

PRODUCT MONOGRAPH

ISOPTIN[®]

(verapamil hydrochloride)

80 mg and 120 mg Tablets

Antianginal/Antiarrhythmic/Antihypertensive Agent

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NAME OF DRUG

ISOPTIN[®]
(verapamil hydrochloride)

80 mg and 120 mg Tablets

THERAPEUTIC CLASSIFICATION

Antianginal/Antiarrhythmic/Antihypertensive Agent

ACTION AND CLINICAL PHARMACOLOGY

Angina and Arrhythmia

ISOPTIN[®] (verapamil hydrochloride) is a calcium ion influx inhibitor (calcium entry blocker or calcium ion antagonist). The mechanism of the antianginal and antiarrhythmic effects of verapamil is believed to be related to its specific cellular action of selectively inhibiting transmembrane influx of calcium in cardiac muscle, coronary and systemic arteries and in cells of the intracardiac conduction system. Verapamil blocks the transmembrane influx of calcium through the slow channel (calcium ion antagonism) without affecting to any significant degree the transmembrane influx of sodium through the fast channel. This results in a reduction of free calcium ions available within cells of the above tissues.

Verapamil's antiarrhythmic effects are believed to be brought about largely by its action on the sinoatrial (S-A) and atrioventricular (A-V) nodes. Verapamil depresses A-V nodal conduction and prolongs functional refractory periods. Verapamil does not alter the normal atrial action potential or intraventricular conduction time, but depresses amplitude, velocity of depolarization and conduction in depressed atrial fibres. Through this action, it interrupts re-entrant pathways and slows the ventricular rate.

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 A-V pathway following administration of verapamil (see **WARNINGS - Conduction Disturbance**). Verapamil has a local anaesthetic action that is 1.6 times that of procaine on an equimolar basis.

Verapamil is a potent smooth muscle relaxant with vasodilatory properties, as well as a depressant of myocardial contractility, and these effects are largely independent of autonomic influences. Its antianginal action in exertional angina seems to result from a decrease in resistance in the systemic vasculature, as well as from a direct effect on myocardial contraction. The net pharmacologic effect

is a decrease in myocardial oxygen consumption. Verapamil's effectiveness in vasospastic angina is due to a decrease in coronary vascular tone.

Essential Hypertension

Verapamil exerts antihypertensive effects by inducing peripheral vasodilation and reducing peripheral vascular resistance usually without reflex tachycardia. Verapamil does not blunt hemodynamic response to isometric or dynamic exercise.

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Compared to baseline, verapamil does not affect electrolytes, glucose, and creatinine. The hypotensive effect of verapamil is not blunted by an increase in sodium intake.

In hypertensive normolipidemic patients, verapamil had no effects on plasma lipoprotein fractions.

Pharmacodynamics

In a study in five healthy males, the S enantiomer was found to be 8 to 20 times more active than the R enantiomer in slowing A-V conduction. In another study using septal strips isolated from the left ventricle of 5 patients with mitral disease, the S enantiomer was 8 times more potent than the R enantiomer in reducing myocardial contractility.

Pharmacokinetics

Verapamil hydrochloride is a racemic mixture consisting of equal portions of the R enantiomer and the S enantiomer. More than 90% of the orally administered dose of ISOPTIN is absorbed. Upon oral administration, there is rapid stereoselective biotransformation during the first pass of verapamil through the portal circulation. The systemic concentrations of R and S enantiomers are dependent upon the route and the rate of administration and the rate and extent of release from the dosage forms.

The following bioavailability information was obtained from healthy volunteers and not from the populations most likely to be treated with verapamil.

In a study in 5 healthy volunteers with oral immediate-release verapamil, the systemic bioavailability varied from 33 to 65% for the R enantiomer and from 13 to 34% for the S enantiomer. The

S enantiomer is pharmacologically more active than the R enantiomer (see **ACTION AND CLINICAL PHARMACOLOGY - Pharmacodynamics** and **PHARMACOLOGY**).

There is a nonlinear correlation between the verapamil dose administered and verapamil plasma levels. In early dose titration with verapamil, a relationship exists between total verapamil (R and S combined) plasma concentration and prolongation of the PR interval. The mean elimination half-life in single-dose studies of immediate release verapamil ranged from 2.8 to 7.4 hours. In these same studies, after steady state was reached, the half-life increased to a range from 4.5 to 12.0 hours (after less than 10 consecutive doses given 6 hours apart). Half-life of verapamil may increase during titration. Aging decreases the clearance and elimination of verapamil.

In healthy men, orally administered ISOPTIN undergoes extensive metabolism by the cytochrome P₄₅₀ system in the liver. The particular isoenzymes involved are CYP3A4, CYP1A2, and CYP2C family. Thirteen metabolites have been identified in urine. Norverapamil can reach steady-state plasma concentrations approximately equal to those of verapamil itself. 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. The degree of biotransformation during the first pass of verapamil may vary according to the status of the liver in different patient populations. In patients with hepatic insufficiency, metabolism is delayed and elimination half-life prolonged up to 14 to 16 hours (see **WARNINGS - Hepatic Insufficiency**, and **DOSAGE AND ADMINISTRATION**).

Verapamil crosses the placental barrier and can be detected in umbilical vein blood at delivery. Verapamil is excreted in human milk.

A study was conducted in which 240 mg single oral doses of ISOPTIN Standard Release (fasting) and ISOPTIN Sustained Release (fed) tablets were given to 12 young, healthy males (19 to 37 years old) in a randomized, crossover (7-day washout) study. Serial blood samples for drug determination were taken over a 48-hour period. The pharmacokinetic data from this study is summarized in the following table.

Parameter	ISOPTIN Standard Release Tablet (240 mg)		ISOPTIN Sustained Release Tablet (240 mg)	
	R-verapamil	S-verapamil	R-verapamil	S-verapamil
C _{max} , ng/mL	258	59.0	60.1	11.3
T _{max} , hr	1.46	1.58	10.8	11.8
AUC ₀₋₄₈ ng/mL/hr	1250	261	918	150

Influence of Food: Administration of ISOPTIN Tablets with food results in marked prolongation of T_{max} (45 to 75%) and slight decreases in C_{max} (about 15%) and AUC (1 to 8%). Food thus produces a slight decrease in bioavailability (AUC), but a narrower peak-to-trough ratio.

INDICATIONS AND CLINICAL USE

1. Chronic stable angina of effort.
2. Angina resulting from coronary artery spasm.
3. Obstructive hypertrophic cardiomyopathy, where surgery is not otherwise indicated.
4. Atrial fibrillation or flutter with rapid ventricular response not otherwise controllable with digitalis preparations.
5. Follow-up treatment to the use of injectable ISOPTIN® (verapamil hydrochloride) in paroxysmal supraventricular tachycardia.
6. ISOPTIN is indicated in the treatment of mild to moderate essential hypertension. ISOPTIN should normally be used in those patients in whom treatment with diuretics or beta blockers has been associated with unacceptable adverse effects.

ISOPTIN can be tried as an initial agent in those patients in whom the use of diuretics and/or beta blockers is contraindicated or in patients with medical conditions in which these drugs frequently cause serious adverse effects.

Combination of ISOPTIN with a diuretic has been found to be compatible and showed additive antihypertensive effect. Concomitant use of ISOPTIN® SR with an angiotensin converting enzyme inhibitor has been shown to be compatible and to have additive blood pressure lowering effects.

ISOPTIN should not be used concurrently with beta adrenoreceptor blockers in the treatment of hypertension (see **PRECAUTIONS - Drug Interactions**).

Safety of concurrent use of ISOPTIN with other antihypertensive agents has not been established and such use cannot be recommended at this time.

CONTRAINDICATIONS

1. Complicated myocardial infarction (patients who have ventricular failure manifested by pulmonary congestion).
2. Severe congestive heart failure and/or severe left ventricular dysfunction (i.e. ejection fraction <40%), unless secondary to a supraventricular tachycardia amenable to oral verapamil therapy.
3. Cardiogenic shock.
4. Severe hypotension.
5. Second- or third-degree A-V block.
6. Sick Sinus Syndrome (see **WARNINGS**).
7. Marked bradycardia.
8. Hypersensitivity to the drug.
9. Patients with atrial flutter or atrial fibrillation and an accessory bypass tract (e.g. Wolff-Parkinson-White, Lown-Ganong-Levine syndromes) (see **WARNINGS**).

WARNINGS

General

In patients with angina or arrhythmias using antihypertensive drugs, the additional hypotensive effect of ISOPTIN® (verapamil hydrochloride) should be taken into consideration.

Heart failure

Because of the drug's negative inotropic effect, verapamil hydrochloride should not be used in patients with poorly compensated congestive heart failure, unless the failure is complicated by or caused by a dysrhythmia. If verapamil is used in such patients, they must be digitalized prior to treatment. It has been reported that digoxin plasma levels may increase with chronic verapamil administration (see **PRECAUTIONS - Drug Interactions: Digoxin**). The use of verapamil in the treatment of hypertension is not recommended in patients with heart failure caused by systolic dysfunction.

Hypotension

Hypotensive symptoms of lethargy and weakness with faintness have been reported following single oral doses and even after some months of treatment. In some patients it may be necessary to reduce the dose.

Conduction Disturbance

Verapamil slows conduction across the A-V node and rarely may produce second or third degree A-V block, bradycardia and in extreme cases, asystole.

Verapamil causes dose-related suppression of the S-A node. In some patients, sinus bradycardia may occur, especially in patients with a sick sinus syndrome (S-A nodal disease), which is more common in older patients (see **CONTRAINDICATIONS**).

Bradycardia

The total incidence of bradycardia (ventricular rate less than 50 beats/min.) was 1.4% in controlled studies. Asystole in patients other than those with sick sinus syndrome is usually of short duration (few seconds or less), with spontaneous return to A-V nodal or normal sinus rhythm. If this does not occur promptly, appropriate treatment should be initiated immediately (see **SYMPTOMS AND TREATMENT OF OVERDOSAGE**).

Accessory Bypass Tract (Wolff-Parkinson-White or Lown-Ganong-Levine)

Verapamil may result in significant acceleration of ventricular response during atrial fibrillation or atrial flutter in the Wolff-Parkinson-White (WPW) or Lown-Ganong-Levine syndromes after receiving intravenous verapamil. 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**).

Concomitant Use with Beta Blockers

Generally, oral verapamil should not be given to patients receiving beta blockers since the depressant effects on myocardial contractility, heart rate and A-V conduction may be additive. However, in exceptional cases when, in the opinion of the physician, concomitant use in angina and arrhythmias is considered essential, such use should be instituted gradually under careful supervision. If combined therapy is used, close surveillance of vital signs and clinical status should be carried out and the need for continued concomitant treatment periodically assessed.

Verapamil gives no protection against the dangers of abrupt beta blocker withdrawal and such withdrawal should be done by the gradual reduction of the dose of beta blocker. Then verapamil may be started with the usual dose.

Patients with Hypertrophic Cardiomyopathy

In 120 patients with hypertrophic cardiomyopathy who received therapy with verapamil at doses up to 720 mg/day, a variety of serious adverse effects was 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 **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 A-V 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, but in some cases, verapamil use had to be discontinued.

Elevated Liver Enzymes

Elevation of transaminase with and without concomitant elevations in alkaline phosphatase and bilirubin have been reported. Several published cases of hepatocellular injury produced by verapamil have been proven by rechallenge. Clinical symptoms of malaise, fever, and/or right upper quadrant pain, in addition to elevation of SGOT, SGPT and alkaline phosphatase have been reported. Periodic monitoring of liver function in patients receiving verapamil is therefore prudent.

Hepatic Insufficiency

Because verapamil is extensively metabolized by the liver, it should be administered cautiously to patients with impaired hepatic function, since the elimination half-life of verapamil in these patients is prolonged 4-fold (from 3.7 to 14.2 hours). A decreased dosage should be used in patients with hepatic insufficiency and careful monitoring for abnormal prolongation of the PR interval or other signs of excessive pharmacologic effect should be carried out (see **ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics**, and **DOSAGE AND ADMINISTRATION**).

Renal Insufficiency

About 70% of an administered dose of verapamil is excreted as metabolites in the urine. In one study in healthy volunteers, the total body clearance after intravenous administration of verapamil was 12.08 mL/min/kg, while in patients with advanced renal disease it was reduced to 5.33 mL/min/kg. This pharmacokinetic finding suggests that renal clearance of verapamil in patients with renal disease is decreased. In two studies with oral verapamil no difference in pharmacokinetics could be demonstrated.

Therefore, until further data are available, verapamil should be used with caution in patients with impaired renal function. These patients should be carefully monitored for abnormal prolongation of the PR interval or other signs of excessive pharmacologic effect (see **DOSAGE AND ADMINISTRATION**).

PRECAUTIONS

A typical lens changes and cataracts were observed in beagle dog studies at high doses. This has been concluded to be species-specific for the beagle dog. (These ophthalmological changes were not seen in a second study.) No similar changes have been observed in long-term prospective human ophthalmological trials.

ISOPTIN® (verapamil hydrochloride) does not alter total serum calcium levels. However, one report suggested that calcium levels above the normal range may decrease the therapeutic effect of verapamil.

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 The Elderly

Caution should be exercised when verapamil is administered to elderly patients (>65 years) especially those prone to developing hypotension or those with a history of cerebrovascular insufficiency (see **DOSAGE AND ADMINISTRATION, ACTIONS AND CLINICAL PHARMACOLOGY - Pharmacokinetics**). The incidence of adverse reactions is approximately 4% higher in the elderly. The adverse reactions occurring more frequently include dizziness and constipation. Serious adverse events associated with heart block have occurred in the elderly.

Pregnancy

Teratology and 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 or impaired fertility. In 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 studies in pregnant women. However, verapamil crosses the placental barrier and can be detected in umbilical vein blood at delivery. ISOPTIN is not recommended for use in pregnant women unless the potential benefits outweigh potential risks to mother and fetus.

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.

Use in 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.

Use in Children

The safety and dosage regimen of verapamil in children has not yet been established.

Interaction with Grapefruit Juice

Grapefruit juice may increase the plasma levels of verapamil hydrochloride.

Drug Interactions

As with all drugs, care should be exercised when treating patients with multiple medications. Calcium channel blockers undergo biotransformation by the cytochrome P₄₅₀ system. Coadministration of verapamil with other drugs which follow the same route of biotransformation may result in altered bioavailability of verapamil or these drugs. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio, and especially in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered verapamil to maintain optimum therapeutic blood levels.

Drugs known to be inhibitors of the cytochrome P₄₅₀ system include: azole antifungals, cimetidine, cyclosporine, erythromycin, quinidine, terfenadine, warfarin.

Drugs known to be inducers of the cytochrome P₄₅₀ system include: phenobarbital, phenytoin, rifampin.

Drugs known to be biotransformed via P₄₅₀ include: benzodiazepines, flecainide, imipramine, propafenone, theophylline.

Acetylsalicylic Acid

Potential adverse reactions in terms of bleeding due to synergistic antiplatelet effects of the two agents should be taken into consideration in patients taking acetylsalicylic acid and verapamil concomitantly.

Alcohol

Verapamil may increase blood alcohol concentrations and prolong its effects.

Anti-neoplastic agents

Verapamil inhibits P-glycoprotein mediated transport of anti-neoplastic agents out of tumour cells, resulting in their decreased metabolic clearance. Dosage adjustments of anti-neoplastic agents should be considered when verapamil is administered concomitantly.

Antihypertensive Agents

Verapamil administered concomitantly with other antihypertensive agents such as vasodilators, ACE inhibitors, and diuretics may have an additive effect on lowering blood pressure. In patients with angina or arrhythmias using antihypertensive drugs, this additional hypotensive effect should be taken into consideration. Verapamil should not be combined with beta blockers for the treatment of hypertension. Concomitant use of verapamil and alpha- adrenoreceptor blockers may result in excessive fall in blood pressure in some patients as observed in one study following the concomitant administration of verapamil and prazosin.

Beta-Adrenergic Blockers

The concomitant administration of verapamil with beta blockers can result in severe adverse effects (see **WARNINGS**).

Carbamazepine

The concomitant oral administration of verapamil and carbamazepine may potentiate the effects of carbamazepine neurotoxicity. Symptoms include nausea, diplopia, headache, ataxia or dizziness.

Cimetidine

Two clinical trials have shown a lack of significant verapamil interaction with cimetidine. A third study showed cimetidine reduced verapamil clearance and increased elimination $t_{1/2}$.

Cyclosporine

Verapamil therapy may increase serum levels of cyclosporine.

Digoxin

Verapamil treatment increases 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- or 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.

Diuretics

No cardiovascular adverse effects have been attributed to any interaction between these agents and verapamil.

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, A-V conduction and repolarization. Concomitant therapy with flecainide and verapamil may result in additive negative inotropic effect and prolongation of atrioventricular conduction.

Inhalation Anaesthetics

When used concomitantly, inhalation anaesthetics and calcium antagonists, such as verapamil, should be titrated carefully because additive hemodynamic depressive effects have been observed.

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.

Midazolam

Concomitant administration of midazolam and verapamil increased plasma levels of midazolam.

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.

Nitrates

No cardiovascular adverse effects have been attributed to any interaction between these agents and verapamil.

Phenobarbital

Phenobarbital therapy may increase verapamil clearance.

Prazosin

Concomitant administration of prazosin and verapamil increased plasma levels of prazosin.

Quinidine

In a small number of patients with hypertrophic cardiomyopathy, 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 A-V conduction were studied in 8 patients. Verapamil significantly counteracted the effects of quinidine on A-V conduction. There has been a report of increased quinidine levels during verapamil therapy.

Rifampin

Therapy with rifampin may markedly reduce oral verapamil bioavailability.

Simvastatin/lovastatin

Concomitant use of simvastatin/lovastatin with verapamil hydrochloride may increase the serum levels of simvastatin or lovastatin.

Sulfinpyrazone

Increased clearance and decreased bioavailability of verapamil may occur.

Theophylline

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

ADVERSE REACTIONS

In 4,826 patients treated with ISOPTIN® (verapamil hydrochloride) immediate release tablets for arrhythmias, angina or hypertension, the overall adverse reaction rate in these patients was 37.1% and the dropout rate was 10.2%. The majority of these patients were seriously ill and treated under emergency drug regulations.

The most common adverse reactions were: constipation (7.3%), dizziness (3.2%), and nausea (2.7%). In hypertension studies, constipation occurred in 18.5% of patients on ISOPTIN and 4.7% of patients on ISOPTIN SR (sustained- release verapamil hydrochloride).

The most serious adverse reactions reported with verapamil are heart failure (1.8%), hypotension (2.5%), A-V block (1.2%) and rapid ventricular response (see **WARNINGS**).

The following adverse reactions divided by body system have been reported in clinical trials or marketing experience. When incidences are shown, they are calculated based on the 4,954 (4,826 + 128) patient base.

Cardiovascular

Hypotension	2.5%
Edema	2.1%
CHF/Pulmonary Edema	1.9%
Bradycardia	1.4%
A-V Block	
Total (1°,2°,3°)	1.2%
2° and 3°	0.8%

Central Nervous System

Dizziness	3.2%
Headache	2.2%
Fatigue	1.7%

Gastrointestinal

Constipation	7.3%
Nausea	2.7%

The following reactions were reported in 1.0% or less of patients:

Cardiovascular

Flushing, angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura, syncope, severe tachycardia, developing or worsening of heart failure, development of rhythm disturbances, ventricular dysrhythmias, painful coldness and numbness of extremities.

Central Nervous System

Cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, excitation, depression, rotary nystagmus, vertigo, tremor, extrapyramidal disorders, muscle fatigue, hyperkinesia.

Gastrointestinal

Abdominal discomfort, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, vomiting.

Respiratory

Dyspnea, bronchospasm.

Urogenital

Gynecomastia, increased frequency of urination, spotty menstruation, oligomenorrhea, impotence.

Hematologic and Lymphatic

Ecchymosis or bruising.

Skin

Arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, pruritis.

Special Senses

Blurred vision, diplopia

Hepatotoxicity with elevated enzymes (SGOT, SGPT, alkaline phosphatase) and bilirubin levels, jaundice and associated symptoms of hepatitis with cholestasis have been reported (see **WARNINGS**).

Isolated cases of angioedema have been reported. Angioedema may be accompanied by breathing difficulty.

In clinical trials related to the control of ventricular response in digitalized patients who had atrial fibrillation or flutter, ventricular rates below 50 at rest occurred in 15% of patients and asymptomatic hypotension occurred in 5% of patients.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Based on reports of intentional overdosage of ISOPTIN® (verapamil hydrochloride), the following symptoms have been observed. Hypotension occurs, varying from transient to severe. Conduction disturbances seen included: prolongation of A-V conduction time, A-V dissociation, nodal rhythm, ventricular fibrillation and ventricular asystole.

Treatment of overdosage should be supportive. Gastric lavage should be undertaken even later than 12 hours after ingestion, if no gastrointestinal motility is present. Beta-adrenergic stimulation or parenteral administration of calcium solutions may increase calcium ion influx across the slow channel. These pharmacologic interventions have been effectively used in treatment of overdosage with verapamil. Clinically significant hypotensive reactions should be treated with vasopressor agents. A-V block is treated with atropine and cardiac pacing. Asystole should be handled by the usual Advanced Cardiac Life Support measures including the use of vasopressor agents, e.g. isoproterenol hydrochloride. Verapamil is not removed by hemodialysis.

Suggested Treatment of Acute Cardiovascular Adverse Reactions

Actual treatment and dosage should depend on the severity of the clinical situation and the judgement of the treating physician. Patients with hypertrophic cardiomyopathy treated with verapamil should not be administered positive inotropic agents. (Marked by asterisks.)

Adverse Reaction	Proven Effective Treatment	Treatment with Good Theoretical Rationale	Supportive Treatment
Shock, cardiac failure, severe hypotension	Calcium salt e.g. calcium gluconate i.v.; i.v. metaraminol bitartrate*	i.v. dopamine HCl*; i.v. dobutamine HCl*	i.v. fluids; Trendelenburg position
Bradycardia, A-V block, asystole	i.v. isoproterenol HCl*; i.v. atropine sulphate; Cardiac pacing		i.v. fluids (slow drip)

Adverse Reaction	Proven Effective Treatment	Treatment with Good Theoretical Rationale	Supportive Treatment
Rapid ventricular rate (due to antegrade conduction in flutter/fibrillation with W-P-W or L-G-L syndrome)	D.C. cardiovascular (high energy may be required); i.v. procainamide; i.v. lidocaine HCl		i.v. fluids (slow drip)

DOSAGE AND ADMINISTRATION

ISOPTIN® (verapamil hydrochloride) should be taken with food (see **ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics: Influence of Food**).

Angina Pectoris

Usual starting dose of ISOPTIN Tablets in adults is 80 mg 3 to 4 times daily. This may be increased to 120 mg 3 to 4 times daily until optimum response is obtained. The dose should not be increased beyond 480 mg/day. In some cases the dose may be decreased following clinical improvement.

Obstructive Hypertrophic Cardiomyopathy

Usual starting dose is 80 to 120 mg 3 to 4 times daily, and occasionally patients may require doses up to 600 to 720 mg/day.

Paroxysmal Supraventricular Tachycardia

Oral treatment should replace intravenous therapy as soon as possible. It can be administered in adults in the same dosage schedule as for angina pectoris. Duration of treatment will depend on the underlying cause and history of recurrence. At this time there is insufficient data to establish a safe and effective oral dose for children.

Atrial Fibrillation and Flutter with Rapid Ventricular Response

ISOPTIN Tablets may be administered to adults not completely controlled with digitalis preparations. The same dosage as for angina pectoris can be used but the physician should be aware that digoxin plasma levels may increase with verapamil administration and downward adjustment of the digoxin dose may be necessary (see **PRECAUTIONS - Drug Interactions**).

Mild to Moderate Essential Hypertension

The dosage should be individualized by titration depending on patient tolerance and responsiveness to verapamil.

The usual initial adult dose is 80 mg three times a day. If required, the dose may be increased up to 160 mg three times a day. A maximum daily dose of 480 mg should not be exceeded.

The antihypertensive effects of ISOPTIN Tablets are evident within the first week of therapy. Optimal doses are usually lower in patients also receiving diuretics since additive antihypertensive effects can be expected.

Elderly

Lower dosage may be warranted in elderly patients (> 65 years) (see **PRECAUTIONS - Use in Elderly**). The dosage should be carefully and gradually adjusted depending on patient tolerability and response. Consideration can be given to beginning titration using one ISOPTIN SR (verapamil hydrochloride sustained-release) 120 mg tablet once a day since no suitable strength of standard tablet is available.

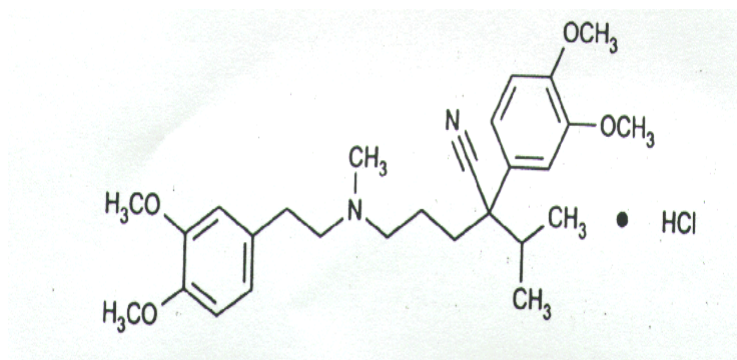
Patients with impaired hepatic and renal function

ISOPTIN Tablets should be administered cautiously to patients with liver or renal function impairment. The dosage should be carefully and gradually adjusted depending on patient tolerance and response. These patients should be monitored carefully for abnormal prolongation of the PR interval or other signs of overdose. At this time, ISOPTIN Tablets should not be used in patients with severe hepatic dysfunction (see **WARNINGS - Hepatic Insufficiency**).

PHARMACEUTICAL INFORMATION

Drug Substance

Structural Formula:



Molecular Formula: $C_{27}H_{38}N_2O_4 \cdot HCl$

Molecular Weight: 491.08

Chemical Name: "-isopropyl-" -[(N-methyl-N-homoveratryl)-(-aminopropyl)] - 3,4-dimethoxyphenylacetonitrile hydrochloride.

Description: Verapamil, as the hydrochloride, is an almost white, bitter-tasting crystalline powder practically free from odour and readily soluble in chloroform and water (1 part in 20), but sparingly soluble in ethanol and practically insoluble in ether. It melts at 140°C and should be protected from light.

Composition: Calcium hydrogen phosphate, colloidal anhydrous silica, croscarmellose sodium, magnesium stearate, methylhydroxypropyl cellulose, microcrystalline cellulose, polyethylene glycol 6000, sodium lauryl sulfate, talc, titanium dioxide.

Recommended Storage Conditions: Store between 15° - 30°C.

AVAILABILITY OF DOSAGE FORMS*

ISOPTIN® 80 mg TABLETS

Each white, biconvex, film coated tablet embossed with "Isoptin 80" on the front and "Knoll" above the score on the back contains 80 mg of verapamil hydrochloride. Non-medicinal ingredients: Calcium hydrogen phosphate, colloidal anhydrous silica, croscarmellose sodium, macrogol 6000, magnesium stearate, methylhydroxypropylcellulose, microcrystalline cellulose, sodium lauryl sulfate, talc, titanium dioxide. Available in bottles of 250.

ISOPTIN® 120 mg TABLETS

Each white, biconvex coated film coated tablet embossed with "Isoptin 120" on the front and "Knoll" above the score on the back contains 120 mg of verapamil hydrochloride. Non-medicinal ingredients: Calcium hydrogen phosphate, colloidal anhydrous silica, croscarmellose sodium, macrogol 6000, magnesium stearate, methylhydroxypropyl-cellulose, microcrystalline cellulose, sodium lauryl sulfate, talc, titanium dioxide. Available in bottles of 250.

*ISOPTIN INJECTABLE and ISOPTIN SR (SUSTAINED-RELEASE) TABLETS are available from Abbott Laboratories, Limited.

PHARMACOLOGY

Verapamil hydrochloride was initially investigated in experimental animals as a smooth muscle relaxant, with vasodilator properties. Subsequent studies have demonstrated that verapamil hydrochloride has significant antiarrhythmic effects when tested in a variety of experimental arrhythmias. The mechanism of action of verapamil hydrochloride seems to be the blocking of transmembrane influx of calcium through the slow channels, without affecting to any significant degree, transmembrane influx of sodium through the fast channels. It does not directly modify calcium uptake, binding or exchange by cardiac microsomes. Its main locus of action seems to be the superficially located membrane storage sites for calcium.

In isolated cardiac tissues, at low to moderate concentrations, verapamil hydrochloride exerts little or no effect on action potential amplitude, but suppresses activity in the sinoatrial (S-A) and atrioventricular (A-V) nodes. Any activity within the S-A and A-V nodes seems to be particularly sensitive to the suppressant effects of verapamil hydrochloride because normal impulse formation in the sinus node and conduction in the A-V node appear to be maintained by operation of slow channel mechanisms. The depressant effects exerted by verapamil hydrochloride on A-V nodal conduction may in part explain its effectiveness in treating supraventricular tachycardia.

Verapamil hydrochloride has a marked negative inotropic effect on isolated cardiac muscle. In intact animals, the depressant effect on cardiac output and stroke volume is dose-dependent.

Although verapamil hydrochloride has local anaesthetic properties, in clinically relevant doses it does not affect the rate of either the depolarization or the repolarization phase of the cardiac action potential. Verapamil hydrochloride does not have beta-blocking properties, although it antagonizes beta-adrenergic influences on the heart by a functional antagonism, due to its basic pharmacodynamic properties at the level of the conduction system and the myocardium.

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.

TOXICOLOGY

Acute Toxicity

	LD₅₀ (mg/kg)			
	I.V.	IP	SC	oral
Rat	16	67	107	114
Mouse	8	68	68	163
Guinea Pig	-	-	-	140
Juvenile Rat	-	-	-	93 (M)
	-	-	-	113 (F)
Juvenile Rabbit	-	-	-	114.2 (M)
	-	-	-	129.8 (F)

Symptoms preceding death were similar in both sexes with marked sedation, decreased excitability, forced respirations, clonic spasms and convulsions.

Subacute Toxicity

Oral Studies

Verapamil was administered orally in doses of 12.5, 25 and 50 mg/kg per day, to rats via food for 14 weeks (29 animals/group) and to dogs for 6 days/week in capsules, for 15 to 16 weeks (4 animals/ group). Baboons received 2, 4, 8, 16, 32 and 64 mg/kg by mouth daily for 4 weeks (2 animals/group).

In rats, a dose-related increase in heart and lung weights was found. Dogs given 25 to 50 mg/kg showed slight weight loss and a significant reduction in heart rate up to week 11, followed by a gradual return to normal. In one dog on 12.5 mg/kg, one on 25 mg/kg and in all animals on 50 mg/kg, there was emesis during the first two weeks of the study. SGPT was elevated for one dog on 25 mg/kg at week 9 and for two animals on 50 mg/kg at the end of the test. Macroscopic examinations at necropsy were negative and there was no drug-attributable histological changes. The baboons showed no drug-related changes.

Intramuscular Studies

Beagle dogs were given 0, 2 and 10 mg/kg, 5 days/week for 30 days (4 animals/group). Injection sites in all animals became edematous and a dose-related reduction in heart rate was observed. At 10 mg/kg, hemoglobin and hematocrit values decreased and one animal had a raised SGPT. At necropsy, edema was noted at injection sites and higher spleen weights were recorded on the 10 mg/kg dose. One dog on this dose also showed increased inflammatory cell infiltration in the liver, with some hepatic cell degenerative changes.

Intravenous Studies

Verapamil was given to Sprague-Dawley rats at 0.2, 1 and 5.0 mg/kg once daily for 4 weeks (30 animals/group) and similarly to beagle dogs at 0.1, 0.4 and 1.6 mg/kg levels (6 animals/group).

At the highest dose level, all dogs showed some restlessness, salivation and laboured breathing, along with delayed A-V conduction in one-half of the animals. In 4 of 6 animals at this highest dose (1.6 mg/kg) sporadic small focal gatherings of Kupffer cells, with death of individual liver cells (necrobioses and/or necrosis of hepatocytes) were found histopathologically.

Chronic Toxicity

Oral

Rats were given verapamil at 10, 15, 25, 30, 60 and 62.5 mg/kg/day (50 animals/group) and beagle dogs at 10, 15, 25, 30, 40, 60, 62.5, 70, 81 and 85 mg/kg (6 animals/group) for 12 and 18 months. Clinical signs were observed and changes in food consumption, consistency of stools, hemograms, clinical chemistry and urinalyses performed. Blood pressure, ECG and ophthalmoscopic examinations were done on the dogs.

In one 18-month rat study, an increase in weight of the thyroid glands in females on the 62.5 mg dose was noted. In a later 12-month study, a slight reduction in weight gain was recorded.

In dogs, at doses of 60 mg and greater, toxic signs such as vomiting, salivation, reversible hyperplasia of the gums, reduced food consumption, slight weight loss and a transitory, slight to moderate elevation of SGPT were noted and three of the animals died. The 40 mg dose caused loss of coat colour and hair, and a delay in A-V conduction.

In another study, atypical lens changes (cataracts) were observed in 8 beagles receiving toxic dose levels (62.5 and 70 mg/kg). In a later study, 4 beagles were given 81 mg/kg for 18 months and none developed cataracts. It was concluded that any changes caused by verapamil in lens transparency are specific to the beagle. This is supported by the absence of similar lesions in other species studied, and by the apparent lack of any impairment by verapamil of carbohydrate or energy metabolism in lenticular tissue. The water-soluble proteins of the canine lens are known to have differences from those in other species.

Mutagenicity

In vitro mutagenicity tests showed that verapamil did not have mutagenic properties in five different strains of *Salmonella typhimurium*, nor in studies on chromosomal aberrations and sister chromatid exchanges (SCE) in human lymphocytes, nor in the HGPRT-test with V-79 Chinese hamster cells, and also not in the cell transformation assay with Syrian hamster embryo cells. Neither did verapamil show any SCE-inducing activity *in vivo* (Chinese hamster).

Carcinogenicity

In a 24-month carcinogenicity study, verapamil hydrochloride was administered orally to 50 male and 50 female rats in the diet as actual mean doses of 9.3/9.5, 32.6/33.2, and 112.2/102.5 mg/kg/day, respectively. Two hundred animals served as controls.

Drug-related significant reductions in body weight and mortality were seen in males and females of the high dose group.

Dose-related cardiac lesions (dilatation, atrial thrombi and myocardial metaplasia, combined with hydrothorax) were seen in the high dose group. These cardiac lesions are considered to be related to a chronic, exaggerated pharmacologic effect at this high dose level.

At the end of the study, all rats were examined histopathologically with regards to tumorigenesis. All non-neoplastic and neoplastic lesions were considered to reflect the spectrum of spontaneous lesions commonly encountered in rats of this age and strain. As compared to the controls, the type and incidence of these lesions were not increased in treated rats.

Reproduction

Studies were carried out in rats and rabbits with verapamil given in food and/or by gastric tube. These studies included fertility and general reproduction performance in rats, teratogenicity studies in rats and rabbits and peri- and postnatal studies in rats. Rats were given 2.5, 12.5, 25 and 100 mg/kg body weight, by gastric tube and 1.3, 1.6, 5.2, 7.5, 13.3, 16 and 55 mg/kg body weight in food. In another teratogenicity study, rats were given 5, 10, and 20 mg/kg body weight by gavage three times daily at an interval of about 4.5 hours. Rabbits were given 5 and 15 mg/kg body weight by gastric tube.

There was no evidence of teratogenicity in either species and no embryotoxic effects observed in the rats dosed via food, or with doses up to 12.5 mg/kg body weight given by gastric tube, or with doses up to 10 mg/kg t.i.d. The single daily dose of 25 mg/kg body weight or more, caused a higher resorption rate in the rat. The dose of 20 mg/kg t.i.d. 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 was no difference in resorption rates observed in the rabbit and no effect on peri- and postnatal development or fertility in the rat.

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