





**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75-138

APPROVED DRAFT LABELING

N 0378-6440-01 6
 240 mg

 NDC 0378-6440-01
 MYLAN®
**VERAPAMIL
 HYDROCHLORIDE
 EXTENDED-RELEASE
 CAPSULES**
 240 mg
 100 CAPSULES 

Each extended-release capsule contains: Verapamil Hydrochloride, USP 240 mg
 N 0378-6440-05 4
 240 mg

 NDC 0378-6440-05
 MYLAN®
**VERAPAMIL
 HYDROCHLORIDE
 EXTENDED-RELEASE
 CAPSULES**
 240 mg
 500 CAPSULES 

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 ROOM TEMPERATURE
 15° to 25°C (59° to 77°F).
 Brief excursions above 25°C while not detrimental, should be avoided.
AVOID EXCESSIVE HEAT.
PROTECT FROM MOISTURE.
 Usual Adult Dosage: See accompanying prescribing information.
 This is a bulk container and not intended for dispensing for household use.
Mylan Pharmaceuticals Inc.
 Morgantown, WV 26505

3 N 0378-6380-01 5

180 mg

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

NDC 0378-6380-01

MYLAN®

VERAPAMIL HYDROCHLORIDE EXTENDED-RELEASE CAPSULES
180 mg

100 CAPSULES R only

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure. Keep this and all medication out of the reach of children. **STORE AT ROOM TEMPERATURE** 15° to 25°C (59° to 77°F). Brief excursions above 25°C while not detrimental, should be avoided. **AVOID EXCESSIVE HEAT.** **PROTECT FROM MOISTURE.** Usual Adult Dosage: See accompanying prescribing information. This is a bulk container and not intended for dispensing for household use. Mylan Pharmaceuticals Inc. Morgantown, WV 26505

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APR 20 1999


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

NDC 0378-6320-01

MYLAN®

VERAPAMIL HYDROCHLORIDE EXTENDED-RELEASE CAPSULES
 120 mg

100 CAPSULES



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 ROOM TEMPERATURE 15° to 25°C (59° to 77°F).** Brief excursions above 25°C while not detrimental, should be avoided. **AVOID EXCESSIVE HEAT. PROTECT FROM MOISTURE.** Usual Adult Dosage: See accompanying prescribing information. Mylan Pharmaceuticals Inc. Morgantown, WV 26505


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

NDC 0378-6320-05

MYLAN®

VERAPAMIL HYDROCHLORIDE EXTENDED-RELEASE CAPSULES
 120 mg

500 CAPSULES



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APR 20 1991

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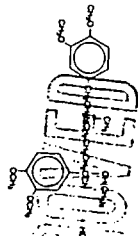
APR 20 1993

VERAPAMIL HYDROCHLORIDE Extended-release Capsules

120 mg, 180 mg and 240 mg

R only

DESCRIPTION: Verapamil hydrochloride extended-release is a calcium ion influx inhibitor (slow channel blocker or calcium ion antagonist). Verapamil hydrochloride extended-release is available for oral administration as a 120 mg hard gelatin capsule, a 180 mg hard gelatin capsule and a 240 mg hard gelatin capsule. These hard gelatin capsules provide an extended-release of the drug in the gastrointestinal tract. The structural formula of verapamil hydrochloride is given below.



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

Chemical name: (S)-5-(1,4-Dimethoxyphenyl)-2-methylpiperazine-2-(1,3,4-dimethoxyphenyl)-2-isopropylvaleronitrile monohydrochloride.

Verapamil hydrochloride is an almost white, crystalline solid, practically free of odor. It is soluble in water, chloroform, methanol. Verapamil hydrochloride is not structurally related to other cardiac drugs.

In addition to verapamil hydrochloride, verapamil hydrochloride extended-release capsules contain the following inactive ingredients: ammonium hydroxide, colloidal silicon dioxide, D&C yellow no. 10 aluminum lake, dibutyl sebacate, dibutyl phthalate, ethylcellulose, FD&C blue no. 2 aluminum lake, FD&C blue no. 1 aluminum lake, FD&C green #3, FD&C red no. 40 aluminum lake, gelatin, hydroxypropyl methylcellulose, isopropyl alcohol, maltodextrin, methacrylic acid copolymer, n-butyl alcohol, oleic acid, pharmaceutical glaze, polyethylene glycol, povidone, propylene glycol, SDA-3A alcohol, silicon dioxide, sodium lauryl sulfate, sugar spheres, synthetic black iron oxide, talc, and titanium dioxide. In addition the 180 mg capsule contains D&C yellow #10.

CLINICAL PHARMACOLOGY: Verapamil hydrochloride extended-release is a calcium ion influx inhibitor (slow channel blocker or calcium ion antagonist) which exerts its pharmacologic effects by modulating the influx of ionic calcium across the cell membrane of the arterial smooth muscle as well as in conductile and contractile myocardial cells.

Normal sinus rhythm is usually not affected by verapamil hydrochloride. However, in patients with sick sinus syndrome, verapamil hydrochloride 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 does not alter the normal atrial action potential or intraventricular conduction time, but decreases amplitude of the QRS complex.

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cellulose, stearic acid, hydroxyethylcellulose, polyethylene glycol, povidone, propylene glycol, SDA-3A alcohol, silicon dioxide, sodium lauryl sulfate, sugar spheres, synthetic black iron oxide, talc, and titanium dioxide. In addition the 180 mg capsule contains D&C yellow #10.

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Verapamil hydrochloride 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.

Mechanism of Action: Essential Hypertension: Verapamil hydrochloride exerts antihypertensive effects by decreasing systemic vascular resistance, usually without antihypertensive effects in blood pressure or reflex tachycardia; bradycardia (rate less than 50 beats/minute is uncommon). Verapamil hydrochloride regularly reduces arterial pressure at rest and at a given level of exercise by dilating peripheral arterioles and reducing the total peripheral resistance (afterload) against which the heart works. **Pharmacokinetics and Metabolism:** With the immediate-release formulations, more than 90% of the orally administered dose is absorbed, and peak plasma concentrations of verapamil are observed 1 to 2 hours after dosing. Because of rapid biotransformation of verapamil during its first pass through the portal circulation, the absolute bioavailability ranges from 20% to 35%. Chronic oral administration of the highest recommended dose (120 mg every 6 hours) resulted in plasma verapamil levels ranging from 125 to 400 ng/mL with higher values reported occasionally. A nonlinear correlation between the verapamil hydrochloride dose administered and verapamil plasma levels does exist.

During initial dose titration with verapamil a relationship exists between verapamil plasma concentrations and the prolongation of the PR interval. However, during chronic administration this relationship may disappear. The quantitative relationship between plasma verapamil concentrations and blood pressure reduction has not been fully characterized.

In a multiple dose pharmacokinetic study, peak concentrations for a single daily dose of verapamil hydrochloride extended-release 240 mg were approximately 65% of those obtained with an 80 mg i.i.d. dose of the conventional immediate-release tablets, and the 24-hour post-dose concentrations were approximately 30% higher. At a total daily dose of 240 mg, verapamil hydrochloride extended-release was shown to have a similar extent of verapamil bioavailability based on the AUC₀₋₂₄ as that obtained with the conventional immediate-release tablets. In this same study verapamil hydrochloride extended-release doses of 120 mg, 240 mg and 360 mg once daily were compared after multiple doses. The ratios of the verapamil and norverapamil AUCs for verapamil hydrochloride extended-release 120 mg, 240 mg and 360 mg once daily doses are 1 (565 ng•hr/mL):3 (1660 ng•hr/mL):5 (2729 ng•hr/mL) and 1 (621 ng•hr/mL):3 (1614 ng•hr/mL):4 (2535 ng•hr/mL), respectively, indicating that the AUC increased non-proportionately with increasing doses.

Food does not affect the extent or rate of the absorption of verapamil from the verapamil hydrochloride extended-release capsule. The verapamil hydrochloride extended-release 240 mg capsule when administered with food had a C_{max} of 77 ng/mL which occurred 9.0 hours after dosing, and an AUC_{0-∞} of 1387 ng•hr/mL. Verapamil hydrochloride extended-release 240 mg under fasting conditions had a C_{max} of 77 ng/mL which occurred 9.8 hours after dosing, and an AUC_{0-∞} of 1541 ng•hr/mL.

The bioequivalence of verapamil hydrochloride extended-release 240 mg administered as the beads sprinkled on applesauce and as the intact capsule, was demonstrated in a single-dose, cross-over study in 32 healthy adults. Comparative ratios (sprinkled/intact) of verapamil were 0.95, 1.02, and 1.01 for C_{max}, T_{max}, and AUC_{0-∞} respectively. Similar results were observed with norverapamil.

The time to reach maximum verapamil concentrations (T_{max}) with verapamil hydrochloride extended-release has been found to be approximately 7 to 9 hours in each of the single dose (fasting), single dose (fed) and the multiple dose (steady-state) studies and are comparable to those reported for the immediate-release formulation.

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The time to reach maximum verapamil concentrations (T_{max}) with verapamil hydrochloride extended-release has been found to be approximately 7 to 9 hours in each of the single dose (fasting), single dose (fed), the multiple dose (fasting) studies, and dose proportionality pharmacokinetic studies. Similarly the apparent half-life ($t_{1/2}$) has been found to be approximately 12 hours independent of dose. Aging may affect the pharmacokinetics of verapamil. Elimination half-life may be prolonged in the elderly.

In healthy man, orally administered verapamil hydrochloride undergoes extensive metabolism in the liver. Twelve metabolites have been identified in plasma; all except noreverapamil are present in trace amounts only. Noreverapamil can reach steady-state plasma concentrations approximately equal to those of verapamil itself. The biologic activity of noreverapamil appears to be approximately 20% that of verapamil.

Approximately 70% of an administered dose of verapamil hydrochloride is excreted as metabolites in the urine and 15% or more in the feces within 5 days. About 3% to 4% is excreted in the urine as unchanged drug. Approximately 90% is bound to plasma proteins. In patients with hepatic insufficiency, metabolism is delayed and elimination half-life prolonged up to 14 to 16 hours (see PRECAUTIONS), the volume of distribution is increased, and plasma clearance reduced to about 30% of normal. 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 (120 mg q.i.d.), verapamil and noreverapamil levels were noted in the cerebrospinal fluid with estimated partition coefficient of 0.05 for verapamil and 0.04 for noreverapamil.

In 10 healthy males, administration of oral verapamil (80 mg every 8 hours for 6 days) and a single oral dose of ethanol (0.8 g/kg) resulted in a 17% increase in mean peak ethanol concentrations (106.45 ± 21.40 to 124.23 ± 24.74 mg/dL) compared with placebo. (See PRECAUTIONS: Drug Interactions.)

The area under the blood ethanol concentration versus time curve (AUC over 12 hours) increased by 30% (365.67 ± 93.52 to 475.07 ± 97.24 mg•hr/dL). Verapamil AUCs were positively correlated ($r=0.71$) to increased ethanol blood AUC values.

Hemodynamics and Myocardial Metabolism: Verapamil hydrochloride reduces afterload and myocardial contractility, improved left ventricular diastolic function in patients with DSS and those with coronary heart disease has also been observed with verapamil hydrochloride therapy. In most patients, including those with organic cardiac disease, the negative inotropic action of verapamil hydrochloride is countered by reduction of afterload and cardiac index is usually not reduced. In patients with severe left ventricular dysfunction however, (e.g., pulmonary wedge pressure above 20 mm Hg or ejection fraction lower than 30%), or in patients on beta-adrenergic blocking agents or other cardiodepressant drugs, deterioration of ventricular function may occur. (See PRECAUTIONS: Drug Interactions.)

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

INDICATIONS AND USAGE: Verapamil hydrochloride extended-release capsules are indicated for the management of essential hypertension.

CONTRAINDICATIONS: Verapamil hydrochloride is contraindicated in

1. Severe left ventricular dysfunction (See WARNINGS)
2. Hypotension (less than 90 mm Hg systolic pressure) 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 (e.g., 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 perfor-

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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) and does not cause a net impairment of ventricular performance. In clinical experience with 4,954 patients, 87 (1.8%) developed congestive heart failure or pulmonary edema. Verapamil should be avoided in patients with severe left ventricular dysfunction (e.g., 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 PRECAUTIONS: Drug Interactions.) Patients with milder ventricular dysfunction should, if possible, be controlled with optimum doses of digitalis and/or diuretics before verapamil treatment (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. The incidence of hypotension observed in 4,954 patients enrolled in clinical trials was 2.5%. 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 elevations 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 flutter or atrial fibrillation 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 lead to 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.

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 hydrochloride and institution of appropriate therapy depending upon the clinical situation.

Patients with Hypertrophic Cardiomyopathy (HCS): In 120 patients with hypertrophic cardiomyopathy (most of them refractory or intolerant to propranolol) who received therapy with verapamil at doses up to 170 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 (over 20 mm Hg) capillary wedge pressure and a marked left ventricular outflow obstruction were present in most of these patients. Concomitant administration of quinidine (see PRECAUTIONS: 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

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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 hydrochloride and institution of appropriate therapy depending upon the clinical situation.

Patients with Hypertrophic Cardiomyopathy (HSC): 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 (over 20 mm Hg) capillary wedge pressure and a marked left ventricular outflow obstruction were present in most of these patients. Concomitant administration of quinidine (see PRECAUTIONS: 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 have to be discontinued.

PRECAUTIONS: THE CONTENTS OF THE VERAPAMIL HYDROCHLORIDE EXTENDED-RELEASE CAPSULE SHOULD NOT BE CRUSHED OR CHEWED.

General 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. 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: When the sprinkle method of administration is pre-

scribed, details of the proper technique should be explained to the patient. (See DOSAGE AND ADMINISTRATION.)
Drug Interactions: 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 extended-release verapamil and beta-adrenergic blocking agents has not been studied. However, there have been reports of excess bradycardia and AV block, including complete heart block, when the combination has been used for the treatment of hypertension.

For hypertensive patients, the risk 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 clearance has been reported when verapamil and metoprolol were administered together. A similar effect has not been observed when verapamil and atenolol are given together.

Digitalis: Clinical use of verapamil in digitalized patients has shown the combination to be well tolerated if digoxin doses are properly adjusted. 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. Maintenance digitalis doses should be reduced when verapamil is administered, and the patient should be carefully monitored to avoid over- or underdigitalization. Whenever overdigitalization is suspected, the daily dose of digoxin should be reduced or temporarily discontinued. Upon discontinuation of verapamil hydrochloride, the patient should be reassessed to avoid underdigitalization.

Antihypertensive Agents: Verapamil administered concomitantly with oral antihypertensive agents (e.g., 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 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 phosphate are obtained, disopyramide should not be administered within 48 hours before or 74 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 (HCS), 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.

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

Alcohol: Verapamil has been found to significantly inhibit ethanol elimination resulting in elevated blood ethanol concentrations that may prolong the intoxicating effects of alcohol. (See CLINICAL PHARMACOLOGY: Pharmacokinetics and Metabolism.)

Other: Aspirin: In a few reported cases, coadministration of verapamil with aspirin has led to increased bleeding times greater than observed with aspirin alone.

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: Pharmacokinetic and pharmacodynamic interactions between oral verapamil and lithium have been reported. The former may result in a lowering of serum lithium levels in patients receiving chronic, stable oral lithium therapy. The latter may result in an increased sensitivity to the effects of 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.

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

Phenobarbital: Phenobarbital therapy may increase verapamil clearance.

Cyclosporine: Verapamil therapy may increase serum levels of cyclosporine.

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 antagonists, such as verapamil, should 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, and 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 per day or approximately 1x, 3.5x, and 12x, respectively, the maximum recommended human daily dose (480 mg per 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, Teratogenic Effects, 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 maximum recommended human 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 hydrochloride in Europe in the treatment of cardiac side effects of beta-adrenergic agonist agents used to treat premature labor.

Nursing Mothers: Verapamil is secreted 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 in pediatric patients below the age of 18 years have not been established.

Animal Pharmacology and/or Animal Toxicology: In chronic animal toxicology studies verapamil causes 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 the rat). Development of cataracts due to verapamil has not been reported in man.

ADVERSE REACTIONS: Serious adverse reactions are uncommon when verapamil hydrochloride 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, para-

mil hydrochloride 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.

In clinical trials involving 263 hypertensive patients on verapamil hydrochloride extended-release for greater than 1 week, the following adverse reactions were reported in greater than 1% of the patients:

Constipation	7.4%
Headache	5.3%
Dizziness	4.7%
Lethargy	3.2%
Dyspepsia	2.5%
Rash	1.4%
Ankle Edema	1.4%
Sleep Disturbance	1.4%
Myalgia	1.1%

In clinical trials of other formulations of verapamil hydrochloride (N=4,954) the following reactions have occurred at rates greater than 1%:

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

In clinical trials related to the control of ventricular response in digitalized patients who had atrial fibrillation or atrial flutter, ventricular rate below 50/min at rest occurred in 15% of patients and asymptomatic hypotension occurred in 15% of patients.

The following reactions, reported in 1% 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, stroke/vascular dissection, 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, paresthesia, psychotic symptoms, shakiness, somnolence.

Respiratory: dyspnea.

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

Special Senses: blurred vision, tinnitus.

Urogenital: gynecostasia, impotence, increased urination, spotty menstruation.

Treatment of Acute Cardiovascular Adverse Reactions: The frequency of cardiovascular adverse reactions which 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, e.g., intravenously administered isoproterenol hydrochloride, norepinephrine, atropine (all in the usual doses), or calcium gluconate (10% solution). In patients with hypertrophic cardiomyopathy (HCS), alpha-adrenergic agents (phenylephrine, metaraminol bitartrate or methoxamine) should be used to maintain blood pressure, and isoproterenol and levaterrenal should be avoided. If further support is necessary, inotropic agents (dopamine or dobutamine) may be administered. Actual treatment and dosage should depend on the severity and the clinical situation and the judgment and experience of the treating physician.

OVERDOSAGE: There is no specific antidote for verapamil overdosage; treatment should be supportive. Delayed pharmacodynamic consequences may occur with extended-release formulations, and patients should be observed for at least 48 hours, preferably under continuous hospital care. Reported effects include hypotension, bradycardia, cardiac conduction defects, arrhythmias, hyperglycemia, and decreased renal status. In addition, there have been literature reports of non-cardiogenic pulmonary edema in patients taking large overdoses of verapamil (up to approximately 9 g).

In acute overdosage, gastrointestinal decontamination with cathartics and whole bowel irrigation should be considered. Calcium,otropes (i.e., isoproterenol, dopamine, and glucagon), atropine, vasopressors (i.e., norepinephrine, and epinephrine), and cardiac pacing have been used with variable results to reverse hypotension and myocardial depression. In a few reported cases, overdose with calcium channel blockers that was initially refractory to atropine became more responsive to this treatment when the patients received large doses (close to 1 gram/hour for more than 24 hours) of calcium chloride. Calcium chloride is preferred to calcium gluconate since it provides 3 times more calcium per volume. Asystole should be handled by the usual measures including cardiopulmonary resuscitation. Verapamil should be given immediately

hours, preferably under continuous hospital care. Reported effects include hypotension, bradycardia, cardiac conduction defects, arrhythmias, hyperkalemia, and decreased mental status. In addition, there have been literature reports of non-cardiogenic pulmonary edema in patients taking large overdoses of verapamil (up to approximately 9 g).

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DOSE AND ADMINISTRATION: Essential Hypertension. The dose of verapamil hydrochloride extended-release should be individualized by titration. The usual daily dose of extended-release verapamil hydrochloride in clinical trials has been 240 mg given by mouth once daily in the morning. However, initial doses of 120 mg a day may be warranted in patients who may have an increased response to verapamil (e.g., elderly, small people, etc.). Upward titration should be based on therapeutic efficacy and safety evaluated approximately 24 hours after dosing. The antihypertensive effects of verapamil hydrochloride extended-release are evident within the first week of therapy.

If adequate response is not obtained with 120 mg of verapamil hydrochloride extended-release, the dose may be titrated upward in the following manner:

- (a) 180 mg in the morning.
- (b) 240 mg in the morning.
- (c) 360 mg in the morning.
- (d) 480 mg in the morning.

Verapamil extended-release capsules are for once-a-day administration. When switching from immediate-release verapamil to verapamil hydrochloride extended-release capsules, the same total daily dose of verapamil hydrochloride extended-release capsules can be used.

As with immediate-release verapamil, dosages of verapamil hydrochloride extended-release capsules should be individualized and titration may be needed in some patients.

Sprinkling the Capsule Contents on Food: Verapamil Hydrochloride Extended-release Bead Filled Capsules may also be administered by carefully opening the capsule and sprinkling the beads on a spoonful of applesauce. The applesauce should be swallowed immediately without chewing and followed with a glass of cool water to ensure complete swallowing of the beads. The applesauce used should not be hot, and it should be soft enough to be swallowed without chewing. Any bead/applesauce mixture should be used immediately and not stored for future use. Subdividing the contents of a verapamil hydrochloride extended-release capsule is not recommended.

HOW SUPPLIED: Verapamil Hydrochloride Extended-release Capsules, are available in 120 mg, 180 mg and 240 mg capsules.

The 120 mg capsule is an elongated capsule with a bluish green opaque cap and white opaque body that are radially printed with MYLAN over 6320 in black ink. They are available as follows:

- NDC 0378-6320-01 bottles of 100 capsules
- NDC 0378-6320-05 bottles of 500 capsules

The 180 mg capsule is an elongated capsule with a bluish green opaque cap and light green opaque body that are radially printed with MYLAN over 6380 in black ink. They are available as follows:

- NDC 0378-6380-01 bottles of 100 capsules
- NDC 0378-6380-05 bottles of 500 capsules

The 240 mg capsule is an elongated capsule with a bluish green opaque cap and bluish green opaque body that are radially printed with MYLAN over 6440 in black ink. They are available as follows:

- NDC 0378-6440-01 bottles of 100 capsules
- NDC 0378-6440-05 bottles of 500 capsules

STORE AT ROOM TEMPERATURE 15° to 25°C (59° to 77°F). Brief excursions above 25°C while not detrimental, should be avoided. **AVOID EXCESSIVE HEAT.** **PROTECT FROM MOISTURE.** Dispense in a light, light-resistant container as defined in the USP using a child-resistant closure.



Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

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