.2)	0 (0.0)
bradycardia	2 (1.4)	0 (0.0)
fibrillation, atrial	2 (1.4)	0 (0.0)
arthralgia	2 (1.4)	0 (0.0)
dream, abnormal	2 (1.4)	0 (0.0)
dyspnea	2 (1.4)	0 (0.0)
pharyngitis	2 (1.4)	1 (2.0)

* Adverse events occurring in 1% or more of patients receiving diltiazem hydrochloride extended-release capsules (once-a-day dosage).

Infrequent Adverse Events: The following additional events (COSTART terms), listed by body system, were reported

asthenia	5 (3.0)	2 (1.0)
headache	4 (2.9)	3 (5.0)
pain, back	4 (2.9)	1 (2.0)
chills	4 (2.9)	1 (2.0)
constipation	3 (2.2)	1 (2.0)
nausea	3 (2.2)	0 (0.0)
edema, peripheral	3 (2.2)	1 (2.0)
dizziness	3 (2.2)	0 (0.0)
cough, increased	3 (2.2)	0 (0.0)
bradycardia	2 (1.4)	0 (0.0)
fibrositis, atrial	2 (1.4)	0 (0.0)
arthralgia	2 (1.4)	0 (0.0)
depression, abnormal	2 (1.4)	0 (0.0)
dyspnea	2 (1.4)	0 (0.0)
pharyngitis	2 (1.4)	1 (2.0)

* Adverse events occurring in 1% or more of patients receiving diltiazem hydrochloride extended-release capsules (once-a-day dosage).

Frequent Adverse Events: The following additional events (COSTART Terms), listed by body system, were reported infrequently (less than 1%) in all subjects, hypertensive (n=425) or anginal (n=318) patients who received diltiazem hydrochloride extended-release capsules (once-a-day dosage), or with other formulations of diltiazem.

Hypertensive Cardiovascular: First-degree AV block, arrhythmias, postural hypotension, tachycardia, palpitations, paresthesia, ECG abnormality, ST elevation.

Nervous System: Vertigo, hypotonia, paresthesia, dizziness, somnolence.

Digestive System: Dry mouth, anorexia, tooth disorder, esophageal reflux.

Skin And Appendages: Sweating, urticaria, skin hyperplasia (nevus).

Respiratory System: Epistaxis, bronchitis, respiratory disorder.

Urogenital System: Cystitis, kidney calculus, impotence, dysmenorrhea, vaginitis, prostatic disease.

Metabolic And Nutritional Disorders: Gout, edema.

Musculoskeletal System: Arthralgia, bursitis, bone pain.

Heinic And Lymphatic System: Lymphadenopathy.

Body As A Whole: Pain, unevaluable reaction, neck pain, neck rigidity, fever, chest pain, malaise.

Special Senses: Amblyopia (blurred vision), ear pain.

Angina: Cardiovascular: Palpitations, AV block, sinus bradycardia, hypotension, angina pectoris, hypertension, myocardial infarct, myocardial ischemia, syncope, vasodilatation, ventricular extrasystole.

Nervous System: Abnormal thinking, neuropathy, paresthesia.

Digestive System: Diarrhea, dyspepsia, vomiting, colitis, flatulence, GI hemorrhage, stomach ulcers.

Skin And Appendages: Contact dermatitis, pruritus, sweating.

Respiratory System: Respiratory distress.

Urogenital System: Kidney failure, pyelonephritis, urinary tract infection.

Metabolic And Nutritional Disorders: Weight increase.

Musculoskeletal System: Myalgia.

Body As A Whole: Chest pain, accidental injury, infection.

Special Senses: Eye hemorrhage, ophthalmitis, otitis media, taste perversion, tinnitus.

There have been post-marketing reports of Stevens-Johnson Syndrome and toxic epidermal necrolysis associated with the use of diltiazem.

OVERDOSAGE OR EXAGGERATED RESPONSE: Overdosage experience with oral diltiazem has been limited. The administration of ipecac to induce vomiting and activated charcoal to reduce drug absorption have been advocated as initial means of intervention. In addition to gastric lavage, the following measures should also be considered:

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

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

Cardiac Failure: Administer inotropic agents (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 as well as the judgment and experience of the treating physician.

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

Charcoal hemoperfusion has been used successfully as an adjunct therapy to hasten drug elimination. Overdoses with as much as 18.0 gm of oral diltiazem have been successfully treated using sequential sequential capsules.

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

Studies have shown a slight increase in the rate of absorption of diltiazem hydrochloride extended-release capsules (once-a-day dosage), when ingested with a high-fat breakfast; therefore, administration in the morning on an empty stomach is recommended.

Patients should be cautioned that the diltiazem hydrochloride extended-release capsules should not be opened, chewed or crushed and should be swallowed whole.

Dosage: Hypertensive: Dosages must be adjusted to each patient's needs, starting with 180 mg or 240 mg once-daily. Based on the antihypertensive effect, the dose may be adjusted as needed. Individual patients, particularly > 60 years

used successfully as an adjunct therapy in hypotensive patients. Overdoses with as much as 28.8 gm of oral diltiazem have been successfully treated using appropriate supportive care.

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

Studies have shown a slight increase in the rate of absorption of diltiazem hydrochloride extended-release capsules (once-a-day dosage), when ingested with a high-fat breakfast; therefore, administration in the morning on an empty stomach is recommended.

Patients should be advised that the diltiazem hydrochloride extended-release capsules should not be opened, chewed or crushed and should be swallowed whole.

Dosage: Appropriate dosages must be adjusted to each patient's needs, starting with 180 mg or 240 mg once-daily. Based on the anti-hypertensive effect, the dose may be adjusted as needed. Individual patients, particularly ≥ 60 years of age, may respond to a lower dose of 120 mg. The usual dosage range studied in clinical trials was 180 mg to 480 mg once-daily.

Current clinical experience with the 540 mg dose is limited; the dose may be increased to 540 mg with little or no increased risk of adverse reactions. Doses should not exceed 540 mg once-daily.

While a dose of diltiazem hydrochloride extended-release capsules given once-daily may produce an antihypertensive effect similar to the same total daily dose given in divided doses, individual dose adjustment may be needed.

Angina: Dosages for the treatment of angina should be adjusted to each patient's needs, starting with a dose of 120 mg once-daily, which may be titrated to doses of up to 600 mg once-daily. When necessary, titration may be carried out over a 7 to 14 day period.

Concomitant Use With Other Cardiovascular Agents: Sublingual Nitroglycerin: Sublingual Nitroglycerin may be taken as required to abort acute anginal attacks during diltiazem therapy.

Preventive Antiplatelet Therapy: Diltiazem hydrochloride extended-release capsules (once-a-day dosage) may be safely administered with short- and long-acting nitrates.

Beta-Blockers: (See WARNINGS and PRECAUTIONS.)

Antihypertensives: Diltiazem has an additive antihypertensive effect when used with other antihypertensive agents. Therefore, the dosage of diltiazem hydrochloride 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) are available in 120 mg, 180 mg and 240 mg.

The 120 mg capsule is a pink opaque cap/flesh opaque body, hard-shell gelatin capsule filled with two white to off-white, round, flat-faced, beveled edge tablets with no markings. The capsule is radially printed with MYLAN over 5228 in black ink on the cap. They are available as follows:

NDC 0378-5220-01
bottles of 100 capsules
NDC 0378-5220-05
bottles of 500 capsules

The 180 mg capsule is a lavender opaque cap/flesh opaque body, hard-shell gelatin capsule filled with three white to off-white, round, flat-faced, beveled edge tablets with no markings. The capsule is radially printed with MYLAN over 5280 in black ink on the cap. They are available as follows:

NDC 0378-5280-01
bottles of 100 capsules
NDC 0378-5280-05
bottles of 500 capsules

The 240 mg capsule is a light blue opaque cap/flesh opaque body, hard-shell gelatin capsule filled with four white to off-white, round, flat-faced, beveled edge tablets with no markings. The capsule is radially printed with MYLAN over 5340 in black ink on both the cap and body. They are available as follows:

NDC 0378-5340-01
bottles of 100 capsules
NDC 0378-5340-05
bottles of 500 capsules

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

Dispense in a light, light-resistant container as defined in the USP using a child resistant closure.

CANTON: Federal law prohibits dispensing without prescription.



Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75124

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. #2 (revised 2/27/98)
2. ANDA # 75-124
3. NAME AND ADDRESS OF APPLICANT
Mylan Pharmaceuticals Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Road
Morgantown, WV 26505-2730

Phone: 304-599-2595
Fax: 304-285-6407
4. LEGAL BASIS FOR SUBMISSION
Firm certifies that in their opinion and to the best of its knowledge, and there is no marketing exclusivity in effect for the listed drug. The two patents will be expired 12/9/2006 and 6/6/2012.

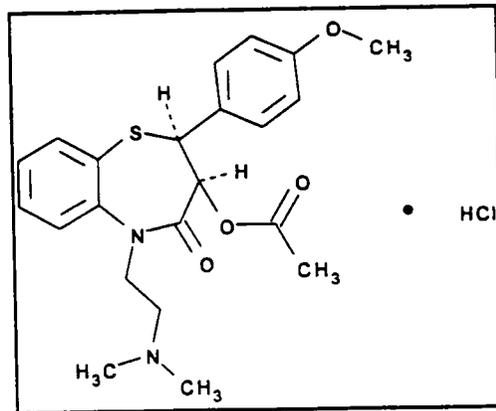
Innovator: Rhone-Poulenc Rorer Pharmaceuticals - Dilacor® XR (Diltiazem HCl) Extended-release Capsules
5. SUPPLEMENT(s)
N/A
6. PROPRIETARY NAME
N/A
7. NONPROPRIETARY NAME
Diltiazem Hydrochloride
8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A
9. AMENDMENTS AND OTHER DATES:
Original ANDA 4/29/97 (for 240 mg capsules)
Refuse to File letter 7/7/97
Acknowledgment letter 7/30/97
Amend 10/6/97 for the addition of 120 mg and 180 mg capsules
Amend 11/26/97 to N/A letter (FACSIMILE AMENDMENT) 11/19/97
Telephone Amend 2/25/98 (Memo attached)
10. PHARMACOLOGICAL CATEGORY
Anti-anginal
11. Rx or OTC
Rx
12. RELATED IND/NDA/DMF(s)
13. DOSAGE FORM
Diltiazem Hydrochloride Extended-release Capsules

14. POTENCY 120 mg, 180 mg and 240 mg

15. CHEMICAL NAME AND STRUCTURE

Diltiazem Hydrochloride USP

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



(+)-5-[2-(Dimethylamino)eth

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

16. RECORDS AND REPORTS

N/A

17. COMMENTS

A. The original submission dated 4/29/97 for ANDA #75-124 contains only 240 mg capsules. In Amendment 10/6/97 Firm resubmits all information including the addition of 120 mg and 180 mg capsules.

B. In Amendment 11/26/97 Firm answers our concerns as follows:

Chemistry

2

C. **Status:**

Labeling: Acceptable

Bio: Acceptable 2/5/98

EER: Acceptable 8/18/97

Sample validation: Compendial; validation not needed

18. CONCLUSIONS AND RECOMMENDATIONS

Approval recommended.

19. REVIEWER:

DATE COMPLETED:

Maria C. Shih

12/10/97 (revised 2/27/98)