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January 13, 2000

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

CITIZEN PETITION

The undersigned submits this petition under Section 505 (j) (2) (c) of the Federal Food Drug and Cosmetic Act, to request that the Commissioner of Food and Drugs permit the filing of an Abbreviated New Drug Application for a generic Verapamil Hydrochloride Extended-Release Tablet (Once-a-day Dosage) based on bioequivalence studies using Covera-HS® Extended-Release Tablets, 240 mg, which is a listed drug in the FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations, 19th Edition*, (1999) but is not currently designated as a reference product. The product currently designated as the reference listed drug is Isoptin® SR.

A. Action Requested

By this petition, the undersigned requests that the Commissioner of Food and Drugs permit the filing of an Abbreviated New Drug Application for Verapamil Hydrochloride Extended-Release Tablets (Once-a-day dosage), 180 mg and 240 mg using Covera-HS® as the reference listed drug.

B. Statement of Grounds

1) Covera-HS® had sales of \$95 million in 1999 and the market is still growing. While Covera-HS® has a relatively small share of the verapamil hydrochloride extended-release tablet market, this share represents significant sales of the drug product and should not be "shielded from direct generic competition" as indicated by Dr. Woodcock in her letter responding to our Citizen's Petition regarding Tiazac® (Attachment 1).

2) Covera-HS® utilizes a different drug delivery technology and has a different release rate and is, therefore, not bioequivalent to Isoptin® SR, which is the reference, listed drug. Andrx Pharmaceuticals, Inc. has developed an extended-release tablet that contains the same active ingredient, the same amount of active ingredient and has the same route of administration as Searle's Covera-HS® Tablets. Attached is a copy of the listing from the *Approved Drug Products with Therapeutic Equivalence Evaluations, 19th Edition*, for the Searle product (Attachment 2). The intended patient population for the Andrx product is the same as that for Covera-HS®. Therefore, no additional clinical studies are necessary to assure the efficacy and safety of the verapamil hydrochloride extended-release tablets.

3) Andrx Pharmaceuticals, Inc. will conduct *in-vivo* bioequivalence studies and *in-vitro* dissolution testing to support our application.

OOP-0219

CP 1

- 4) Andrx's verapamil hydrochloride extended-release tablet will be labeled identically to Covera-HS®. A copy of Searle's labeling for Covera-HS® and a sample of Andrx's proposed labeling are attached (Attachment 3).

C. Environmental Impact

Andrx Pharmaceuticals, Inc. claims a categorical exclusion, as defined in 21 CFR § 25.24 (c) (1), from the filing of an environmental assessment as listed in §25.31 for its verapamil hydrochloride extended-release tablets.

The undersigned certifies that our formulation will not be administered at higher dosage levels, for longer duration or for different indications than were previously in effect for the approved brand formulation Covera-HS® Tablets by Searle.

D. Economic Impact

This information will be submitted if requested by the agency.

E. Certification

The undersigned certifies, that to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies and includes information that may be unfavorable to the petition.



Diane Servello
Director, Regulatory Affairs

ATTACHMENT 1



JUL 31 1998

David A. Gardner
Andrx Pharmaceuticals, Inc.
4001 SW 47th Avenue, Suite 201
Ft. Lauderdale, FL 33314

Re: Docket No. 98P-0429/CP1

Dear Mr. Gardner:

This letter responds to your citizen petition submitted on behalf of Andrx Pharmaceuticals, Inc., dated June 10, 1998. Your petition requests that the Food and Drug Administration (FDA) permit the submission of an abbreviated new drug application (ANDA) for diltiazem hydrochloride extended-release capsules that names Tiazac as the reference listed drug, and that the Agency not require that the reference listed drug be either Cardizem CD or Dilacor XR.¹ For the reasons set forth below, your petition has been granted.

The marketing of a generic version of a previously approved drug product is permitted when the generic drug is the subject of an ANDA approved under section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)). To gain approval, the ANDA must contain information showing, among other things, that with respect to a *listed drug* (i.e., a previously approved drug product) the generic drug has the same active ingredient in the same strength, that its labeling is essentially identical, and that it is bioequivalent. The specific drug product to which an ANDA refers is the *reference listed drug*.

FDA's policy on the designation of reference listed drugs is described in the preamble to the final rule establishing the requirements for ANDAs, published in the *Federal Register* of April 28, 1992 (57 FR 17950, 17958):

. . . FDA will designate all reference listed drugs. Generally, the reference listed drug will be the NDA drug product for a single source drug product. For multiple source NDA drug products or multiple source drug products without an NDA, the reference listed drug generally will be the market leader as determined by FDA on the basis of commercial data. FDA recognizes that, for multiple source products, a product not designated as the listed drug and not

¹ Tiazac, Cardizem CD, and Dilacor XR are sponsored by, respectively, Biovail Laboratories Inc., Hoechst Marion Roussel, Inc., and Watson Laboratories, Inc.

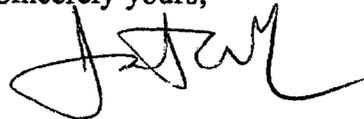
Docket No. 98P-0429/CP1

shown bioequivalent to the listed drug may be shielded from direct generic competition. If an applicant believes that there are sound reasons for designating another drug as a reference listed drug, it should consult FDA.

FDA has examined the issues presented in your petition and has determined that although Tiazac has a comparatively small share of the diltiazem hydrochloride extended-release capsule market, this share nevertheless represents significant sales of the drug product, as measured in both the dollar value of those sales and the number of filled prescriptions. The Agency has further determined that it would not be in the public interest to have Tiazac shielded from direct generic competition. Accordingly, FDA will designate Tiazac, in addition to Cardizem CD and Dilacor XR, as a reference listed drug in the *Approved Drug Products with Therapeutic Equivalence Evaluations* (the *Orange Book*).

FDA is aware that the presence of three reference listed drugs in the *Orange Book* creates the potential for some confusion and inappropriate generic substitution. Therefore, when generic versions of Tiazac, Cardizem CD, or Dilacor XR are approved, FDA will take appropriate steps to make the *Orange Book* clear that Tiazac, Cardizem CD, and Dilacor XR are not therapeutically equivalent to each other, and that generic drug products that are therapeutically equivalent to one of the three reference listed drugs for diltiazem hydrochloride are not therapeutically equivalent to either of the other two.

Sincerely yours,



Janet Woodcock, M.D.

Director

Center for Drug Evaluation and Research

ATTACHMENT 2

PRESCRIPTION DRUG PRODUCT LIST

3-333

VENLAFAXINE HYDROCHLORIDE

CAPSULE, EXTENDED RELEASE; ORAL

EFFEXOR XR

+ WYETH AYERST EQ 37.5MG BASE
 + EQ 75MG BASE
 + EQ 150MG BASE

TABLET; ORAL

EFFEXOR

+ WYETH AYERST EQ 25MG BASE
 EQ 37.5MG BASE
 EQ 50MG BASE
 EQ 75MG BASE
 + EQ 100MG BASE

VERAPAMIL HYDROCHLORIDE

INJECTABLE; INJECTION

VERAPAMIL HCL

ABBOTT

N20699 001 AP 2.5MG/ML
 OCT 20, 1997
 N20699 002 AP 2.5MG/ML
 OCT 20, 1997
 N20699 004 AP 2.5MG/ML
 OCT 20, 1997
AP 2.5MG/ML
AP 2.5MG/ML
 N20151 002 AP 2.5MG/ML
 DEC 28, 1993
 N20151 006 AP 2.5MG/ML
 DEC 28, 1993
 N20151 003 AP BEDFORD 2.5MG/ML
 DEC 28, 1993
 N20151 004 AP INTL MEDICATION 2.5MG/ML
 DEC 28, 1993
 N20151 005 AP LUITPOLD 2.5MG/ML
 DEC 28, 1993
AP 2.5MG/ML
AP SMITH AND NEPHEW 2.5MG/ML

N70577 001
 FEB 02, 1987
 N70737 001
 MAY 06, 1987
 N70738 001
 MAY 06, 1987
 N70739 001
 MAY 06, 1987
 N70740 001
 MAY 06, 1987
 N75136 001
 OCT 20, 1998
 N72888 001
 JUL 28, 1995
 N70451 001
 DEC 16, 1985
 N70225 001
 NOV 12, 1985
 N70617 001
 NOV 12, 1985
 N70696 001
 JUL 31, 1987

VERAPAMIL HYDROCHLORIDE

CAPSULE, EXTENDED RELEASE; ORAL

VERELAN

+ ELAN 120MG
 + 180MG
 + 240MG
 + 360MG

VERELAN PM

+ ELAN PHARM 100MG
 + 200MG
 + 300MG

INJECTABLE; INJECTION

ISOPTIN

AP + KNOLL PHARM 2.5MG/ML

N19614 001 AB
 MAY 29, 1990
 N19614 003 AB
 JAN 09, 1992
 N19614 002 AB
 MAY 29, 1990
 N19614 004 AB
 MAY 10, 1996
 N20943 001 AB
 NOV 25, 1998
 N20943 002 AB
 NOV 25, 1998
 N20943 003 AB
 NOV 25, 1998

TABLET; ORAL

CALAN

SEARLE

40MG
80MG
120MG

ISOPTIN

KNOLL PHARM

40MG

80MG

120MG

VERAPAMIL HCL

DANBURY PHARMA

80MG

120MG

GENEVA PHARMS

40MG

N18817 003
 FEB 23, 1988
 N18817 001
 SEP 10, 1984
 N18817 002
 SEP 10, 1984
 N18593 003
 NOV 23, 1987
 N18593 001
 MAR 08, 1982
 N18593 002
 MAR 08, 1982
 N70855 001
 SEP 24, 1986
 N70856 001
 SEP 24, 1986
 N73168 001
 JUL 31, 1992

PRESCRIPTION DRUG PRODUCT LIST

3-334

VERAPAMIL HYDROCHLORIDE

VERAPAMIL HYDROCHLORIDE

<u>TABLET; ORAL</u>		
<u>VERAPAMIL HCL</u>		
<u>AB</u>	GENEVA PHARMS	<u>80MG</u>
<u>AB</u>		<u>120MG</u>
<u>AB</u>	LEDERLE	<u>80MG</u>
<u>AB</u>		<u>120MG</u>
<u>AB</u>	MUTUAL PHARM	<u>80MG</u>
<u>AB</u>		<u>120MG</u>
<u>AB</u>	MYLAN	<u>80MG</u>
<u>AB</u>		<u>120MG</u>
<u>AB</u>	PUREPAC PHARM	<u>80MG</u>
<u>AB</u>		<u>120MG</u>
<u>AB</u>	SIDMAK LABS NJ	<u>40MG</u>
<u>AB</u>		<u>80MG</u>
<u>AB</u>		<u>120MG</u>
<u>AB</u>	WATSON LABS	<u>40MG</u>
<u>AB</u>		<u>40MG</u>
<u>AB</u>		<u>80MG</u>
<u>AB</u>		<u>80MG</u>
<u>AB</u>		<u>120MG</u>
<u>AB</u>		<u>120MG</u>

<u>TABLET, EXTENDED RELEASE; ORAL</u>		
<u>ISOPTIN SR</u>		
<u>AB</u>	+ KNOLL PHARM	<u>120MG</u>
<u>AB</u>		<u>180MG</u>
<u>AB</u>		<u>240MG</u>
<u>VERAPAMIL HCL</u>		
<u>AB</u>	MYLAN	<u>120MG</u>
<u>AB</u>		<u>180MG</u>
<u>AB</u>		<u>240MG</u>
<u>AB</u>	SIDMAK LABS NJ	<u>240MG</u>
<u>AB</u>	ZENITH GOLDLINE	<u>120MG</u>
<u>AB</u>		<u>180MG</u>
<u>AB</u>		<u>240MG</u>

N19152 003
MAR 06, 1991
N19152 002
DEC 15, 1989
N19152 001
DEC 16, 1986

N74587 002
FEB 21, 1997
N74587 003
SEP 09, 1997
N74587 001
MAR 23, 1996
N72922 001
MAR 01, 1996
N73568 002
OCT 10, 1997
N74330 001
JAN 31, 1994
N73568 001
JUL 31, 1992

VERAPAMIL HYDROCHLORIDE; *MULTIPLE*
SEE TRANDOLAPRIL; VERAPAMIL HYDROCHLORIDE

VIDARABINE

OINTMENT; OPHTHALMIC
VIRA-A
+ PARKEDALE 3%

N50486 001

VINBLASTINE SULFATE

INJECTABLE; INJECTION
VELBAN
AP + LILLY 10MG/VIAL
VINBLASTINE SULFATE
+ AM PHARM PARTNERS 1MG/ML
AP BEDFORD 10MG/VIAL

N12665 001
N89515 001
APR 29, 1987
N89395 001
APR 09, 1987

TABLET, EXTENDED RELEASE; ORAL

<u>COVERA-HS</u>		
<u>BC</u>	SEARLE	<u>180MG</u>
<u>BC</u>		<u>240MG</u>

N20552 001
FEB 26, 1996
N20552 002
FEB 26, 1996

ATTACHMENT 3

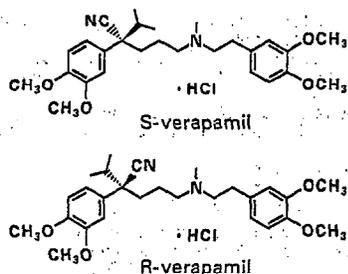


SEARLE
Covera-HS®
 (verapamil hydrochloride)
Extended-Release Tablets
Controlled-Onset

Revised: May 1, 1997

DESCRIPTION

Covera-HS (verapamil hydrochloride) is a calcium ion influx inhibitor (slow-channel blocker or calcium ion antagonist). Covera-HS is available for oral administration as pale yellow, round, film-coated tablets containing 240 mg of verapamil hydrochloride and as lavender, round, film-coated tablets containing 180 mg of verapamil hydrochloride. Verapamil is administered as a racemic mixture of the R and S enantiomers. The structural formulae of the verapamil HCl enantiomers are:



$C_{27}H_{38}N_2O_4 \cdot HCl$ M.W. = 491.07

Benzeneacetonitrile, (\pm)- α -[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]-3,4-dimethoxy- α -(1-methylethyl) hydrochloride

Verapamil HCl is an almost white, crystalline powder, practically free of odor, with a bitter taste. It is soluble in water, chloroform, and methanol. Verapamil HCl is not chemically related to other cardioactive drugs.

Inactive ingredients are black ferric oxide, BHT, cellulose acetate, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol, polyethylene oxide, polysorbate 80, povidone, sodium chloride, titanium dioxide, and coloring agents: 240-mg—FD&C Blue No. 2 Lake and D&C Yellow No. 10 Lake; 180-mg—FD&C Blue No. 2 Lake and D&C Red No. 30 Lake.

System components and performance: The Covera-HS formulation has been designed to initiate the release of verapamil 4-5 hours after ingestion. This delay is introduced by a layer between the active drug core and outer semipermeable membrane. As water from the gastrointestinal tract enters the tablet, this delay coating is solubilized and released. As tablet hydration continues, the osmotic layer expands and pushes against the drug layer, releasing drug through precision laser-drilled orifices in the outer membrane at a constant rate. This controlled rate of drug delivery in the gastrointestinal lumen is independent of posture, pH, gastrointestinal motility, and fed or fasting conditions.

The biologically inert components of the delivery system remain intact during GI transit and are eliminated in the feces as an insoluble shell.

CLINICAL PHARMACOLOGY

Covera-HS has a unique delivery system, designed for bedtime dosing, incorporating a 4 to 5-hour delay in drug delivery. The unique controlled-onset, extended-release (COER) delivery system, which is designed for bedtime dosing, results in a maximum plasma concentration (C_{max}) of verapamil in the morning hours.

Verapamil is a calcium ion influx inhibitor (L-type calcium channel blocker or calcium channel antagonist). Verapamil exerts its pharmacologic effects by selectively inhibiting the transmembrane influx of ionic calcium into arterial smooth muscle as well as in conductile and contractile myocardial cells without altering serum calcium concentrations.

Mechanism of action

In vitro: Verapamil binding is voltage-dependent with affinity increasing as the vascular smooth muscle membrane potential is reduced. In addition, verapamil binding is frequency dependent and apparent affinity increases with increased frequency of depolarizing stimulus.

The L-type calcium channel is an oligomeric structure consisting of five putative subunits designated alpha-1, alpha-2, beta, tau, and epsilon. Biochemical evidence points to separate binding sites for 1,4-dihydropyridines, phenylalkylamines, and the

benzothiazepines (all located on the alpha-1 subunit). Although they share a similar mechanism of action, calcium channel blockers represent three heterogeneous categories of drugs with differing vascular-cardiac selectivity ratios.

Essential hypertension: Verapamil produces its antihypertensive effect by a combination of vascular and cardiac effects. It acts as a vasodilator with selectivity for the arterial portion of the peripheral vasculature. As a result the systemic vascular resistance is reduced and usually without orthostatic hypotension or reflex tachycardia. Bradycardia (rate less than 50 beats/min) is uncommon (<1% with Covera-HS as assessed by ECG). During isometric or dynamic exercise Covera-HS does not alter systolic cardiac function in patients with normal ventricular function.

Covera-HS does not alter total serum calcium levels. However, one report has suggested that calcium levels above the normal range may alter the therapeutic effect of verapamil.

Covera-HS regularly reduces the total systemic resistance (afterload) against which the heart works both at rest and at a given level of exercise by dilating peripheral arterioles.

Effects in hypertension: Covera-HS was evaluated in two placebo-controlled, parallel design, double-blind studies of 382 patients with mild to moderate hypertension.

In a clinical trial, 287 patients were randomized to placebo, 120 mg, 180 mg, 360 mg, or 540 mg and treated for 8 weeks (the two higher doses were titrated from low doses and maintained for 6 and 4 weeks, respectively). Covera-HS or placebo was given once daily at 10 pm and blood pressure changes were measured with 36-hour ambulatory blood pressure monitoring (ABPM). The results of these studies demonstrate that Covera-HS, at 180-540 mg, is a consistently and significantly more effective antihypertensive agent than placebo in reducing ambulatory blood pressures. Over this dose range, the placebo-subtracted net decreases in diastolic BP at trough (averaged over 6-10 pm) were dose-related, ranged from 4.5 to 11.2 mm Hg after 4-8 weeks of therapy, and correlated well with sitting cuff blood pressures.

These studies demonstrate that clinically and statistically significant blood pressure reductions are achieved with Covera-HS throughout the 24-hour dosing period.

There were no significant treatment differences between patient subgroups of different age (older or younger than 65 years), sex, race (Caucasian and non-Caucasian) and severity of hypertension at baseline (cuff BP below and above 105 mm Hg).

Angina: Verapamil dilates the main coronary arteries and coronary arterioles, both in normal and ischemic regions, and is a potent inhibitor of coronary artery spasm, whether spontaneous or ergonovine-induced. This property increases myocardial oxygen delivery in patients with coronary artery spasm and is responsible for the effectiveness of verapamil in vasospastic (Prinzmetal's or variant) as well as unstable angina at rest. Whether this effect plays any role in classical effort angina is not clear, but studies of exercise tolerance have not shown an increase in the maximum exercise rate-pressure product, a widely accepted measure of oxygen utilization. This suggests that, in general, relief of spasm or dilation of coronary arteries is not an important factor in classical angina.

Verapamil regularly reduces the total systemic resistance (afterload) against which the heart works both at rest and at a given level of exercise by dilating peripheral arterioles.

Effect in chronic stable angina: Covera-HS was evaluated in two placebo-controlled, parallel design, double-blind studies of 453 patients with chronic stable angina.

In the first clinical trial 277 patients were randomized to placebo, 180 mg, 360 mg, or 540 mg and treated for 4 weeks (the two higher doses were titrated from low doses and maintained for 3 and 2 weeks, respectively). A single dose of 240 mg was compared to placebo in a separate study of 176 patients. In these studies Covera-HS was significantly more effective than placebo in improvement of exercise tolerance. Placebo-adjusted net increases in median exercise times at the end of the dosing interval were 0.1 to 1.0 minute for symptom limited duration, 0.3 to 1.4 minutes for time to angina, and 0.1 to 1.1 minutes for time to ST change. Increases in exercise tolerance were in general greater at higher doses, but dose-response relationship was not well defined due to shorter treatment duration for high doses.

In addition, in the first study, 24 to 34% of patients treated with Covera-HS did not experience exercise-limiting angina on exercise treadmill testing (ETT) versus 12% of patients on placebo.

Electrophysiologic effects: Electrical activity through the AV node depends, to a significant degree, upon the transmembrane influx of extracellular calcium through the L-type (slow) channel. By decreasing the influx of calcium, verapamil prolongs the effective refractory period within the AV node and slows AV conduction in a rate-related manner.

Normal sinus rhythm is usually not affected, but in patients with sick sinus syndrome, verapamil may interfere with sinus node impulse generation and may induce sinus arrest or sinoatrial block. Atrioventricular block can occur in patients without preexisting conduction defects (see **Warnings**).

Covera-HS does not alter the normal atrial action potential or intraventricular conduction time, but depresses amplitude, velocity of depolarization, and conduction in depressed atrial fibers. Verapamil may shorten the antegrade effective refractory period of the accessory bypass tract. Acceleration of ventricular rate and/or ventricular fibrillation has been reported in patients with atrial flutter or atrial fibrillation and a coexisting accessory AV pathway following administration of verapamil (see **Warnings**).

Verapamil has a local anesthetic action that is 1.6 times that of procaine on an equimolar basis. It is not known whether this action is important at the doses used in man.

Pharmacokinetics and metabolism: Verapamil is administered as a racemic mixture of the R and S enantiomers. The systemic concentrations of R and S enantiomers, as well as overall bioavailability, are dependent upon the route of administration and the rate and extent of release from the dosage forms. Upon oral administration, there is rapid stereoselective biotransformation during the first pass of verapamil through the portal circulation. In a study in 5 subjects with oral immediate-release verapamil, the systemic bioavailability was from 33% to 65% for the R enantiomer and from 13% to 34% for the S enantiomer. The R and S enantiomers have differing levels of pharmacologic activity. In studies in animals and humans, the S enantiomer has 8 to 20 times the activity of the R enantiomer in slowing AV conduction. In animal studies, the S enantiomer has 15 and 50 times the activity of the R enantiomer in reducing myocardial contractility in isolated blood-perfused dog papillary muscle and isolated rabbit papillary muscle, respectively, and twice the effect in reducing peripheral resistance. In isolated septal strip preparations from 5 patients, the S enantiomer was 8 times more potent than the R in reducing myocardial contractility. Dose escalation study data indicate that verapamil concentrations increase disproportionately to dose as measured by relative peak plasma concentrations (C_{max}) or areas under the plasma concentration vs time curves (AUC).

Pharmacokinetic Characteristics of Verapamil Enantiomers After Administration of Escalating Doses

	Isomer	Total Dose of Racemic Verapamil (mg)			
		120	180	360	540
Dose Ratio	—	1	1.5	3	4.5
Relative C_{max}	R	1	1.55	4.47	7.06
	S	1	1.62	5.17	9.21
Relative AUC	R	1	1.59	6.14	11.1
	S	1	1.89	8.17	15.9

Pharmacokinetic Characteristics of Verapamil Enantiomers After Administration of a Single 180 mg Dose and at Steady State

	Isomer	First Dose	Steady State
		(Verapamil-naïve subject)	(Current verapamil exposure)
C_{max} (ng/ml)	R	59.4	90.5
	S	11.7	21.2
AUC (0-24h) (ng·hr/ml)	R	644	1,223
	S	111	266

Racemic verapamil is released from Covera-HS at a constant rate following solubilization and release of the delay coat through the tablet orifices. This delay coat produces a lag period in drug release for approximately 4-5 hours. The drug release phase is prolonged with the peak plasma concentration (C_{max}) occurring approximately 11 hours after administration. Trough concentrations occur approximately 4 hours after bedtime dosing while the patient is sleeping. Steady-state pharmacokinetics were determined in healthy volunteers. Steady-state concentration is reached by the third or fourth day of dosing.

Steady-State Pharmacokinetics of Verapamil Enantiomers in Healthy Humans

	Isomer	Verapamil Dose (mg)	
		180	240
Mean C_{max} (ng/ml)	R	90.5	120
	S	21.2	28.7
AUC (0-24h) (ng·hr/ml)	R	1,223	1,470
	S	266	322

In general, bioavailability of Covera-HS is higher and half life longer in older (> 65 yrs) subjects. Lean body weight also affects its pharmacokinetics inversely, but no gender difference was observed in the clinical trials of Covera-HS. However, there are conflicting data in literature suggesting that verapamil clearance decreased with age in women to a greater degree than in men.

Consumption of a high fat meal just prior to dosing at night had no effect on the pharmacokinetics of Covera-HS. The pharmacokinetics were also not affected by whether the volunteers were supine or ambulatory for the 8 hours following dosing. Administering Covera-HS in the morning led to a slower rate of absorption and/or elimination, but did not affect the extent of absorption or extent of metabolism to norverapamil.

Orally administered verapamil undergoes extensive metabolism in the liver. Thirteen metabolites have been identified in

urine. Norverapamil enantiomers can reach steady-state plasma concentrations approximately equal to those of the enantiomers of the parent drug. The cardiovascular activity of norverapamil appears to be approximately 20% that of verapamil. Approximately 70% of an administered dose is excreted as metabolites in the urine and 16% or more in the feces within 5 days. About 3% to 4% is excreted in the urine as unchanged drug. R-verapamil is 94% bound to plasma albumin, while S-verapamil is 88% bound. In addition, R-verapamil is 92% and S-verapamil 86% bound to alpha-1 acid glycoprotein. In patients with hepatic insufficiency, metabolism of immediate-release verapamil is delayed and elimination half-life prolonged up to 14 to 16 hours because of the extensive hepatic metabolism (see **Precautions**). In addition, in these patients there is a reduced first pass effect, and verapamil is more bioavailable. Verapamil clearance values suggest that patients with liver dysfunction may attain therapeutic verapamil plasma concentrations with one third of the oral daily dose required for patients with normal liver function.

After four weeks of oral dosing of immediate release verapamil (120 mg q.i.d.), verapamil and norverapamil levels were noted in the cerebrospinal fluid with estimated partition coefficient of 0.06 for verapamil and 0.04 for norverapamil.

Hemodynamics: Verapamil reduces afterload and myocardial contractility. In most patients, including those with organic cardiac disease, the negative inotropic action of verapamil is countered by reduction of afterload and cardiac index remains unchanged. During isometric or dynamic exercise, verapamil does not alter systolic cardiac function in patients with normal ventricular function. Improved left ventricular diastolic function in patients with IHSS and those with coronary heart disease has also been observed with verapamil. In patients with severe left ventricular dysfunction (eg, pulmonary wedge pressure above 20 mm Hg or ejection fraction less than 30%), or in patients taking beta-adrenergic blocking agents or other cardiodepressant drugs, deterioration of ventricular function may occur (see **Drug Interactions**).

Pulmonary function: Verapamil does not induce bronchoconstriction and, hence, does not impair ventilatory function.

Verapamil has been shown to have either a neutral or relaxant effect on bronchial smooth muscle.

INDICATIONS AND USAGE

Covera-HS is indicated for the management of hypertension and angina.

CONTRAINDICATIONS

Covera-HS is contraindicated in:

1. Severe left ventricular dysfunction (see **Warnings**)
2. Hypotension (systolic pressure less than 90 mm Hg) or cardiogenic shock
3. Sick sinus syndrome (except in patients with a functioning artificial ventricular pacemaker)
4. Second- or third-degree AV block (except in patients with a functioning artificial ventricular pacemaker)
5. Patients with atrial flutter or atrial fibrillation and an accessory bypass tract (eg, Wolff-Parkinson-White, Lown-Ganong-Levine syndromes). (See **Warnings**.)
6. Patients with known hypersensitivity to verapamil hydrochloride.

WARNINGS

Heart failure: Verapamil has a negative inotropic effect, which in most patients is compensated by its afterload reduction (decreased systemic vascular resistance) properties without a net impairment of ventricular performance. In previous clinical experience with 4,954 patients primarily with immediate-release verapamil, 1.8% developed congestive heart failure or pulmonary edema. Verapamil should be avoided in patients with severe left ventricular dysfunction (eg, ejection fraction less than 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-adrenergic blocker (see **Drug Interactions**). Patients with milder ventricular dysfunction should, if possible, be controlled with optimum doses of digitalis and/or diuretics before verapamil treatment is started. (Note interactions with digoxin under **Precautions**.)

Hypotension: Occasionally, the pharmacologic action of verapamil may produce a decrease in blood pressure below normal levels, which may result in dizziness or symptomatic hypotension. In previous verapamil clinical trials the incidence observed in 4,954 patients was 2.5%. In clinical studies of Covera-HS, 0.4% of hypertensive patients and 1.0% of angina patients developed significant hypotension. In hypertensive patients, decreases in blood pressure below normal are unusual. Tilt-table testing (60 degrees) was not able to induce orthostatic hypotension.

Elevated liver enzymes: Elevations of transaminases with and without concomitant elevations in alkaline phosphatase and bilirubin have been reported. Such elevations have sometimes been transient and may disappear even in the face of continued verapamil treatment. Several cases of hepatocellular injury related to verapamil have been proven by rechallenge; half of these had clinical symptoms (malaise, fever, and/or right upper quadrant pain) in addition to elevation of SGOT, SGPT, and alkaline phosphatase. Periodic monitoring of liver function in patients receiving verapamil is therefore prudent.

Accessory bypass tract (Wolff-Parkinson-White or Lown-Ganong-Levine): Some patients with paroxysmal and/or chronic atrial fibrillation or atrial flutter and a coexisting accessory AV pathway have developed increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving intravenous verapamil (or digitalis). Although a risk of this occurring with oral verapamil has not been established, such patients receiving oral verapamil may be at risk and its use in these patients is contraindicated (see **Contraindications**). Treatment is usually DC-cardioversion. Cardioversion has been used safely and effectively after oral verapamil.

Atrioventricular block: The effect of verapamil on AV conduction and the SA node may be asymptomatic first-degree AV block and transient bradycardia, sometimes accompanied by nodal escape rhythms. PR-interval prolongation is correlated with verapamil plasma concentrations, especially during the early titration phase of therapy. Higher degrees of AV block, however, were infrequently (0.8%) observed in previous verapamil clinical trials. Marked first-degree block or progressive development to second- or third-degree AV block requires a reduction in dosage or, in rare instances, discontinuation of verapamil HCl and institution of appropriate therapy, depending upon the clinical situation.

Patients with hypertrophic cardiomyopathy (IHSS): In 120 patients with hypertrophic cardiomyopathy (most of them refractory or intolerant to propranolol) who received therapy with verapamil at doses up to 720 mg/day, a variety of serious adverse effects were seen. Three patients died in pulmonary edema; all had severe left ventricular outflow obstruction and a past history of left ventricular dysfunction. Eight other patients had pulmonary edema and/or severe hypotension; abnormally high (greater than 20 mm Hg) pulmonary wedge pressure and a marked left ventricular outflow obstruction were present in most of these patients. Concomitant administration of quinidine (see *Drug Interactions*) preceded the severe hypotension in 3 of the 8 patients (2 of whom developed pulmonary edema). Sinus bradycardia occurred in 11% of the patients, second-degree AV block in 4%, and sinus arrest in 2%. It must be appreciated that this group of patients had a serious disease with a high mortality rate. Most adverse effects responded well to dose reduction, and only rarely did verapamil use have to be discontinued.

PRECAUTIONS

General

Formulation specific: As with any other non-deformable dosage form caution should be used when administering Covera-HS in patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). In patients with extremely short GI transit time (<7 hrs), pharmacokinetic data are not available and dosage adjustment may be required.

Use in patients with impaired hepatic function: Since verapamil is highly metabolized by the liver, it should be administered cautiously to patients with impaired hepatic function. Severe liver dysfunction prolongs the elimination half-life of immediate-release verapamil to about 14 to 16 hours; hence, approximately 30% of the dose given to patients with normal liver function should be administered to these patients. Careful monitoring for abnormal prolongation of the PR interval or other signs of excessive pharmacologic effects (see *Overdosage*) should be carried out.

Use in patients with attenuated (decreased) neuromuscular transmission: It has been reported that verapamil decreases neuromuscular transmission in patients with Duchenne's muscular dystrophy, and that verapamil prolongs recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease the dosage of verapamil when it is administered to patients with attenuated neuromuscular transmission.

Use in patients with impaired renal function: About 70% of an administered dose of verapamil is excreted as metabolites in the urine. Verapamil is not removed by hemodialysis. Until further data are available, verapamil should be administered cautiously to patients with impaired renal function. These patients should be carefully monitored for abnormal prolongation of the PR interval or other signs of overdosage (see *Overdosage*).

Information for patients: Covera-HS tablets should be swallowed whole; do not break, crush, or chew. The medication in the Covera-HS tablet is released slowly through an outer shell that does not dissolve. The patient should not be concerned if they occasionally observe this outer shell in their stool as it passes from the body.

Drug interactions

Alcohol: Verapamil may increase blood alcohol concentrations and prolong its effects.

Beta-blockers: Concomitant therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility. The combination of sustained-release verapamil and beta-adrenergic blocking agents has not been studied. However, there have been reports of excessive bradycardia and AV block, including complete heart block, when the combination has been used for the treatment of hypertension. For hypertensive patients, the risks of combined therapy may outweigh the potential benefits. The combination should be used only with caution and close monitoring.

Asymptomatic bradycardia (36 beats/min) with a wandering atrial pacemaker has been observed in a patient receiving concomitant timolol (a beta-adrenergic blocker) eyedrops and oral verapamil.

A decrease in metoprolol and propranolol clearance has been observed when either drug is administered concomitantly with verapamil. A variable effect has been seen when verapamil and atenolol were given together.

Digitalis: Clinical use of verapamil in digitalized patients has shown the combination to be well tolerated if digoxin doses are properly adjusted. However, chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, and this can result in digitalis toxicity. In patients with hepatic cirrhosis the influence of verapamil on digoxin kinetics is magnified. Verapamil may reduce total body clearance and extrahepatic clearance of digitoxin by 27% and 29%, respectively. Maintenance and digitalization doses should be reduced when verapamil is administered, and the patient should be reassessed to avoid over- to underdigitalization. Whenever overdigitalization is suspected, the daily dose of digitalis should be reduced or temporarily discontinued. On discontinuation of verapamil use, the patient should be reassessed to avoid underdigitalization. In previous clinical trials with other verapamil

formulations related to the control of ventricular response in digitalized patients with atrial fibrillation or atrial flutter, ventricular rates below 50/min at rest occurred in 15% of patients, and asymptomatic hypotension occurred in 5% of patients.

Antihypertensive agents: Verapamil administered concomitantly with oral antihypertensive agents (eg, vasodilators, angiotensin-converting enzyme inhibitors, diuretics, beta-blockers) will usually have an additive effect on lowering blood pressure. Patients receiving these combinations should be appropriately monitored. Concomitant use of agents that attenuate alpha-adrenergic function with verapamil may result in a reduction in blood pressure that is excessive in some patients. Such an effect was observed in one study following the concomitant administration of verapamil and prazosin.

Antiarrhythmic agents:

Disopyramide: Until data on possible interactions between verapamil and disopyramide are obtained, disopyramide should not be administered within 48 hours before or 24 hours after verapamil administration.

Flecainide: A study in healthy volunteers showed that the concomitant administration of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Concomitant therapy with flecainide and verapamil may result in additive negative inotropic effect and prolongation of atrioventricular conduction.

Quinidine: In a small number of patients with hypertrophic cardiomyopathy (IHSS), concomitant use of verapamil and quinidine resulted in significant hypotension. Until further data are obtained, combined therapy of verapamil and quinidine in patients with hypertrophic cardiomyopathy should probably be avoided.

The electrophysiologic effects of quinidine and verapamil on AV conduction were studied in 8 patients. Verapamil significantly counteracted the effects of quinidine on AV conduction. There has been a report of increased quinidine levels during verapamil therapy.

Other:

Nitrates: Verapamil has been given concomitantly with short- and long-acting nitrates without any undesirable drug interactions. The pharmacologic profile of both drugs and clinical experience suggest beneficial interactions.

Cimetidine: The interaction between cimetidine and chronically administered verapamil has not been studied. Variable results on clearance have been obtained in acute studies of healthy volunteers; clearance of verapamil was either reduced or unchanged.

Lithium: Increased sensitivity to the effects of lithium (neurotoxicity) has been reported during concomitant verapamil-lithium therapy; lithium levels have been observed sometimes to increase, sometimes to decrease, and sometimes to be unchanged. Patients receiving both drugs must be monitored carefully.

Carbamazepine: Verapamil therapy may increase carbamazepine concentrations during combined therapy. This may produce carbamazepine side effects such as diplopia, headache, ataxia, or dizziness.

Rifampin: Therapy with rifampin may markedly reduce oral verapamil bioavailability.

Phenobarbital: Phenobarbital therapy may increase verapamil clearance.

Cyclosporin: Verapamil therapy may increase serum levels of cyclosporin.

Theophylline: Verapamil may inhibit the clearance and increase the plasma levels of theophylline.

Inhalation anesthetics: Animal experiments have shown that inhalation anesthetics depress cardiovascular activity by decreasing the inward movement of calcium ions. When used concomitantly, inhalation anesthetics and calcium channel blocking agents, such as verapamil, should each be titrated carefully to avoid excessive cardiovascular depression.

Neuromuscular blocking agents: Clinical data and animal studies suggest that verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing). It may be necessary to decrease the dose of verapamil and/or the dose of the neuromuscular blocking agent when the drugs are used concomitantly.

Carcinogenesis, mutagenesis, impairment of fertility: An 18-month toxicity study in rats, at a low multiple (6-fold) of the maximum recommended human dose, not the maximum tolerated dose, did not suggest a tumorigenic potential. There was no evidence of a carcinogenic potential of verapamil administered in the diet of rats for two years at doses of 10, 35, and 120 mg/kg/day or approximately 1, 3.5, and 12 times, respectively, the maximum recommended human daily dose (480 mg/day or 9.6 mg/kg/day).

Verapamil was not mutagenic in the Ames test in 5 test strains at 3 mg per plate with or without metabolic activation.

Studies in female rats at daily dietary doses up to 5.5 times (55 mg/kg/day) the maximum recommended human dose did not show impaired fertility. Effects on male fertility have not been determined.

Pregnancy: Pregnancy Category C. Reproduction studies have been performed in rabbits and rats at oral doses up to 1.5 (15 mg/kg/day) and 6 (60 mg/kg/day) times the human oral daily dose, respectively, and have revealed no evidence of teratogenicity. In the rat, however, this multiple of the human dose was embryocidal and retarded fetal growth and development, probably because of adverse maternal effects reflected in reduced weight gains of the dams. This oral dose has also been shown to cause hypotension in rats. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if

clearly needed. Verapamil crosses the placental barrier and can be detected in umbilical vein blood at delivery.

Labor and delivery: It is not known whether the use of verapamil during labor or delivery has immediate or delayed adverse effects on the fetus, or whether it prolongs the duration of labor or increases the need for forceps delivery or other obstetric intervention. Such adverse experiences have not been reported in the literature, despite a long history of use of verapamil in Europe in the treatment of cardiac side effects of beta-adrenergic agonist agents used to treat premature labor.

Nursing mothers: Verapamil is excreted in human milk. Because of the potential for adverse reactions in nursing infants from verapamil, nursing should be discontinued while verapamil is administered.

Pediatric use: Safety and effectiveness in pediatric patients have not been established.

Elderly use: Dosage adjustment may be required in elderly patients with impaired renal function. Verapamil should be administered cautiously in patients with impaired renal function.

Animal pharmacology and/or animal toxicology: In chronic animal toxicology studies verapamil caused lenticular and/or suture line changes at 30 mg/kg/day or greater, and frank cataracts at 62.5 mg/kg/day or greater in the beagle dog but not in the rat. Development of cataracts due to verapamil has not been reported in man.

ADVERSE REACTIONS

Serious adverse reactions are uncommon when verapamil therapy is initiated with upward-dose titration within the recommended single and total daily dose. See **Warnings** for discussion of heart failure, hypotension, elevated liver enzymes, AV block, and rapid ventricular response. Reversible (upon discontinuation of verapamil) non-obstructive, paralytic ileus has been infrequently reported in association with the use of verapamil. The following reactions to orally administered Covera-HS occurred at rates greater than 2.0% or occurred at lower rates but appeared drug-related in clinical trials in hypertension and angina:

	Placebo n=261 %	All doses studied n=572 %
Constipation	2.7	11.7*
Headache	7.3	6.6
Upper respiratory infection	4.6	5.4
Dizziness	2.7	4.7
Fatigue	3.8	4.5
Edema	3.1	3.0
Nausea	1.9	2.1
AV block (1°)	0.0	1.7
Elevated liver enzymes (see Warnings)	0.8	1.4
Bradycardia	0.4	1.4
Paresthesia	0.0	1.0
Flushing	0.3	0.8
Hypotension	0.0	0.7
Postural hypotension	0.3	0.4

*Constipation was typically mild, easily manageable, and the incidence usually diminished within about one week. At a typical once-daily dose of 240 mg, the observed incidence was 7.2%.

In previous experience with other formulations of verapamil, the following reactions occurred at rates greater than 1.0% or occurred at lower rates but appeared clearly drug related in clinical trials in 4,954 patients.

Constipation	7.3%	Dyspnea	1.4%
Dizziness	3.3%	Bradycardia	
Nausea	2.7%	(HR < 50/min)	1.4%
Hypotension	2.5%	AV Block	
Headache	2.2%	total (1°, 2°, 3°)	1.2%
Edema	1.9%	AV Block	
CHF/Pulmonary		2° and 3°	0.8%
Edema	1.8%	Rash	1.2%
Fatigue	1.7%	Flushing	0.6%

Elevated liver enzymes (see **Warnings**)

The following reactions, reported with orally administered verapamil in 2% or less of patients, occurred under conditions (open trials, marketing experience) where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship:

Cardiovascular: angina pectoris, AV block (2° & 3°), atrioventricular dissociation, CHF, pulmonary edema, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope.

Digestive system: diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia.

Hemic and lymphatic: ecchymosis or bruising.

Nervous system: cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, psychotic symptoms, shakiness, somnolence.

Skin: arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme.

Special senses: blurred vision, tinnitus.

Urogenital: gynecomastia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

Other: allergy aggravated, dyspnea.

Treatment of acute cardiovascular adverse reactions: The frequency of cardiovascular adverse reactions that require therapy is rare; hence, experience with their treatment is limited. Whenever severe hypotension or complete AV block occurs following oral administration of verapamil, the appropriate emergency measures should be applied immediately; eg, intravenously

administered norepinephrine, atropine sulfate, isoproterenol HCl (all in usual doses), or calcium gluconate (10% solution). In patients with hypertrophic cardiomyopathy (HSS), alpha-adrenergic agents (phenylephrine HCl, metaraminol bitartrate, or methoxamine HCl) should be used to maintain blood pressure, and isoproterenol and norepinephrine should be avoided. If further support is necessary, dopamine HCl or dobutamine HCl may be administered. Actual treatment and dosage should depend on the severity of the clinical situation and the judgement and experience of the treating physician.

OVERDOSAGE

Treat all verapamil overdoses as serious and maintain observation for at least 48 hours (especially sustained-release verapamil products), preferably under continuous hospital care. Delayed pharmacodynamic consequences may occur with the sustained-release formulations. Verapamil is known to decrease gastrointestinal transit time.

Treatment of overdosage should be supportive. Beta-adrenergic stimulation or parenteral administration of calcium solutions may increase calcium ion flux across the slow channel and have been used effectively in treatment of deliberate overdosage with verapamil. In a few reported cases, overdose with calcium channel blockers has been associated with hypotension and bradycardia, initially refractory to atropine but becoming more responsive to this treatment when the patients received large doses (close to 1 gram/hour for more than 24 hours) of calcium chloride. Verapamil cannot be removed by hemodialysis. Clinically significant hypotensive reactions or high degree AV block should be treated with vasopressor agents or cardiac pacing, respectively. Asystole should be handled by the usual measures including cardiopulmonary resuscitation.

DOSAGE AND ADMINISTRATION

Covera-HS should be administered once daily at bedtime. Clinical trials explored dose ranges between 180 mg and 540 mg given at bedtime and found effects to persist throughout the dosing interval.

Covera-HS tablets should be swallowed whole and not chewed, broken, or crushed.

For both hypertension and angina the dose of Covera-HS should be individualized by titration. Initiate therapy with 180 mg of Covera-HS.

If an adequate response is not obtained with 180 mg of Covera-HS, the dose may be titrated upward in the following manner:

- 240 mg each evening
- 360 mg each evening (2 x 180 mg)
- 480 mg each evening (2 x 240 mg)

When Covera-HS is administered at bedtime, office evaluation of blood pressure during morning and early afternoon hours is essentially a measure of peak effect. The usual evaluation of trough effect, which sometimes might be needed to evaluate the appropriateness of any given dose of Covera-HS, would be just prior to bedtime.

HOW SUPPLIED

Covera-HS 240-mg tablets are pale yellow, round, film coated with COVERA-HS 2021 printed on one side, supplied as:

NDC Number	Size
0025-2021-31	bottle of 100
0025-2021-34	carton of 100 unit dose

Covera-HS 180-mg tablets are lavender, round, film coated, with COVERA-HS 2011 printed on one side, supplied as:

NDC Number	Size
0025-2011-31	bottle of 100
0025-2011-34	carton of 100 unit dose

Store at controlled room temperature 20°-25°C (68°-77°F) [see USP]. Dispense in tight, light-resistant containers.

Caution: Federal law prohibits dispensing without prescription.

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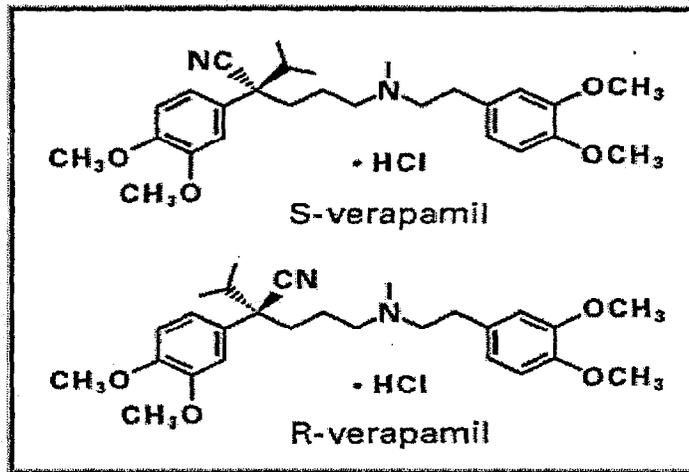
SEARLE
Covera-HS®
(verapamil hydrochloride)
Extended-Release Tablets
Controlled-Onset

Verapamil Hydrochloride Extended-Release Tablets

Controlled-Onset

DESCRIPTION

Verapamil hydrochloride is a calcium ion influx inhibitor (slow-channel blocker or calcium ion antagonist). Verapamil hydrochloride extended-release tablets are available for oral administration as (color and shape to be determined), film-coated tablets containing 240 mg of verapamil hydrochloride and as (color and shape to be determined), film-coated tablets containing 180 mg of verapamil hydrochloride. Verapamil is administered as a racemic mixture of the R and S enantiomers. The structural formulae of the verapamil HCl enantiomers are:



$C_{27}H_{38}N_2O_4 \cdot HCl$

M.W.=491.07

Benzeneacetonitrile, (\pm)-*alpha*-[3[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]-3,4-dimethoxy-*alpha*-(1-methylethyl)hydrochloride

Verapamil HCl is an almost white, crystalline powder, practically free of odor, with a bitter taste. It is soluble in water, chloroform, and methanol. Verapamil HCl is not chemically related to other cardioactive drugs.

Inactive ingredients are to be determined.

System components and performance: The Verapamil Hydrochloride Extended-Release Tablet formulation has been designed to initiate the release of verapamil 4-5 hours after ingestion. This delay is introduced by a layer between the active drug core and outer semipermeable membrane. As water from the gastrointestinal tract enters the tablet, this delay coating is solubilized and released. As tablet hydration continues, the osmotic layer expands and pushes against the drug layer, releasing drug through precision laser-drilled orifices in the outer membrane at a constant rate. This controlled rate of drug delivery in the gastrointestinal lumen is independent of posture, pH, gastrointestinal motility, and fed or fasting conditions. The biologically inert components of the delivery system remain intact during GI transit and are eliminated in the feces as an insoluble shell.

CLINICAL PHARMACOLOGY

Verapamil hydrochloride extended-release tablets have a unique delivery system, designed for bedtime dosing, incorporating a 4 to 5-hour delay in drug delivery. The unique controlled-onset, extended-release (COER) delivery system, which is designed for bedtime dosing, results in a maximum plasma concentration (C_{max}) of verapamil in the morning hours.

Verapamil is a calcium ion influx inhibitor (L-type calcium channel blocker or calcium channel antagonist). Verapamil exerts its pharmacologic effects by selectively inhibiting the transmembrane influx of ionic calcium into arterial smooth muscle as well as in conductile and contractile myocardial cells without altering serum calcium concentrations.

Mechanism of action

In vitro: Verapamil binding is voltage-dependent with affinity increasing as the vascular smooth muscle membrane potential is reduced. In addition, verapamil binding is frequency dependent and apparent affinity increases with increased frequency of depolarizing stimulus.

The L-type calcium channel is an oligomeric structure consisting of five putative subunits designated alpha-1, alpha-2, beta, tau, and epsilon. Biochemical evidence points to separate binding sites for 1,4-dihydropyridines, phenylalkylamines, and the benzothiazepines (all located on the alpha-1 subunit). Although they share a similar mechanism of action, calcium channel blockers represent three heterogeneous categories of drugs with differing vascular-cardiac selectivity ratios.

Essential hypertension: Verapamil produces its antihypertensive effect by a combination of vascular and cardiac effects. It acts as a vasodilator with selectivity for the arterial portion of the peripheral vasculature. As a result the systemic vascular resistance is reduced and usually without orthostatic hypotension or reflex tachycardia. Bradycardia (rate less than 50 beats/min) is uncommon (<1% with Verapamil hydrochloride extended-release tablets as assessed by ECG). During isometric or dynamic exercise Verapamil hydrochloride extended-release tablets do not alter systolic cardiac function in patients with normal ventricular function.

Verapamil hydrochloride extended-release tablets do not alter total serum calcium levels. However, one report has suggested that calcium levels above the normal range may alter the therapeutic effect of verapamil.

Verapamil hydrochloride extended-release tablets regularly reduce the total systemic resistance (afterload against which the heart works both at rest and at a given level of exercise by dilating peripheral arterioles.

Effects in hypertension: Verapamil hydrochloride extended-release tablets were evaluated in two placebo-controlled, parallel design, double-blind studies of 382 patients with mild to moderate hypertension.

In a clinical trial, 287 patients were randomized to placebo, 120 mg, 180 mg, 360 mg, or 540 mg and treated for 8 weeks (the two higher doses were titrated from low doses and maintained for 6 and 4 weeks, respectively). Verapamil Hydrochloride Extended-Release Tablet or placebo was given once daily at 10 pm and blood pressure changes were measured with 36-hour ambulatory blood pressure monitoring (ABPM). The results of these studies demonstrate that the Verapamil hydrochloride extended-release tablet, at 180-540 mg, is a consistently and significantly more effective antihypertensive agent than placebo in reducing ambulatory blood pressures. Over this dose range, the placebo-subtracted net decreases in diastolic BP at trough (averaged over 6-10 pm) were dose-related, ranged from 4.5 to 11.2 mm Hg after 4-8 weeks of therapy, and correlated well with sitting cuff blood pressures.

These studies demonstrate that clinically and statistically significant blood pressure reductions are achieved with Verapamil hydrochloride extended-release tablets throughout the 24-hour dosing period.

There were no significant treatment differences between patient subgroups of different age (older or younger than 65 years), sex, race (Caucasian and non-Caucasian) and severity of hypertension at baseline (cuff BP below and above 105 mm Hg).

Angina: Verapamil dilates the main coronary arteries and coronary arterioles, both in normal and ischemic regions, and is a potent inhibitor of coronary artery spasm, whether spontaneous or ergonovine-induced. This property increases myocardial oxygen delivery in patients with coronary artery spasm and is responsible for the effectiveness of verapamil in vasospastic (Prinzmetal's or variant) as well as unstable angina at rest. Whether this effect plays any role in classical effort angina is not clear, but studies of exercise tolerance have not shown an increase in the maximum exercise rate-pressure product, a widely accepted measure of oxygen utilization. This suggests that, in general, relief of spasm or dilation of coronary arteries is not an important factor in classical angina.

Verapamil regularly reduces the total systemic resistance (afterload) against which the heart works both at rest and at a given level of exercise by dilating peripheral arterioles.

Effect in chronic stable angina: Verapamil hydrochloride extended-release tablets were evaluated in two placebo-controlled, parallel design, double-blind studies of 453 patients with chronic stable angina.

In the first clinical trial 277 patients were randomized to placebo, 180 mg, 360 mg, or 540 mg and treated for 4 weeks (the two higher doses were titrated from low doses and maintained for 3 and 2 weeks,

respectively). A single dose of 240 mg was compared to placebo in a separate study of 176 patients. In these studies Verapamil hydrochloride extended-release tablets were significantly more effective than placebo in improvement of exercise tolerance. Placebo-adjusted net increases in median exercise times at the end of the dosing interval were 0.1 to 1.0 minute for symptom limited duration, 0.3 to 1.4 minutes for time to angina, and 0.1 to 1.1 minutes for time to ST change. Increases in exercise tolerance were in general greater at higher doses, but dose-response relationship was not well defined due to shorter treatment duration for high doses.

In addition, in the first study, 24 to 34% of patients treated with Verapamil hydrochloride extended-release tablets did not experience exercise-limiting angina on exercise treadmill testing (ETT) versus 12% of patients on placebo.

Electrophysiologic effects: Electrical activity through the AV node depends, to a significant degree, upon the transmembrane influx of extracellular calcium through the L-type (slow) channel. By decreasing the influx of calcium, verapamil prolongs the effective refractory period within the AV node and slows AV conduction in a rate-related manner.

Normal sinus rhythm is usually not affected, but in patients with sick sinus syndrome, verapamil may interfere with sinus-node impulse generation and may induce sinus arrest or sinoatrial block. Atrioventricular block can occur in patients without preexisting conduction defects (see *Warnings*).

Verapamil hydrochloride extended-release tablets do not alter the normal atrial action potential or intraventricular conduction time, but depresses amplitude, velocity of depolarization, and conduction in depressed atrial fibers. Verapamil may shorten the antegrade effective refractory period of the accessory bypass tract. Acceleration of ventricular rate and/or ventricular fibrillation has been reported in patients with atrial flutter or atrial fibrillation and a coexisting accessory AV pathway following administration of verapamil (see *Warnings*).

Verapamil has a local anesthetic action that is 1.6 times that of procaine on an equimolar basis. It is not known whether this action is important at the doses used in man.

Pharmacokinetics and metabolism: Verapamil is administered as a racemic mixture of the R and S enantiomers. The systemic concentrations of R and S enantiomers, as well as overall bioavailability, are dependent upon the route of administration and the rate and extent of release from the dosage forms. Upon oral administration, there is rapid stereoselective biotransformation during the first pass of verapamil through the portal circulation. In a study in 5 subjects with oral immediate-release verapamil, the systemic bioavailability was from 33% to 65% for the R enantiomer and from 13% to 34% for the S enantiomer. The R and S enantiomers have differing levels of pharmacologic activity. In studies in animals and humans, the S enantiomer has 8 to 20 times the activity of the R enantiomer in slowing AV conduction. In animal studies, the S enantiomer has 15 and 50 times the activity of the R enantiomer in reducing myocardial contractility in isolated blood-perfused dog papillary muscle and isolated rabbit papillary muscle, respectively, and twice the effect in reducing peripheral resistance. In isolated septal strip preparations from 5 patients, the S enantiomer was 8 times more potent than the R in reducing myocardial contractility. Dose escalation study data indicate that verapamil concentrations increase disproportionately to dose as measured by relative peak plasma concentrations (C_{max}) or areas under the plasma concentration vs time curves (AUC).

Pharmacokinetic Characteristics of Verapamil Enantiomers After Administration of Escalating Doses					
	Isomer	Total Dose of Racemic Verapamil (mg)			
		120	180	360	540
Dose Ratio	—	1	1.5	3	4.5
Relative C _{max}	R	1	1.55	4.47	7.06
	S	1	1.62	5.17	9.21
Relative AUC	R	1	1.59	6.14	11.1
	S	1	1.89	8.17	15.9

Pharmacokinetic Characteristics of Verapamil Enantiomers After Administration of a Single 180 mg Dose and at Steady State			
	Isomer	First Dose (Verapamil-naive subject)	Steady State (Current verapamil exposure)
C _{max} (ng/ml)	R	59.4	90.5
	S	11.7	21.2
AUC (0-24h) (ng·hr/ml)	R	644	1,223
	S	111	266

Racemic verapamil is released from Verapamil hydrochloride extended-release tablets at a constant rate following solubilization and release of the delay coat through the tablet orifices. This delay coat produces a lag period in drug release for approximately 4-5 hours. The drug release phase is prolonged with the peak plasma concentration (C_{max}) occurring approximately 11 hours after administration. Trough concentrations occur approximately 4 hours after bedtime dosing while the patient is sleeping. Steady-state pharmacokinetics were determined in healthy volunteers. Steady-state concentration is reached by the third or fourth day of dosing.

Steady-State Pharmacokinetics of Verapamil Enantiomers in Healthy Humans			
		Verapamil Dose (mg)	
	Isomer	180	240
Mean C _{max} (ng/ml)	R	90.5	120
	S	21.2	28.7
AUC (0-24h) (ng·hr/ml)	R	1,223	1,470
	S	266	322

In general, bioavailability of Verapamil hydrochloride extended-release tablets is higher and half life longer in older (>65 yrs) subjects. Lean body weight also affects its pharmacokinetics inversely, but no gender difference was observed in the clinical trials of Verapamil hydrochloride extended-release tablets. However, there are conflicting data in literature suggesting that verapamil clearance decreased with age in women to a greater degree than in men.

Consumption of a high fat meal just prior to dosing at night had no effect on the pharmacokinetics of Verapamil hydrochloride extended-release tablets. The pharmacokinetics were also not affected by whether the volunteers were supine or ambulatory for the 8 hours following dosing. Administering Verapamil hydrochloride extended-release tablets in the morning led to a slower rate of absorption and/or elimination, but did not affect the extent of absorption or extent of metabolism to norverapamil.

Orally administered verapamil undergoes extensive metabolism in the liver. Thirteen metabolites have been identified in urine. Norverapamil enantiomers can reach steady-state plasma concentrations approximately equal to those of the enantiomers of the parent drug. The cardiovascular activity of norverapamil appears to be approximately 20% that of verapamil. Approximately 70% of an administered dose is excreted as metabolites in the urine and 16% or more in the feces within 5 days. About 3% to 4% is excreted in the urine as unchanged drug. R-verapamil is 94% bound to plasma albumin, while S-verapamil is 88% bound. In addition, R-verapamil is 92% and S-verapamil 86% bound to alpha-1 acid glycoprotein. In patients with hepatic insufficiency, metabolism of immediate-release verapamil is delayed and elimination half-life prolonged up to 14 to 16 hours because of the extensive hepatic metabolism (see *Precautions*). In addition, in these patients there is a reduced first pass effect, and verapamil is more bioavailable. Verapamil clearance values suggest that patients with liver dysfunction may attain therapeutic verapamil plasma concentrations with one third of the oral daily dose required for patients with normal liver function.

After four weeks of oral dosing of immediate release verapamil (120 mg q.i.d.), verapamil and norverapamil levels were noted in the cerebrospinal fluid with estimated partition coefficient of 0.06 for verapamil and 0.04 for norverapamil.

Hemodynamics: Verapamil reduces afterload and myocardial contractility. In most patients, including those with organic cardiac disease, the negative inotropic action of verapamil is countered by reduction of afterload and cardiac index remains unchanged. During isometric or dynamic exercise, verapamil does not alter systolic cardiac function in patients with normal ventricular function. Improved left ventricular diastolic function in patients with IHSS and those with coronary heart disease has also been observed with verapamil. In patients with severe left ventricular dysfunction (e.g., pulmonary wedge pressure above 20 mm Hg or ejection fraction less than 30%), or in patients taking beta-adrenergic blocking agents or other cardiodepressant drugs, deterioration of ventricular function may occur (see *Drug interactions*).

Pulmonary function: Verapamil does not induce bronchoconstriction and, hence, does not impair ventilatory function.

Verapamil has been shown to have either a neutral or relaxant effect on bronchial smooth muscle.

INDICATIONS AND USAGE

Verapamil hydrochloride extended-release tablets are indicated for the management of hypertension and angina.

CONTRAINDICATIONS

Verapamil hydrochloride extended-release tablets are contraindicated in:

1. Severe left ventricular dysfunction (see *Warnings*)
2. Hypotension (systolic pressure less than 90 mm Hg) or cardiogenic shock
3. Sick sinus syndrome (except in patients with a functioning artificial ventricular pacemaker)
4. Second- or third-degree AV block (except in patients with a functioning artificial ventricular pacemaker)
5. Patients with atrial flutter or atrial fibrillation and an accessory bypass tract (eg, Wolff-Parkinson-White, Lown-Ganong-Levine syndromes). (See *Warnings*.)
6. Patients with known hypersensitivity to verapamil hydrochloride.

WARNINGS

Heart failure: Verapamil has a negative inotropic effect, which in most patients is compensated by its afterload reduction (decreased systemic vascular resistance) properties without a net impairment of ventricular performance. In previous clinical experience with 4,954 patients primarily with immediate-release verapamil, 1.8% developed congestive heart failure or pulmonary edema. Verapamil should be avoided in patients with severe left ventricular dysfunction (eg, ejection fraction less than 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-adrenergic blocker (see *Drug interactions*). Patients with milder ventricular dysfunction should, if possible, be controlled with optimum doses of digitalis and/or diuretics before verapamil treatment is started. (Note interactions with digoxin under *Precautions*.)

Hypotension: Occasionally, the pharmacologic action of verapamil may produce a decrease in blood pressure below normal levels, which may result in dizziness or symptomatic hypotension. In previous verapamil clinical trials the incidence observed in 4,954 patients was 2.5%. In clinical studies of Verapamil hydrochloride extended-release tablets, 0.4% of hypertensive patients and 1.0% of angina patients developed significant hypotension. In hypertensive patients, decreases in blood pressure below normal are unusual. Tilt-table testing (60 degrees) was not able to induce orthostatic hypotension.

Elevated liver enzymes: Elevations of transaminases with and without concomitant elevations in alkaline phosphatase and bilirubin have been reported. Such elevations have sometimes been transient and may disappear even in the face of continued verapamil treatment. Several cases of hepatocellular injury related to verapamil have been proven by rechallenge; half of these had clinical symptoms (malaise, fever, and/or right upper quadrant pain) in addition to elevation of SGOT, SGPT, and alkaline phosphatase. Periodic monitoring of liver function in patients receiving verapamil is therefore prudent.

Accessory bypass tract (Wolff-Parkinson-White or Lown-Ganong-Levine): Some patients with paroxysmal and/or chronic atrial fibrillation or atrial flutter and a coexisting accessory AV pathway have

developed increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving intravenous verapamil (or digitalis). Although a risk of this occurring with oral verapamil has not been established, such patients receiving oral verapamil may be at risk and its use in these patients is contraindicated (see *Contraindications*). Treatment is usually DC-cardioversion. Cardioversion has been used safely and effectively after oral verapamil.

Atrioventricular block: The effect of verapamil on AV conduction and the SA node may cause asymptomatic first-degree AV block and transient bradycardia, sometimes accompanied by nodal escape rhythms. PR-interval prolongation is correlated with verapamil plasma concentrations, especially during the early titration phase of therapy. Higher degrees of AV block, however, were infrequently (0.8%) observed in previous verapamil clinical trials. Marked first-degree block or progressive development to second- or third-degree AV block requires a reduction in dosage or, in rare instances, discontinuation of verapamil HCl and institution of appropriate therapy, depending upon the clinical situation.

Patients with hypertrophic cardiomyopathy (IHSS): In 120 patients with hypertrophic cardiomyopathy (most of them refractory or intolerant to propranolol) who received therapy with verapamil at doses up to 720 mg/day, a variety of serious adverse effects were seen. Three patients died in pulmonary edema; all had severe left ventricular outflow obstruction and a past history of left ventricular dysfunction. Eight other patients had pulmonary edema and/or severe hypotension; abnormally high (greater than 20 mm Hg) pulmonary wedge pressure and a marked left ventricular outflow obstruction were present in most of these patients. Concomitant administration of quinidine (see *Drug interactions*) preceded the severe hypotension in 3 of the 8 patients (2 of whom developed pulmonary edema). Sinus bradycardia occurred in 11% of the patients, second-degree AV block in 4%, and sinus arrest in 2%. It must be appreciated that this group of patients had a serious disease with a high mortality rate. Most adverse effects responded well to dose reduction, and only rarely did verapamil use have to be discontinued.

PRECAUTIONS

General

Formulation specific: As with any other non-deformable dosage form caution should be used when administering Verapamil hydrochloride extended-release tablets in patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). In patients with extremely short GI transit time (<7 hrs), pharmacokinetic data are not available and dosage adjustment may be required.

Use in patients with impaired hepatic function: Since verapamil is highly metabolized by the liver, it should be administered cautiously to patients with impaired hepatic function. Severe liver dysfunction prolongs the elimination half-life of immediate-release verapamil to about 14 to 16 hours; hence, approximately 30% of the dose given to patients with normal liver function should be administered to these patients. Careful monitoring for abnormal prolongation of the PR interval or other signs of excessive pharmacologic effects (see *Overdosage*) should be carried out.

Use in patients with attenuated (decreased) neuromuscular transmission: It has been reported that verapamil decreases neuromuscular transmission in patients with Duchenne's muscular dystrophy, and that verapamil prolongs recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease the dosage of verapamil when it is administered to patients with attenuated neuromuscular transmission.

Use in patients with impaired renal function: About 70% of an administered dose of verapamil is excreted as metabolites in the urine. Verapamil is not removed by hemodialysis. Until further data are available, verapamil should be administered cautiously to patients with impaired renal function. These patients should be carefully monitored for abnormal prolongation of the PR interval or other signs of overdosage (see *Overdosage*).

Information for patients: Verapamil hydrochloride extended-release tablets should be swallowed whole; do not break, crush, or chew. The medication in the Verapamil hydrochloride extended-release tablets is released slowly through an outer shell that does not dissolve. The patient should not be concerned if they occasionally observe this outer shell in their stool as it passes from the body.

Drug interactions

Alcohol: Verapamil may increase blood alcohol concentrations and prolong its effects.

Beta-blockers: Concomitant therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility. The combination of sustained-release verapamil and beta-adrenergic blocking agents has not been studied. However, there have been reports of excessive bradycardia and AV block, including complete heart block, when the combination has been used for the treatment of hypertension. For hypertensive patients, the risks of combined therapy may outweigh the potential benefits. The combination should be used only with caution and close monitoring.

Asymptomatic bradycardia (36 beats/min) with a wandering atrial pacemaker has been observed in a patient receiving concomitant timolol (a beta-adrenergic blocker) eyedrops and oral verapamil.

A decrease in metoprolol and propranolol clearance has been observed when either drug is administered concomitantly with verapamil. A variable effect has been seen when verapamil and atenolol were given together.

Digitals: Clinical use of verapamil in digitalized patients has shown the combination to be well tolerated if digoxin doses are properly adjusted. However, chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, and this can result in digitalis toxicity. In patients with hepatic cirrhosis the influence of verapamil on digoxin kinetics is magnified. Verapamil may reduce total body clearance and extrarenal clearance of digitoxin by 27% and 29%, respectively. Maintenance and digitalization doses should be reduced when verapamil is administered, and the patient should be reassessed to avoid over- to underdigitalization. Whenever overdigitalization is suspected, the daily dose of digitalis should be reduced or temporarily discontinued. On discontinuation of verapamil use, the patient should be reassessed to avoid underdigitalization. In previous clinical trials with other verapamil formulations related to the control of ventricular response in digitalized patients who had atrial fibrillation or atrial flutter, ventricular rates below 50/min at rest occurred in 15% of patients, and asymptomatic hypotension occurred in 5% of patients.

Antihypertensive agents: Verapamil administered concomitantly with oral antihypertensive agents (eg, vasodilators, angiotensin-converting enzyme inhibitors, diuretics, beta-blockers) will usually have an additive effect on lowering blood pressure. Patients receiving these combinations should be appropriately monitored. Concomitant use of agents that attenuate alpha-adrenergic function with verapamil may result in a reduction in blood pressure that is excessive in some patients. Such an effect was observed in one study following the concomitant administration of verapamil and prazosin.

Antiarrhythmic agents:

Disopyramide: Until data on possible interactions between verapamil and disopyramide are obtained, disopyramide should not be administered within 48 hours before or 24 hours after verapamil administration.

Flecainide: A study in healthy volunteers showed that the concomitant administration of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Concomitant therapy with flecainide and verapamil may result in additive negative inotropic effect and prolongation of atrioventricular conduction.

Quinidine: In a small number of patients with hypertrophic cardiomyopathy (IHSS), concomitant use of verapamil and quinidine resulted in significant hypotension. Until further data are obtained, combined therapy of verapamil and quinidine in patients with hypertrophic cardiomyopathy should probably be avoided.

The electrophysiologic effects of quinidine and verapamil on AV conduction were studied in 8 patients. Verapamil significantly counteracted the effects of quinidine on AV conduction. There has been a report of increased quinidine levels during verapamil therapy.

Other:

Nitrates: Verapamil has been given concomitantly with short- and long-acting nitrates without any undesirable drug interactions. The pharmacologic profile of both drugs and clinical experience suggest beneficial interactions.

Cimetidine: The interaction between cimetidine and chronically administered verapamil has not been studied. Variable results on clearance have been obtained in acute studies of healthy volunteers; clearance of verapamil was either reduced or unchanged.

Lithium: Increased sensitivity to the effects of lithium (neurotoxicity) has been reported during concomitant verapamil-lithium therapy with either no change or an increase in serum lithium levels. However, the addition of verapamil has also resulted in the lowering of serum lithium levels in patients receiving chronic stable oral lithium. Patients receiving both drugs must be monitored carefully.

Carbamazepine: Verapamil therapy may increase carbamazepine concentrations during combined therapy. This may produce carbamazepine side effects such as diplopia, headache, ataxia, or dizziness.

Rifampin: Therapy with rifampin may markedly reduce oral verapamil bioavailability.

Phenobarbital: Phenobarbital therapy may increase verapamil clearance.

Cyclosporin: Verapamil therapy may increase serum levels of cyclosporin.

Theophylline: Verapamil may inhibit the clearance and increase the plasma levels of theophylline.

Inhalation anesthetics: Animal experiments have shown that inhalation anesthetics depress cardiovascular activity by decreasing the inward movement of calcium ions. When used concomitantly, inhalation anesthetics and calcium channel blocking agents, such as verapamil, should each be titrated carefully to avoid excessive cardiovascular depression.

Neuromuscular blocking agents: Clinical data and animal studies suggest that verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing). It may be necessary to decrease the dose of verapamil and/or the dose of the neuromuscular blocking agent when the drugs are used concomitantly.

Carcinogenesis, mutagenesis, impairment of fertility: An 18-month toxicity study in rats, at a low multiple (6-fold) of the maximum recommended human dose, not the maximum tolerated dose, did not suggest a tumorigenic potential. There was no evidence of a carcinogenic potential of verapamil administered in the diet of rats for two years at doses of 10, 35, and 120 mg/kg/day or approximately 1, 3.5, and 12 times, respectively, the maximum recommended human daily dose (480 mg/day or 9.6 mg/kg/day).

Verapamil was not mutagenic in the Ames test in 5 test strains at 3 mg per plate with or without metabolic activation.

Studies in female rats at daily dietary doses up to 5.5 times (55 mg/kg/day) the maximum recommended human dose did not show impaired fertility. Effects on male fertility have not been determined.

Pregnancy: Pregnancy Category C. Reproduction studies have been performed in rabbits and rats at oral doses up to 1.5 (15 mg/kg/day) and 6 (60 mg/kg/day) times the human oral daily dose, respectively, and have revealed no evidence of teratogenicity. In the rat, however, this multiple of the human dose was embryocidal and retarded fetal growth and development, probably because of adverse maternal effects reflected in reduced weight gains of the dams. This oral dose has also been shown to cause hypotension in rats. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Verapamil crosses the placental barrier and can be detected in umbilical vein blood at delivery.

Labor and delivery: It is not known whether the use of verapamil during labor or delivery has immediate or delayed adverse effects on the fetus, or whether it prolongs the duration of labor or increases the need for forceps delivery or other obstetric intervention. Such adverse experiences have not been reported in the literature, despite a long history of use of verapamil in Europe in the treatment of cardiac side effects of beta-adrenergic agonist agents used to treat premature labor.

Nursing mothers: Verapamil is excreted in human milk. Because of the potential for adverse reactions in nursing infants from verapamil, nursing should be discontinued while verapamil is administered.

Pediatric use: Safety and efficacy of Verapamil hydrochloride extended-release tablets in children below the age of 18 years have not been established.

Elderly use: Dosage adjustment may be required in elderly patients with impaired renal function. Verapamil should be administered cautiously in patients with impaired renal function.

Animal pharmacology and/or animal toxicology: In chronic animal toxicology studies verapamil caused lenticular and/or suture line changes at 30 mg/kg/day or greater, and frank cataracts at 62.5 mg/kg/day or greater in the beagle dog but not in the rat. Development of cataracts due to verapamil has not been reported in man.

ADVERSE REACTIONS

Serious adverse reactions are uncommon when verapamil therapy is initiated with upward dose titration within the recommended single and total daily dose. See *Warnings* for discussion of heart failure, hypotension, elevated liver enzymes, AV block, and rapid ventricular response. Reversible (upon discontinuation of verapamil) non-obstructive, paralytic ileus has been infrequently reported in association with the use of verapamil. The following reactions to orally administered Verapamil hydrochloride extended-release tablets occurred at rates greater than 2.0% or occurred at lower rates but appeared drug-related in clinical trials in hypertension and angina:

	Placebo n=261 %	All doses studied n=572 %
Constipation	2.7	11.7*
Headache	7.3	6.6
Upper respiratory infection	4.6	5.4
Dizziness	2.7	4.7
Fatigue	3.8	4.5
Edema	3.1	3.0
Nausea	1.9	2.1
AV block (1°)	0.0	1.7
Elevated liver enzymes (see <i>Warnings</i>)	0.8	1.4
Bradycardia	0.4	1.4
Paresthesia	0.0	1.0
Flushing	0.3	0.8
Hypotension	0.0	0.7
Postural hypotension	0.3	0.4

*Constipation was typically mild, easily manageable, and the incidence usually diminished within about one week. At a typical once-daily dose of 240 mg, the observed incidence was 7.2%.

In previous experience with other formulations of verapamil, the following reactions occurred at rates greater than 1.0% or occurred at lower rates but appeared clearly drug related in clinical trials in 4,954 patients.

Constipation	7.3%
Dizziness	3.3%
Nausea	2.7%
Hypotension	2.5%
Headache	2.2%
Edema	1.9%
CHF/Pulmonary Edema	1.8%
Fatigue	1.7%
Dyspnea	1.4%
Bradycardia (HR<50/min)	1.4%
AV Block (total 1°,2°,3°)	1.2%
AV Block (2° and 3°)	0.8%
Rash	1.2%
Flushing	0.6%
Elevated liver enzymes (see <i>Warnings</i>)	

The following reactions, reported with orally administered verapamil in 2% or less of patients, occurred under conditions (open trials, marketing experience) where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship:

Cardiovascular: angina pectoris, AV block (2° & 3°), atrioventricular dissociation, CHF, pulmonary edema, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope.

Digestive system: diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia.

Hemic and lymphatic: ecchymosis or bruising.

Nervous system: cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, psychotic symptoms, shakiness, somnolence.

Skin: arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme.

Special senses: blurred vision.

Urogenital: gynecomastia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

Other: allergy aggravated, dyspnea.

Treatment of acute cardiovascular adverse reactions: The frequency of cardiovascular adverse reactions that require therapy is rare; hence, experience with their treatment is limited. Whenever severe hypotension or complete AV block occurs following oral administration of verapamil, the appropriate emergency measures should be applied immediately; eg, intravenously administered norepinephrine bitartrate, atropine sulfate, isoproterenol HCl (all in usual doses), or calcium gluconate (10% solution). In patients with hypertrophic cardiomyopathy (IHSS), alpha-adrenergic agents (phenylephrine HCl, metaraminol bitartrate, or methoxamine HCl) should be used to maintain blood pressure, and isoproterenol and norepinephrine should be avoided. If further support is necessary, dopamine HCl or dobutamine HCl may be administered. Actual treatment and dosage should depend on the severity of the clinical situation and the judgement and experience of the treating physician.

OVERDOSAGE

Treat all verapamil overdoses as serious and maintain observation for at least 48 hours (especially sustained-release verapamil products), preferably under continuous hospital care. Delayed pharmacodynamic consequences may occur with the sustained-release formulations. Verapamil is known to decrease gastrointestinal transit time.

Treatment of overdose should be supportive. Beta-adrenergic stimulation or parenteral administration of calcium solutions may increase calcium ion flux across the slow channel and have been used effectively in treatment of deliberate overdose with verapamil. Verapamil cannot be removed by hemodialysis. Clinically significant hypotensive reactions or high degree AV block should be treated with vasopressor agents or cardiac pacing, respectively. Asystole should be handled by the usual measures including cardiopulmonary resuscitation.

DOSAGE AND ADMINISTRATION

Verapamil hydrochloride extended-release tablets should be administered once daily at bedtime. Clinical trials explored dose ranges between 180 mg and 540 mg given at bedtime and found effects to persist throughout the dosing interval.

Verapamil hydrochloride extended-release tablets should be swallowed whole and not chewed, broken, or crushed.

For both hypertension and angina the dose of Verapamil hydrochloride extended-release tablets should be individualized by titration. Initiate therapy with 180 mg of Verapamil hydrochloride extended-release tablets.

If an adequate response is not obtained with 180 mg of Verapamil hydrochloride extended-release tablets, the dose may be titrated upward in the following manner:

- a) 240 mg each evening
- b) 360 mg each evening (2 x 180 mg)
- c) 480 mg each evening (2 x 240 mg)

When Verapamil hydrochloride extended-release tablets are administered at bedtime, office evaluation of blood pressure during morning and early afternoon hours is essentially a measure of peak effect. The usual evaluation of trough effect, which sometimes might be needed to evaluate the appropriateness of any given dose of Verapamil hydrochloride extended-release tablets, would be just prior to bedtime.

HOW SUPPLIED

Verapamil hydrochloride extended-release 240-mg tablets are (color, print, etc. to be determined), supplied as:

<u>NDC Number</u>	<u>Size</u>
62037-	bottle of 30
62037-	bottle of 100
62037-	carton of 100 unit dose

Verapamil hydrochloride extended-release 180-mg tablets are (color, print, etc. to be determined), supplied as:

<u>NDC Number</u>	<u>Size</u>
62037-	bottle of 30
62037-	bottle of 100
62037-	carton of 100 unit dose

Store at controlled room temperature 20-25°C (68-77°F) [see USP]. Dispense in tight, light-resistant containers.

Caution: Federal law prohibits dispensing without prescription.

1/12/99

*Manufactured
By Andrx Pharmaceutical, Inc.
Fort Lauderdale, FL USA*

DIANE SERVELLO
ANDRX PHARMACEUTICALS
4001 SW 47TH AVE
SUITE 201
FT. LAUDERDALE FL 33314
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SHIP DATE: 13Jan00
ACCOUNT #: 168916973
ACTUAL WGT: 2 LBS.M.

TO: DOCKETS MANAGEMENT BRANCH
FOOD AND DRUG ADMINISTRATION
DEPT. OF HEALTH/HUMAN SVC.
12420 PARKLAWN DRIVE
ROCKVILLE MD 20857

FedEx

4625 1387 5919

REF: REGULATORY AFFAIRS - DOCUMENTS

PRIORITY OVERNIGHT

FRI

cad# 600899 13Jan00 16:55
Trk#

Deliver by:
14Jan00

4625 1387 5919 Form 0201

AA

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Part# 154254-354 GTI: 9/99

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