PRODUCT MONOGRAPH

PrAPO-VERAP SR

Verapamil Hydrochloride Sustained - Release Tablets

120 mg, 180 mg, and 240 mg

Apotex Standard

Antihypertensive Agent

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PrAPO-VERAP SR
Verapamil Hydrochloride Sustained - Release Tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage form/Strength	All Non-Medicinal Ingredients
oral	sustained-release tablets/120 mg, 180 mg, 240 mg	carnauba wax, colloidal silicon dioxide, hydroxyethyl cellulose, magnesium stearate, polyethylene glycol, sodium alginate, and titanium dioxide. The 180 mg tablet also contains the non-medicinal ingredient ferric oxide red. The 240 mg tablet also contains the non-medicianl ingredient ferric oxide yellow and brilliant blue FCF AL lake (240 mg) This is a complete listing of all Non-medicinal ingredients.

INDICATIONS AND CLINICAL USE

APO-VERAP SR (verapamil hydrochloride) sustained-release tablets is indicated for:

- the treatment of mild to moderate essential hypertension. APO-VERAP SR should normally be used in those patients in whom treatment with diuretics or beta-blockers has been associated with unacceptable adverse effects.

APO-VERAP SR 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.

Concomitant use of APO-VERAP SR with a diuretic or an angiotensin converting enzyme (ACE) inhibitor has been shown to be compatible and to have additive blood pressure lowering effects.

APO-VERAP SR should not be used concurrently with beta-adrenoreceptor blockers in the treatment of hypertension. See (**DRUG INTERACTIONS, Table 2**).

Geriatrics (≥65 years of age):

Caution should be exercised when APO-VERAP SR is administered to elderly patients. See [**WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics (≥ 65 years of age)**].

Pediatrics (< 18 years of age):

The safety and efficacy of APO-VERAP SR has not been established in children and therefore use in this age group is not recommended.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS**, **COMPOSITION AND PACKAGING** section of the Product Monograph.
- Complicated myocardial infarction (patients who have ventricular failure manifested by pulmonary congestion).
- Severe left ventricular dysfunction. See (**WARNINGS AND PRECAUTIONS, Cardiovascular, Heart Failure).**
- Cardiogenic shock.
- Severe hypotension.
- Second- or third-degree atrioventricular. (A-V) block.
- Sick Sinus Syndrome. See (**WARNINGS AND PRECAUTIONS**, **Cardiovascular, Conduction Disturbance**).
- Marked bradycardia.
- Patients with atrial flutter or atrial fibrillation in the presence of an accessory bypass tract (e.g. Wolff-Parkinson-White, Lown-Ganong-Levine syndromes). These patients are at risk to develop ventricular arrhythmias including ventricular fibrillation and Torsade de pointes if verapamil hydrochloride is administered. See (**WARNINGS AND PRECAUTIONS**, **Cardiovascular**, **Accessory Bypass Tract**).

WARNINGS AND PRECAUTIONS

General

In patients with angina or arrhythmias using antihypertensive drugs, the additional hypotensive effect of verapamil hydrochloridesustained-release tablets should be taken into consideration.

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 hydrochloride.

Carcinogenesis and Mutagenesis

There was no evidence of a carcinogenic effect when verapamil hydrochloride was administered orally (diet) to male and female rats at doses up to 112.2 and 102.5 mg/kg/day, respectively, for 24 months.

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 hypoxanthine guanine phosphoribosyltransferase (HGPRT)-test with V-79 Chinese hamster cells, and also not in the cell transformation assay with Syrian hamster embryo cells. In addition, verapamil did not show any SCE-inducing activity *in vivo* (Chinese hamster). See (**TOXICOLOGY, Carcinogenicity and Mutagenicity)**.

Cardiovascular

Heart Failure

Because of the drug's negative inotropic effect, verapamil hydrochloride should not be used in patients with poorly compensated congestive heart failure

Heart failure patients with ejection fraction higher than 40% should be treated with adequate doses of digoxin and/or diuretics before starting verapamil hydrochloride SR treatment.

If verapamil hydrochloride administered concomitantly with digoxin, reduce digoxin dosage. See (**DRUG INTERACTIONS, Table 2**). The use of verapamil hydrochloride 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 of verapamil hydrochloride.

Conduction Disturbance

Verapamil hydrochloride affects the A-V and sinoatrial (S-A) nodes. verapamil hydrochloride slows conduction across the A-V node. APO-VERAP SR should be used with caution in the presence of first degree A-V block. Patients with first degree A-V block may progress to second or third-degree A-V block; they require a reduction in the dose or discontinuation of verapamil hydrochloride, and the institution of appropriate therapy depending upon the patient's clinical condition.

Verapamil hydrochloride causes dose-related suppression of the S-A node and rarely may produce second or third degree A-V block, bradycardia and in extreme cases, asystole. 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**). 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 (**ADVERSE REACTIONS**) and (**OVERDOSAGE)**.

Bradycardia
The total incidence of bradycardia (ventricular rate less than 50 beats/minute) was 1.4% in controlled studies.

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

Verapamil hydrochloride may result in significant acceleration of ventricular response during atrial fibrillation or atrial flutter in the Wolff-Parkinson-White (WPW) or Lown-Ganong-Levine (LGL) syndromes.The use of verapamil hydrochloride in these patients is contraindicated. See (**CONTRAINDICATIONS**).

Concomitant Use with Antiarrhythmics or Beta Blockers

Concomitant use of verapamil hydrochloride with antiarrhythmics or beta-blockers may cause mutual potentiation of cardiovascular effects (higher-grade AV block, higher-grade lowering of heart rate, induction of heart failure and potentiated hypotension). Asymptomatic bradycardia (< 36 beats/minute) with a wandering atrial pacemaker has been observed in a patient receiving concomitant timolol (a beta-adrenergic blocker) eye drops and oral verapamil hydrochloride. See (**DRUG INTERACTIONS, Table 2**).

Generally, oral verapamil hydrochloride 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 hydrochloride 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 hydrochloride may be started with the usual dose.

Concomitant Use with HMG-CoA Reductase Inhibitors ("Statins")

Concomitant use of verapamil hydrochloride and HMG-CoA reductase inhibitors may require dosage adjustments. See (**DRUG INTERACTIONS, Table 2**).

Patients with Hypertrophic Cardiomyopathy
In 120 patients with hypertrophic cardiomyopathy who received therapy with verapamil hydrochloride 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 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 hydrochloride use had to be discontinued.

Hepatic/Biliary/Pancreatic

Elevated Liver Enzymes

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

Hepatic Insufficiency

Because verapamil hydrochloride is extensively metabolized by the liver, it should be administered cautiously to patients with impaired hepatic function, since the elimination half-life of verapamil hydrochloride 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**).

Neurologic

Neuromuscular Transmission Disorders

Due to verapamil hydrochloride neuromuscular blocking action, verapamil hydrochloride should be used with caution in the presence of diseases in which neuromuscular transmission is affected (myasthenia gravis, Lambert-Eaton syndrome, advanced Duchenne muscular dystrophy). The decision to administer verapamil hydrochloride should be based on the physician's assessment of the risk and benefit to the patient. It may be necessary to decrease the dose. Ventilation support should be available if required. See (**DRUG INTERACTIONS, Drug-Drug Interaction, Use in Patients with Attenuated (Decreased) Neuromuscular Transmission**).

Ophthalmologic

Atypical 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.

Renal

Renal Insufficiency

About 70% of an administered dose of verapamil hydrochloride is excreted as metabolites in the urine. In one study in healthy volunteers, the total body clearance after intravenous administration of verapamil hydrochloride 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 hydrochloride in patients with renal disease is decreased. In two studies with oral verapamil hydrochloride no difference in pharmacokinetics could be demonstrated. Therefore, until further data are available, verapamil hydrochloride 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**).

Verapamil hydrochloride is not removed by hemodialysis.

Special Populations

Pregnant Women

There are no studies in pregnant women. However, verapamil hydrochloride crosses the placental barrier and can be detected in umbilical vein blood at delivery. APO-VERAP SR (verapamil hydrochloride) is not recommended for use in pregnant women unless the potential benefits outweigh potential risks to mother and fetus.

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.

Labour and Delivery-- It is not known whether the use of verapamil hydrochloride during labour or delivery has immediate or delayed adverse effects on the fetus, or whether it prolongs the duration of labour or increases the need for forceps delivery or other obstetric intervention.

Nursing Women

Verapamil hydrochloride is excreted in human breast milk. Because of the potential for adverse reactions in nursing infants from verapamil hydrochloride, nursing should be discontinued while APO-VERAP SR is administered.

Pediatrics (< 18 years of age)

The safety and dosage regimen of APO-VERAP SR in children below the age of 18 years has not yet been established. Therefore, use in this group is not recommended.

Geriatrics (≥65 years of age)

Caution should be exercised when verapamil hydrochloride 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**,). 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.

Monitoring and Laboratory Tests

Patients should be monitored by measuring the blood pressure response.

Concomitant Use with Beta-Blockers

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.

Elevated Liver Enzymes

Periodic monitoring of liver function in patients receiving verapamil hydrochloride is prudent.

Hepatic Insufficiency

Careful monitoring for abnormal prolongation of the PR interval or other signs of excessive pharmacologic effect should be carried out.

Renal Insufficiency

Patients with renal insufficiency should be carefully monitored for abnormal prolongation of the PR interval or other signs of excessive pharmacologic effect.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In 4,826 patients treated with 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.

In controlled pivotal studies with 128 patients treated with verapamil hydrochloride sustained-release tablets for hypertension, the overall adverse reaction rate was 21.7% and the dropout rate was 3.9%.

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 verapamil immediate release tablets and 4.7% of patients on verapamil sustained-release tablets.

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

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

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.

Table 1. Adverse Reactions Reported in Clinical Trials

	Verapamil Hydrochloride (N = 4,954)
Vascular Disorders	
Hypotension	2.5%
Cardiac Disorders	
Edema	2.1%
CHF/Pulmonary Edema	1.9%
Bradycardia	1.4%

	Verapamil Hydrochloride (N = 4,954)
A-V Block	
Total (1˚, 2˚, 3˚)	1.2%
2˚ and 3˚	0.8%
Nervous System Disorders	
Dizziness	3.2%
Headache	2.2%
General Disorders and Administration Site Conditions	
Fatigue	1.7%
Gastrointestinal Disorders	
Constipation	7.3%
Nausea	2.7%
Respiratory, Thoracic and Mediastinal Disorders	
Dyspnea	1.4%

Less Common Clinical Trial Adverse Drug Reactions (< 1%)

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

Cardiac Disorders:	angina pectoris, atrioventricular dissociation, cardiac failure, chest pain, claudication, development of rhythm disturbances, myocardial infarction, painful coldness and numbness of extremities, palpitations, syncope, severe tachycardia, ventricular dysrhythmias
Ear and Labyrinth Disorders:	vertigo
Eye Disorders:	blurred vision, diplopia
Nervous System Disorders:	cerebrovascular accident, confusion, equilibrium disorders, excitation, extrapyramidal disorders, hyperkinesis, paresthesia, rotary nystagmus, shakiness, somnolence, tremor
Gastrointestinal Disorders:	abdominal discomfort, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, vomiting
Musculoskeletal and Connective Tissue Disorders:	arthralgia, muscle cramps, muscle fatigue
Psychiatric Disorders:	depression, insomnia, psychotic symptoms
Renal and Urinary Disorders:	increased frequency of urination
Respiratory, Thoracic and	bronchospasm, dyspnea

Mediastinal Disorders:	
Reproductive System and Breast Disorders:	erectile dysfunction, gynecomastia, oligomenorrhea, spotty menstruation
Skin and Subcutaneous System Disorders:	alopecia, ecchymosis or bruising, erythema multiforme, exanthema, hyperkeratosis, macules, pruritus, purpura, rash, Stevens-Johnson syndrome, sweating, urticaria
Vascular Disorders:	Flushing

Isolated cases of renal failure and 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.

Abnormal Hematologic and Clinical Chemistry Findings

Hepatotoxicity with elevated enzymes (SGOT, SGPT, alkaline phosphatase) and bilirubin levels, jaundice and associated symptoms of hepatitis with cholestasis have been reported. See (**WARNINGS AND PRECAUTIONS**). Elevated prolactin levels have also been reported.

Post-Market Adverse Drug Reactions

The following adverse events have been reported with verapamil hydrochloride from post- marketing surveillance or Phase 4 clinical trials.

Cardiac Disorders:	asystole, sinus arrest, sinus bradycardia
Ear and Labyrinth Disorders:	tinnitus
Gastrointestinal Disorders:	abdominal pain, ileus
General Disorders and Administration Site Conditions:	edema peripheral
Immune System Disorders:	hypersensitivity

Musculoskeletal and Connective Tissue Disorders:	muscle weakness, myalgia
Nervous System Disorders:	paralysis (tetraparesis)[1], seizure
Skin and Subcutaneous System Disorders:	hyperhidrosis, itching, rash maculopapular
Reproductive System and Breast Disorders:	galactorrhea

[1] There has been a single post-marketing report of paralysis (tetraparesis) associated with the combined use of verapamil hydrochloride and colchicine. This may have been caused by colchicine crossing the blood-brain barrier due to CYP3A4 and P-glycoprotein (P-gp) inhibition by verapamil hydrochloride. See (**DRUG INTERACTIONS**).

DRUG INTERACTIONS

Drug-Drug Interactions

As with all drugs, care should be exercised when treating patients with multiple medications. Verapamil hydrochloride undergoes biotransformation by the CYP3A4, CYP1A2, CYP2C8, CYP2C9 and CYP2C18 isoenzymes of the cytochrome P450 system. Verapamil hydrochloride has also been shown to be an inhibitor of CYP3A4 enzymes and P-glycoprotein (P-gp). Co-administration of verapamil hydrochloride with other drugs which follow the same route of biotransformation or are inhibitors or inducers of these enzymes may result in altered bioavailability of verapamil hydrochloride 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 hydrochloride to maintain optimum therapeutic blood levels.

The following table provides a list of potential drug interactions:

Table 2. Potential Drug Interactions Associated with Verapamil Hydrochloride

Concomitant Drug Class: Drug Name	Ref	Effect on Concentration of Verapamil Hydrochloride or Concomitant Drug	Clinical Comment
Alpha-Blockers			
Prazosin	T	↑ prazosin C_{max} (~40%) with no effect on t½	Concomitant use of verapamil hydrochloride and alpha-adrenoceptor blockers may result in excessive fall in blood pressure in some patients as observed in one study following the concomitant administration of verapamil hydrochloride and prazosin.
Terazosin	CT	↑ terazosin AUC (~24%) and C_{max} (~25%)	
Antiarrhythmics			
Disopyramide	T		Until data on possible interactions between verapamil hydrochloride and disopyramide are obtained, disopyramide should not be administered within 48 hours before or 24 hours after verapamil hydrochloride administration.
Flecainide	CT C	Minimal effect on flecainide plasma clearance (< ~10%); no effect on verapamil plasma clearance.	The concomitant administration of flecainide and verapamil hydrochloride may have additive effects on myocardial contractility, A-V conduction, and repolarisation. May alsohave negative inotropic effect and prolongation of atrioventricular conduction.
Quinidine	CT	↓ oral quinidine clearance (~35%)	In a small number of patients with hypertrophic cardiomyopathy, concomitant use of verapamil hydrochloride and quinidine resulted in significant hypotension and may result in pulmonary edema. Until further data are obtained, combined therapy of verapamil hydrochloride and quinidine in patients with hypertrophic cardiomyopathy should be avoided. The electrophysiological effects of quinidine and verapamil hydrochloride on A-V conduction were studied in 8 patients. Verapamil hydrochloride significantly counteracted the effects of quinidine on A-V conduction. There has been a report of

Concomitant Drug Class: Drug Name	Ref	Effect on Concentration of Verapamil Hydrochloride or Concomitant Drug	Clinical Comment
			increased quinidine levels during verapamil hydrochloride therapy.
Antiasthmatics			
Theophylline	C	↓ oral and systemic clearance of theophylline by ~20%. Reduction of clearance was lessened in smokers (~11%).	Caution should be exercised when co-administering theophylline and verapamil hydrochloride.
Anticoagulants			
Dabigatran	CT	↑ dabigatran (C_{max} up to 90%) and AUC (up to 70%)	To minimize potential interaction, dabigatran should be given at least 2 hours before verapamil.
Anticonvulsants / Antiepileptics			
Carbamazepine	C	↑ carbamazepine AUC (~46%) in refractory partial epilepsy patients	Concomitant oral use may potentiate the effects of carbamazepine neurotoxicity. Symptoms include nausea, diplopia, headache, ataxia or dizziness.
Phenytoin	C	↓ verapamil plasma concentrations	Verapamil plasma concentration may not achieve its therapeutic level when it is administrated concomitantly with phenytoin.
Antidepressants			
Imipramine	T	↑ imipramine AUC (~15%). No effect on level of active metabolite desipramine.	As with all antihypertensive agents, there is an elevated risk of orthostatic hypotension when combining verapamil hydrochloride with major tranquilizers or tricyclic antidepressants, such as imipramine.
Antidiabetics			
Glibenclamide (glyburide)	T	↑ glibenclamide C_{max} (~28%), AUC (~26%)	
Anti-gout			
Colchicine	CT	↑ colchicine AUC (~ 2.0-fold) and C_{max} (~1.3-fold)	Colchicine is a substrate for both CYP3A and the efflux transporter P-gp. Verapamil hydrochloride is known to inhibit CYP3A and P-gp. When verapamil hydrochloride and colchicine are administered together, inhibition of P-gp and/or CYP3A by verapamil hydrochloride may lead to

Concomitant Drug Class: Drug Name	Ref	Effect on Concentration of Verapamil Hydrochloride or Concomitant Drug	Clinical Comment
			increased exposure to colchicine. Combined use is not recommended.
Antihypertensive Agents			
	C		Verapamil hydrochloride administered concomitantly with 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.
Anti-Infectives			
Clarithromycin	C	Possible ↑ in verapamil when used in combination with clarithromycin	Severe hypotension and bradycardia have been observed in patients receiving concurrent clarithromycin.
Erythromycin	C	Possible ↑ in verapamil when used in combination with erythromycin	
Rifampicin	T	↓ verapamil AUC (~97%), C_{max} (~94%) oral bioavailability (~92%)	Blood pressure lowering effect of verapamil hydrochloride may be reduced when used concomitantly with rifampicin.
Telithromycin	T	Possible ↑ in verapamil when used in combination with telithromycin	
Antimanic Agents			
Lithium	T		Increased sensitivity to the effects of lithium (neurotoxicity) has been reported during concomitant verapamil hydrochloride-lithium therapy. Lithium based drugs should be administered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be further

Concomitant Drug Class: Drug Name	Ref	Effect on Concentration of Verapamil Hydrochloride or Concomitant Drug	Clinical Comment
			increased.
Antineoplastics			
Doxorubicin	T	↑ doxorubicin AUC (104%) and C_{max} (61%) with oral verapamil administration in patients with small cell lung cancer. In patients with advanced neoplasm, intravenous verapamil administration did not change significantly doxorubicin PK.	Verapamil hydrochloride inhibits P-glycoprotein (P-gp)-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 hydrochloride is administered concomitantly.
Barbiturates			
Phenobarbital	T	↑ oral verapamil clearance (~5-fold)	
Benzodiazepines and Other Anxiolytics			
Buspirone	T	↑ buspirone AUC, C_{max} by ~3.4-fold	
Midazolam	T C	↑ midazolam AUC (~3-fold) and, C_{max} (~2-fold)	
Beta-Blockers			
Atenolol	T C	A variable increase in atenolol plasma concentration at steady state has been reported in patients with angina pectoris.	
Metoprolol	T C	↑ metoprolol AUC (~32.5%) and C_{max} (~41%) in patients with angina pectoris	Concomitant therapy may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility. See (**WARNINGS AND PRECAUTIONS**). Verapamil hydrochloride should not be combined

Concomitant Drug Class: Drug Name	Ref	Effect on Concentration of Verapamil Hydrochloride or Concomitant Drug	Clinical Comment
			with beta-blockers for the treatment of hypertension.
Propranolol	T C	↑ propanolol AUC (~65%), C_{max} (~94%) in patients with angina pectoris	
Timolol	T C		Asymptomatic bradycardia (< 36 beats/min) with a wandering atrial pacemaker has been observed in a patient receiving concomitant timolol (a beta-adrenergic blocker) eye drops and oral verapamil hydrochloride.
Cardiac Glycosides			
Digitoxin	T	↓ digitoxin total body clearance (~27%) and extrarenal clearance (~29%)	The increase in digoxin levels can result in digoxin toxicity. Maintenance digoxin doses should be reduced when verapamil hydrochloride is administered, and the patient should be carefully monitored to avoid over- or under-digitalization. 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. See (**WARNINGS AND PRECAUTIONS**).
Digoxin	C	↑ digoxin levels ~50-75% during the first week of therapy ↑ digoxin AUC (~ 32%), C_{max} (~ 98%) in hepatic cirrhosis patients ↑ digoxin C_{max} (~44%), ↑ digoxin C_{12h} (~53%), ↑ C_{ss} (~44%) and ↑ AUC (~50%) in healthy subjects	
Diuretics			
	T		Concomitant use with diuretics may cause a potentiation of the hypotensive effect.
H2-Receptor Antagonists			
Cimetidine	T	In healthy subjects, ↑ AUC of R-(~25%) and	

Concomitant Drug Class: Drug Name	Ref	Effect on Concentration of Verapamil Hydrochloride or Concomitant Drug	Clinical Comment
		S-(~40%) verapamil with corresponding ↓ in R- and S-verapamil clearance	
HIV Antiviral Agents			
	T		Due to the metabolic inhibitory potential of some of the HIV antiviral agents, such as ritonavir, plasma concentrations of verapamil hydrochloride may increase. Caution should be used or the dose of verapamil hydrochloride may be decreased.
Immunosuppressive Agents			
Cyclosporine	T	↑ cyclosporine AUC, C_{ss}, C_{max} by 45% in renal transplant patients	The co-administration of verapamil and immunosuppressive agents both known substrates and inhibitors for CYP 3A4 may increase the plasma levels of these drugs. Dose adjustment should be considered when these drugs are concomitantly administered, which may be assessed by blood levels, blood pressure monitoring and clinical monitoring of other patient symptoms.
Everolimus	T	Everolimus: ↑ AUC (~3.5-fold) and ↑ C_{max} (~2.3-fold) Verapamil: ↑ C_{trough} (~2.3-fold)	
Sirolimus	T C	Sirolimus ↑ AUC (~2.2-fold); S-verapamil ↑ AUC (~1.5-fold)	
Tacrolimus	T	Possible ↑ tacrolimus levels	
Inhalation Anesthetics			
	T		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 hydrochloride, should be titrated carefully to avoid excessive hemodynamic effects.
Lipid Metabolism Regulators (HMG-CoA Reductase Inhibitors)			

Concomitant Drug Class: Drug Name	Ref	Effect on Concentration of Verapamil Hydrochloride or Concomitant Drug	Clinical Comment
Atorvastatin	T	Possible ↑ atorvastatin levels ↑ verapamil AUC by ~43%	Treatment with HMG-CoA reductase inhibitors (e.g. atorvastatin, simvastatin or lovastatin) in a patient taking verapamil hydrochloride should be started at the lowest possible dose and titrated upwards. If verapamil hydrochloride treatment is to be added to patients already taking an HMG- CoA reductase inhibitor (e.g. atorvastatin, simvastatin or lovastatin), consider a reduction in the statin dose and retitrate against serum cholesterol concentrations. Fluvastatin, pravastatin and rosuvastatin are not metabolized by CYP3A4 and are less likely to interact with verapamil hydrochloride.
Lovastatin	C	Possible ↑ lovastatin levels ↑ verapamil AUC (by~63%) and C_{max} by (~32%)	
Simvastatin	C	↑ simvastatin AUC (~2.6-fold), C_{max} (~4.6 fold) in healthy subject	
Neuromuscular Blocking Agents			
	CT C		Clinical data and animal studies suggest that verapamil hydrochloride may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing). It may, therefore, be necessary to decrease the dose of verapamil hydrochloride and/or the dose of the neuromuscular blocking agent when the drugs are used concomitantly.
Non-Steroidal Anti-Inflammatory Agents (NSAIDs)			
Acetylsalicylic acid	T		Potential adverse reactions in terms of bleeding due to synergistic antiplatelet effects of acetylsalicylic acid and verapamil hydrochloride should be taken into consideration in patients taking the two agents concomitantly.
Serotonin Receptor Agonists			
Almotriptan	T	↑ almotriptan AUC (~20%) ↑ C_{max} (~24%)	
Uricosurics			

Concomitant Drug Class: Drug Name	Ref	Effect on Concentration of Verapamil Hydrochloride or Concomitant Drug	Clinical Comment
Sulfinpyrazone	T	↑ verapamil oral clearance (~3-fold) ↓ bioavailability (~60%)	The blood pressure lowering effect of verapamil hydrochloride may be reduced
Vasodilators			
	T		Concomitant use with vasodilators may cause a potentiation of the hypotensive effect.
Legend: C= Case Study; CT = Clinical Trial; T = Theoretical			

Drug-Food Interactions

In healthy volunteers, multiple high doses of grapefruit juice increased the AUC for R-verapamil and S-verapamil by up to 49 and 37%, respectively. The increase in C_{max} for R-verapamil and S- verapamil were up to 75 and 51%, respectively. Elimination half-life and renal clearance of both S- and R-verapamil were not affected. Grapefruit juice should therefore not be ingested with verapamil.

Drug-Herb Interactions

In healthy volunteers, multiple doses of St John's wort decreased the AUC for R- and S-verapamil hydrochloride by 78 and 80%, respectively, with similar decreases in C_{max}.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been evaluated.

Drug-Lifestyle Interactions

Verapamil hydrochloride may increase blood alcohol (ethanol) concentrations and prolong its effects.

Depending on the individual response, verapamil hydrochloride may affect the ability to react to the point of impairing the ability to drive a vehicle, operate machinery or work under hazardous conditions. This applies all the more at the start of treatment, when the dose is raised, when switching from another drug and in conjunction with alcohol.

DOSAGE AND ADMINISTRATION

Dosing Considerations

The antihypertensive effects of APO-VERAP SR (verapamil hydrochloride) sustained-release 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.

Patients with Hepatic and Renal Impairment

APO-VERAP SR 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 overdosage. APO-VERAP SR should not be used in severe hepatic dysfunction. See (**WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Hepatic Insufficiency**). Verapamil hydrochloride is not removed by hemodialysis.

Use in Patients with Attenuated (Decreased) Neuromuscular Transmission

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

Switching from APO-VERAP Tablets to APO-VERAP SR Tablets

When switching from APO-VERAP (verapamil hydrochloride) immediate-release tablets to APO-VERAP SR (verapamil hydrochloride) sustained-release tablets, the total daily dose in milligrams may remain the same.

Recommended Dose and Dosage Adjustment

Mild to Moderate Essential Hypertension

The dosage should be individualized by titration depending on patient tolerance and responsiveness to APO-VERAP SR. Titration should be based on therapeutic efficacy and safety, evaluated weekly and approximately 24 hours after the previous dose.

The usual initial adult dose is 180to 240 mg/day. If required, the dose may be increased up to 240 mg twice a day. A maximum daily dose of 480 mg should not be exceeded.

Recommended dosing intervals for specific daily dosages are given in Table 3 below:

Table 3. Recommended Dosing Intervals for Specific Daily Dosages

Total Daily Apo-Verap SR Dose	Recommended Dosing Intervals
180 mg	Once each morning with food
240 mg	Once each morning with food
360 mg	180 mg each morning plus 180 mg each evening with food; or 240 mg each morning plus 120 mg each evening, with food
480 mg	240 mg each morning plus 240 mg each evening with food

Elderly

Lower dosages of APO-VERAP S,R i.e., 120 mg a day, may be warranted in elderly patients (i.e. 65 years and older). See (**WARNINGS AND PRECAUTIONS , Special Populations, Geriatrics**). The dosage should be carefully and gradually adjusted depending on patient tolerability and response.

Administration

Crushing or chewing APO-VERAP SR (verapamil hydrochloride) sustained-release tablets is not recommended since the sustained-release effect will be altered by damage to the tablet structure. The APO-VERAP SR 240 mg tablet may be split in half.

APO-VERAP SR tablets should be taken with food. See (**ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacokinetics, Influence of Food**).

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Symptoms

Based on reports of intentional overdosage of verapamil hydrochloride, the following symptoms have been observed: Hypotension (varying from transient to severe), bradycardia to high degree A-V block and sinus arrest, hyperglycemia, stupor and metabolic acidosis. Conduction disturbances seen included: prolongation of A-V conduction time, A-V dissociation, nodal rhythm, ventricular fibrillation and ventricular asystole. Fatalities have occurred as a result of overdose.

Treatment

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 hydrochloride. 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 beta-adrenergic receptor agonists (e.g., isoproterenol hydrochloride), other vasopressor agents, or cardiopulmonary resuscitation. Verapamil hydrochloride is not removed by hemodialysis.

In case of overdosage with large amounts of APO-VERAP SR (verapamil hydrochloride) sustained- release product, it should be noted that the release of the active drug and the absorption in the intestine may take more than 48 hours. Depending on the time of ingestion, incompletely dissolved tablets may be present along the entire length of the gastrointestinal tract which function as active drug depots. Extensive elimination measures are indicated, such as induced vomiting, removal of the contents of the stomach and the small intestine under endoscopy, intestinal lavage and high enemas.

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 hydrochloride should not be administered positive inotropic agents marked by asterisks in **Table 4.**

Table 4. Overdosage Adverse Reactions and Recommended Treatments

Adverse Reaction	**Proven Effective Treatment**	**Treatment with Good Theoretical Rationale**	**Supportive Treatment**
Shock, cardiac failure, severe hypotension	Calcium salt (e.g. i.v.calcium gluconate; 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)
Rapid ventricular rate (due to antegrade conduction in	D.C. cardioversion (high energy may be required); i.v. procainamide;		Intravenous fluids (slow drip)

Adverse Reaction	Proven Effective Treatment	Treatment with Good Theoretical Rationale	Supportive Treatment
flutter/fibrillation with W-P-W or L-G-L syndrome)	i.v. lidocaine HCl		

* positive inotropic agent
Definition: i.v. = intravenous

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Verapamil hydrochloride) is a calcium ion influx inhibitor (calcium entry blocker or calcium ion antagonist) that exerts its pharmacological effects by modulating the influx of ionic calcium across the cell membrane of the arterial smooth muscle as well as in conducting and contractile myocardial cells.

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

Verapamil hydrochloride depresses A-V nodal conduction and prolongs functional refractory periods. Verapamil hydrochloride does not alter the normal atrial action potential or intraventricular conduction time, but depresses amplitude, velocity of depolarization and conduction in depressed atrial fibres.

Verapamil hydrochloride 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 hydrochloride. See (**WARNINGS AND PRECAUTIONS, Cardiovascular, Conduction Disturbance**). Verapamil hydrochloride has a local anesthetic action that is 1.6 times that of procaine on an equimolar basis.

Verapamil hydrochloride 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.

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

In hypertensive normolipidemic patients, verapamil hydrochloride 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

Absorption

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 verapamil hydrochloride is absorbed from the small intestine. Steady state after multiple once daily dosing is reached after three to four days. Upon oral administration, there is rapid stereoselective biotransformation during the first pass of verapamil hydrochloride 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 hydrochloride.

In a study in five healthy volunteers with oral immediate-release verapamil hydrochloride, 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 (**DETAILED PHARMACOLOGY, Animal Pharmacology, Pharmacodynamics**).

There is a nonlinear correlation between the verapamil hydrochloride dose administered and verapamil hydrochloride plasma levels. In early dose titration with verapamil, a relationship exists between total verapamil hydrochloride (R- and S- enantiomer combined) plasma concentration and prolongation of the PR interval. The mean elimination $t_{½}$ in single-dose studies of immediate-release verapamil hydrochloride ranged from 2.8 to 7.4 hours. In these same studies, after steady state was reached, the $t_{½}$ 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 hydrochloride may increase during titration. Aging decreases the clearance and elimination of verapamil hydrochloride.

In a randomized, multiple-dose study in 44 healthy young subjects, administration of 240 mg verapamil hydrochloride sustained-release tablets with food produced peak plasma concentrations at approximately 8 hours postdose of 188 and 76 ng/mL and AUC's (0 to 24 hours) of 2,553 and 1,046 ng.hr/mL for the R- and S- enantiomers, respectively. Similar results were demonstrated for plasma norverapamil.

A study was conducted in which 240 mg single oral doses of verapamil hydrochloride immediate- release tablets (fasting) and verapamil hydrochloride sustained-release tablets (fed)

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 48hour period. The pharmacokinetic data from this study is summarized in the following table.

Table 5. Pharmacokinetic Data Comparing a Single-Dose of Verapamil Hydrochloride Immediate-Release Tablet vs. Verapamil Hydrochoride Sustained-Release Tablet

Parameter	Verapamil Hydrochloride Immediate-Release Tablet (240 mg)		Verapamil Hydrochloride 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

The steady-state pharmacokinetic data from a study in which 11 volunteers were treated with the sustained release formulation twice daily at 12 hourly intervals and with the immediate-release formulation three time daily at 8 hourly intervals for five days is summarized in the following table.

Table 6. Steady-State Pharmacokinetic Data Comparing Verapamil Hydrochloride Immediate-Release Tablet vs. Verapamil Hydrochloride Sustained-Release Tablet

Parameters	Verapamil Hydrochloride Immediate-release 120 mg Tablet ** (360 mg daily)	Verapamil Hydrochloride Sustained-Release 240 mg Tablet ** (360 mg daily)	Verapamil Hydrochloride Sustained-Release 240 mg Tablet ** (480 mg daily)
$C_{max,}$ ng/mL	289.4	250.5	298.4
$C_{min,}$ ng/mL	80.1	110.7	152.0
$T_{max,}$ hr	1.4	4.5	4.4
$T_{1/2,}$ hr	6.1	8.2	8.7
AUC_{0-4} ng/mL/hr	1850	3466	4484
AUC_{0-48} ng/mL/hr	1809	3154	4116

* last dose = 240 mg
** last dose = 120 mg
The data have been calculated from samples taken at frequent intervals for 36 hours after the last dose.

Distribution

Verapamil is widely distributed throughout the body tissues, the volume of distribution ranging from 1.8 to 6.8 L/kg in healthy subjects. 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.

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

Metabolism

In healthy men, orally administered verapamil hydrochloride undergoes extensive metabolism by the cytochrome P-450 system in the liver. The particular isoenzymes involved are CYP3A4, CYP1A2, and CYP2C family. Thirteen metabolites have been identified in urine, most in only trace amounts. The major metabolites have been identified as various N- and O-dealkylated products of verapamil. 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, which was observed in a study in dogs. The degree of biotransformation during the first pass of verapamil hydrochloride may vary according to the status of the liver in different patient populations. In patients with hepatic insufficiency, metabolism is delayed and elimination t½ prolonged up to 14 to 16 hours.

Excretion

Approximately 50% of an administered dose of verapamil is eliminated renally within 24 hours, 70% within five days. Up to 16% of a dose is excreted in the feces. About 3% to 4% of an administered dose is excreted renally as unchanged drug. The total clearance of verapamil is nearly as high as the hepatic blood flow, approximately 1 L/h/kg (range: 0.7-1.3 L/h/kg).

Influence of Food

Administration of verapamil hydrochloride sustained-release 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.

Special Populations and Conditions

Geriatrics

The pharmacokinetics of verapamil hydrochloride are significantly different in elderly (≥ 65 years), compared to younger subjects. AUCs are increased approximately 80% with verapamil hydrochloride. In the elderly, verapamil hydrochloride clearance is reduced resulting in increases in elimination $t_{½}$.

Gender

The effect of gender on verapamil hydrochloride, when administered as APO-VERAP SR, has not been investigated.

Race

The effect of different races on verapamil hydrochloride, when administered as APO-VERAP SR, has not been investigated.

Hepatic Insufficiency

The degree of biotransformation during the first pass of verapamil hydrochloride may vary according to the status of the liver in different patient populations. In patients with hepatic insufficiency, verapamil hydrochloride clearance is reduced by 30% and elimination t½ prolonged up to 14 to 16 hours. See (**WARNINGS AND PRECAUTIONS, Hepatic /Biliary /Pancreatic, Hepatic Insufficiency**) and (**DOSAGE AND ADMINISTRATION**).

Renal Insufficiency

About 70% of an administered dose of verapamil hydrochloride is excreted as metabolites in the urine. In one study in healthy volunteers, the total body clearance after intravenous administration of verapamil hydrochloride 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 hydrochloride in patients with renal disease is decreased. In two studies with oral verapamil hydrochloride, no difference in pharmacokinetics could be demonstrated. See (**WARNINGS AND PRECAUTIONS, Renal, Renal Insufficiency**). Verapamil hydrochloride and norverapamil are not removed by hemodialysis.

Genetic Polymorphism

The effect of genetic polymorphism on verapamil hydrochloride pharmacokinetics has not been investigated.

STORAGE AND STABILITY

Store at room temperature 15˚C to 30˚C. Protect from light. Do not use beyond the expiry date indicated on the label.

DOSAGE FORMS, COMPOSITION AND PACKAGING

APO-VERAP SR tablets are formulated for oral administration containing verapamil hydrochloride in a sustained-release formulation in three strengths: 120 mg, 180 mg and 240 mg.

APO-VERAP SR 120 mg tablets are white, round, biconvex, film-coated tablets, engraved “APO” on one side and "VSR" and "120" on the other side. Available in bottles of 100.

APO-VERAP SR 180 mg tablets are light pink, oval, biconvex, film-coated tablets, engraved “APO” on one side and "VSR" over "180" and scored on the other. Available in bottles of 100.

APO-VERAP SR 240 mg tablets are light green, capsule shaped, biconvex, film-coated tablets, engraved "APO" on one side and "VSR" and "240" and scored on the other side. Available in bottles of 100 and 500.

Listing of Non-Medicinal Ingredients

In addition to verapamil hydrochloride, each tablet contains the non-medicinal ingredients carnauba wax, colloidal silicon dioxide, hydroxyethyl cellulose, magnesium stearate, polyethylene glycol, sodium alginate, and titanium dioxide. The 180 mg tablet also contains the non-medicinal ingredient ferric oxide red. The 240 mg tablet also contains the non-medicinal ingredients ferric oxide yellow and brilliant blue FCF AL lake.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

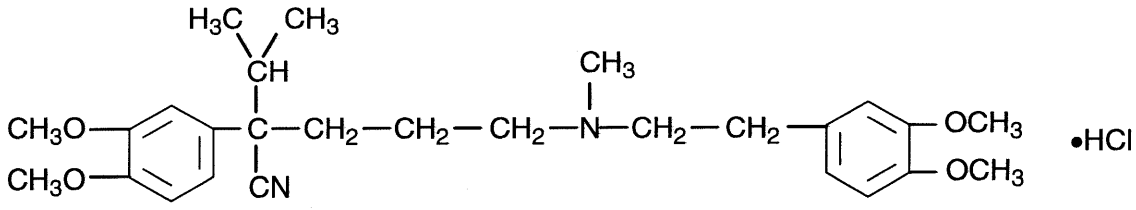
Drug Substance

Proper/Common Name: Verapamil hydrochloride

Chemical Name: α-isopropyl-α-[(N-methyl-N-homoveratryl)-γ-amino-propyl]-3,4-dimethoxyphenylacetonitrile hydrochloride

Molecular Formula and molecular mass: $C_{27}H_{38}N_2O_4 \cdot HCl$ 491 g/mol

Structural Formula:



Physicochemical properties: Verapamil, as the hydrochloride salt, is an almost-white, bitter-tasting crystalline powder, practically odourless 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.

CLINICAL TRIALS

Comparative Bioavailability

Three studies were performed using sustained release tablets: one under fasting conditions, one under fed conditions and one at steady state. In the fasting and fed studies the rate and extent of the absorption of verapamil were determined and compared after a single, oral dose of 240 mg of Apo-Verap SR and Isoptin® SR 240 mg. In the steady state study the dosage was 240 mg of either Apo-Verap SR, or Isoptin® SR every 24 hours for six days. The results of these studies are summarized below.

Summary Table of the Comparative Bioavailability Data
Verapamil SR (Dose: 1 x 240 mg) From Measured Data – Under Fasting Conditions
Based on Verapamil

Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**	90% Confidence Interval (%)**
	Apo-Verap SR	Isoptin® SR†		
AUC_T (ng.h/mL)	1221 1314 (40)	1236 1310 (36)	98.8	82.7 – 118.1
AUC_I (ng.h/mL)	1263 1355 (40)	1284 1355 (35)	98.4	83.1 – 116.5
C_{MAX} (ng/mL)	117 133 (55)	124 140 (44)	93.9	73.4 – 120.2
T_{MAX}* (h)	6.71 (58)	5.36 (48)	-	-
$T_{½}$* (h)	8.21 (18)	9.34 (22)	-	-

*Arithmetic means (CV%).

** Based on the least squares estimate.

†Isoptin® SR is marketed by Knoll Pharma Inc., Canada.

Summary Table of the Comparative Bioavailability Data Verapamil SR (Dose: 1 x 240 mg) From Measured Data – Under Fed Conditions Based on Verapamil				
	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**	90% Confidence Interval (%)**
Parameter	Apo-Verap SR	Isoptin® SR†		
AUC_T (ng.h/mL)	1113 1194 (37)	1088 1189 (43)	102.3	87.8 – 119.2
AUC_I (ng.h/mL)	1160 1245 (37)	1135 1248 (44)	101.1	86.1 – 118.7
C_{MAX} (ng/mL)	79.8 90.7 (53)	75.1 84.7 (57)	106.2	76.9 – 146.8
T_{MAX}* (h)	12.4 (57)	12.8 (53)	-	-
$T_{½}$* (h)	7.92 (30)	7.89 (32)	-	-
* Arithmetic means (CV%). ** Based on the least squares estimate. †Isoptin® SR is marketed by Knoll Pharma Inc., Canada.				

Summary Table of the Comparative Bioavailability Data Verapamil SR (Dose: 1 x 240 mg every 24 hours for 6 days) From Measured Data – At Steady State Based on Verapamil				
	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**	90% Confidence Interval (%)**
Parameter	Apo-Verap SR	Isoptin® SR†		
AUC_{9} (ng.h/mL)	2165 2325 (38)	2179 2389 (43)	99.3	91.5 – 107.9
C_{MAX} (ng/mL)	202 218 (39)	215 243 (48)	93.8	82.6 – 106.6
C_{MIN} (ng/mL)	37.1 42.1 (49)	33.1 37.8 (52)	112.1	102.3 – 122.9

Summary Table of the Comparative Bioavailability Data Verapamil SR (Dose: 1 x 240 mg every 24 hours for 6 days) From Measured Data – At Steady State Based on Verapamil				
	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**	90% Confidence Interval (%)**
Parameter	Apo-Verap SR	Isoptin® SR†		
T_{MAX}* (h)	4.50 (22)	5.48 (26)	-	-
Fluctuation* (%)	190 (41)	204 (29)	-	-
* Arithmetic means (CV%). ** Based on the least squares estimate. † Isoptin® SR is marketed by Knoll Pharma Inc., Canada.				

DETAILED PHARMACOLOGY

Animal Pharmacology

Pharmacodynamics

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 focus of action seems to be the superficially located membrane storage sites for calcium.

In isolated cardiac tissues, at low to moderate concentrations, verapamil 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 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 on A-V nodal conduction may in part explain its effectiveness in treating supraventricular tachycardia.

Verapamil 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 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 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

Table 7. Lethal Dose 50 (LD_{50}) (mg/kg) of Verapamil

	Intravenous	Intraperitoneal	Subcutaneous	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)

Definitions: M = male; F = female

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 to16 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 to50 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. Serum glutamic-pyruvic transaminase (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 were 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 the 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, electrocardiogram (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 eight beagles receiving toxic dose levels (62.5 and 70 mg/kg). In a later study, four 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 and Carcinogenicity

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 hypoxanthine guanine phosphoribosyltransferase (HGPRT)-test with V-79 Chinese hamster cells, and also not in the cell transformation assay with Syrian hamster embryo cells. In addition, verapamil did not 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 and Teratology

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 post-natal 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 three times a day . 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 three times a day 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 post-natal development or fertility in the rat.