PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]**APO-VERAP**

Verapamil Hydrochloride

Tablets, 80 mg and 120 mg, oral

BP

Antianginal / Antiarrhythmic / Antihypertensive Agent

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Date of Initial Authorization:
JUN 30, 1989

Date of Revision:
MAY 12, 2022

Submission Control Number: 258995

RECENT MAJOR LABEL CHANGES

1 Indications, 1.1 Pediatrics	05/2022
1 Indications, 1.2 Geriatrics	05/2022
2 Contraindications	05/2022
4 Dosage and Administration, 4.2 Recommended Dose and Dosage Adjustment	05/2022
7 Warnings and Precautions, Cardiovascular	05/2022
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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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

- Chronic stable angina of effort.
- Angina resulting from coronary artery spasm.
- Obstructive hypertrophic cardiomyopathy, where surgery is not otherwise indicated.
- Atrial fibrillation or flutter with rapid ventricular response not otherwise controllable with digitalis preparations.
- Follow-up treatment to the use of injectable verapamil hydrochloride in paroxysmal supraventricular tachycardia.
- Treatment of mild to moderate essential hypertension.

Concomitant use of verapamil hydrochloride with a diuretic or an angiotensin converting enzyme inhibitor has been shown to be compatible and to have additive blood pressure lowering effects.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness. Caution should be exercised when verapamil hydrochloride is administered to elderly patients. (see 7 WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics).

2 CONTRAINDICATIONS

APO-VERAP is contraindicated in:

- Patients who are hypersensitive to verapamil hydrochloride or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, See 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Complicated myocardial infarction (patients who have ventricular failure manifested by pulmonary congestion).
- 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 hydrochloride therapy.

- Cardiogenic shock.
- Severe hypotension.
- Second- or third-degree A–V block.
- Sick Sinus Syndrome. See 7 WARNINGS AND PRECAUTIONS, Cardiovascular.
- Marked bradycardia.
- Patients with atrial flutter or atrial fibrillation and an accessory bypass tract (e.g. Wolff–Parkinson–White, Lown–Ganong–Levine syndromes). See 7 WARNINGS AND PRECAUTIONS, Cardiovascular.
- Women who are breast-feeding. See 7 WARNINGS AND PRECAUTIONS, Special Populations, Breast-feeding.APO-VERAP is contraindicated with co-administration of ivabradine as it may result in increased concentrations of ivabradine due to inhibition of CYP3. see 7 WARNINGS AND PRECAUTIONS and 9 DRUG INTERACTIONS, Drug-Drug Interactions.
- APO-VERAP is contraindicated with co-administration of flibanserin as it may result in significantly increased concentrations of flibanserin, which can lead to severe hypotension and syncope. see 7 WARNINGS AND PRECAUTIONS and 9 DRUG INTERACTIONS, Drug-Drug Interactions.
- APO-VERAP is contraindicated with co-administration of beta-blockers in patients with poor ventricular function and in the treatment of hypertension. see 7 WARNINGS AND PRECAUTIONS, Cardiovascular and 9 DRUG INTERACTIONS, Drug-Drug Interactions, Table 4.
- Concomitant ingestion with grapefruit juice.

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

Angina Pectoris

The usual starting dose of APO-VERAP 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

The 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

APO-VERAP 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 hydrochloride administration and a reduction in the digoxin dose may be necessary. See 7 WARNINGS AND PRECAUTIONS, Cardiovascular and 9 DRUG INTERACTIONS, Drug-Drug Interactions.

Mild to Moderate Essential Hypertension

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

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 verapamil hydrochloride 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.

Pediatrics

Health Canada has not authorized an indication for pediatric use.

Geriatrics

A lower dosage may be warranted in elderly patients (≥65 years) (see 7 WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics). The dosage should be carefully and gradually adjusted depending on patient tolerability and response. Elderly patients may be more sensitive to the effects of the usual adult dose.

Patients with Impaired Hepatic and Renal Function

APO-VERAP 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. At this time, APO-VERAP should not be used in patients with severe hepatic dysfunction (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Hepatic Insufficiency)**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.

4.4 Administration

APO-VERAP should be taken with food. See 10 CLINICAL PHARMACOLOGY, Pharmacokinetics, Influence of Food.

4.5 Missed Dose

If the patient misses a dose, instruct the patient to take the dose as soon as they remember. If it is almost time for the next dose, inform the patient to skip the missed dose and continue the regular dosing schedule.

5 OVERDOSAGE

Based on reports of intentional overdosage of verapamil hydrochloride, the following symptoms have been observed. Hypotension occurs, varying from transient to severe, bradycardia to high degree A-V block and sinus arrest, hyperglycemia, stupor, metabolic acidosis and acute respiratory distress syndrome (ARDS). 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 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 vasopressor agents, e.g. isoproterenol hydrochloride. Verapamil hydrochloride is not removed by hemodialysis.

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 1).

Table 1. Overdosage Adverse Reactions and Recommended Treatments

Adverse Reaction	Proven Effective Treatment	Treatment with Good Theoretical Rationale	Supportive Treatment
1. Shock, cardiac failure, severe hypertension	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

Adverse Reaction	Proven Effective Treatment	Treatment with Good Theoretical Rationale	Supportive Treatment
2. Bradycardia, A–V block, asystole	i.v. isoproterenol HCl* i.v. atropine sulphate Cardiac pacing	-	i.v. fluids (slow drip)
3. Rapid ventricular rate (due to antegrade conduction in flutter/fibrillation with WPW or LGL syndrome)	D.C. cardioversion (high energy may be required) i.v. procainamide i.v. lidocaine HCl	-	i.v. fluids (slow drip)
* positive inotropic agent Definition: i.v. = intravenous			

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	tablets 80 mg, 120 mg of Verapamil hydrochloride	carnauba wax, colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol and titanium dioxide. The 80 mg tablet also contains the non–medicinal ingredients D&C yellow #10 aluminium lake 14-18% and FD&C yellow #6 aluminium lake 40%.

APO-VERAP 80 mg Tablets are yellow, round, biconvex, film-coated tablets, engraved "APO" over "V80" on one side, other side plain, containing 80 mg of verapamil hydrochloride. Available in bottles of 100 and 500.

APO-VERAP 120 mg Tablets are white, round, biconvex, film-coated tablets, engraved "APO" over "V120" on one side, other side plain, containing 120 mg of verapamil hydrochloride. Available in bottles of 100 and 500.

7 WARNINGS AND PRECAUTIONS

General

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

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, unless the failure is complicated by or caused by a dysrhythmia. If verapamil hydrochloride 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 hydrochloride administration. See 9 DRUG INTERACTIONS, Drug-Drug Interactions, Digoxin. 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.

Occasionally, the pharmacologic action of verapamil may produce a decrease in blood pressure below normal levels which may result in dizziness or symptomatic hypotension.

Use of a moderate CYP3A4 inhibitor such as verapamil with flibanserin significantly increases flibanserin concentrations, which can lead to severe hypotension and syncope (see 2 CONTRAINDICATIONS). Discontinue APO-VERAP at least 2 weeks prior to starting flibanserin. Do not administer APO-VERAP within 2 days of discontinuing flibanserin.

Conduction Disturbance: Verapamil hydrochloride 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 hydrochloride should be used with caution in the presence of first degree AV 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 causes dose–related suppression of the sino-atrial (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 2 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 (a 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 5 OVERDOSAGE.

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 syndromes after receiving intravenous verapamil hydrochloride. Although a risk of this occurring with oral verapamil hydrochloride has not been established, such patients receiving oral verapamil hydrochloride may be at risk and its use in these patients is contraindicated. See 2 CONTRAINDICATIONS.

Concomitant Use with Beta Blockers: 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. See 9 DRUG INTERACTIONS, Drug-Drug Interactions, Table 4).

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 was seen. Three patients died in pulmonary edema; all had severe left ventricular out flow obstruction and a past history of left ventricular dysfunction. Eight other patients had pulmonary edema and/or severe hypotension, abnormally high (greater than 20 mmHg) pulmonary wedge pressure and a marked left ventricular outflow obstruction were present in most of these patients. Concomitant administration of quinidine (see 9 DRUG INTERACTIONS, Drug-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.

Endocrine and Metabolism

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.

Hepatic/Biliary/Pancreatic

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 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 4 DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment and 10 CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and conditions.

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.

Neurologic

Neuromuscular Transmission Disorders: Due to verapamil hydrochloride's neuromuscular blocking action, it 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 9 DRUG INTERACTIONS.

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, 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 4 DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment.

Reproductive Health: Female and Male Potential

- **Fertility**

  Teratology and reproduction studies in animals have not revealed any evidence of impaired fertility. See 7 WARNINGS AND PRECAUTIONS, Pregnant Women.

- **Function**

  Information is not available.

- **Teratogenic Risk**

  Teratology and reproduction studies in animals have not revealed any evidence of teratogenic effect. See 7 WARNINGS AND PRECAUTIONS, Pregnant Women.

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well-controlled study data in pregnant women. Verapamil hydrochloride crosses the placental barrier and can be detected in umbilical vein blood at delivery. 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 with oral verapamil hydrochloride administered at doses up to 15 mg/kg/day and 60mg/kg/day (human equivalent doses of 288 mg/day and 576 mg/day, respectively, assuming human body weight at 60 kg) respectively, and have revealed no evidence of teratogenicity or impaired fertility. In the rat, however, a dose of 60 mg/kg/day (human equivalent dose of 576 mg/day, similar to the maximum clinical dose of 480 mg/day) was embryocidal and retarded fetal growth and development. These effects occurred in the presence of maternal toxicity (reflected by reduced food consumption and weight gain of 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.

7.1.2 Breast-feeding

Verapamil hydrochloride is excreted in human milk. Because of the potential for adverse reactions in nursing infants from verapamil hydrochloride, nursing should be discontinued while verapamil hydrochloride is administered. see 2 CONTRAINDICATIONS.

7.1.3 Pediatrics

Pediatrics (<18 years of age): The safety and dosage regimen of verapamil hydrochloride in children below the age of 18 years has not yet been established. Therefore, use in this group is not recommended.

7.1.4 Geriatrics

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 4 DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment and 10 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.

8 ADVERSE REACTIONS

8.1 Adverse Reactions 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 sustainedrelease 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 hydrochloride immediate release tablets and 4.7% of patients on verapamil hydrochloride 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 7 WARNINGS AND PRECAUTIONS).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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 a 4,954 patient base.

Table 3. Adverse Reactions Reported in Clinical Trials

	Verapamil hydrochloride (N = 4,954)
Cardiac Disorders	
Edema	2.1%
CHF/Pulmonary Edema	1.9%
Bradycardia	1.4%
A–V Block	
Total (1°, 2°, 3°)	1.2%
2° and 3° [text]	0.8%
Gastrointestinal Disorders	
Constipation	7.3%
Nausea	2.7%
Nervous System Disorders	
Dizziness	3.2%
Headache	2.2%
Fatigue	1.7%
Respiratory, Thoracic and Mediastinal Disorders	
Dyspnea	1.4%
Vascular Disorders	
Hypotension	2.5%

8.3 Less Common Clinical Trial Adverse Reactions

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

Cardiac Disorders: 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.

Ear and Labyrinth Disorders: vertigo.

Eye disorders: blurred vision, diplopia.

Nervous System Disorders: cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, excitation, depression, rotary nystagmus, , tremor, extrapyramidal disorders, muscle fatigue, hyperkinesis.

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 Mediastinal Disorders: dyspnea, bronchospasm.

Reproductive system and breast disorders: erectile dysfunction, gynecomastia, , spotty menstruation, oligomenorrhea.

Skin and Subcutaneous System Disorders: arthralgia, rash, ecchymosis or bruising, exanthema, alopecia, hyperkeratosis, macules, sweating, urticaria, Stevens–Johnson Syndrome, erythema multiforme, pruritus, purpura.

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.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Hepatotoxicity with elevated enzymes (SGOT, SGPT, alkaline phosphatase) and bilirubin levels, jaundice and associated symptoms of hepatitis with cholestasis have been reported (see 7 WARNINGS AND PRECAUTIONS). Elevated prolactin levels have also been reported.

8.5 Post-Market Adverse Reactions

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

Cardiac Disorders: bradycardia	asystole, sinus arrest, sinus
Ear and Labyrinth Disorders:	tinnitus
Gastrointestinal Disorders:	abdominal pain, ileus
General Disorders and Administration Site Conditions:	edema peripheral
Immune System Disorders:	hypersensitivity
Metabolism and Nutrition Disorders:	hyperkalaemia
Musculoskeletal and Connective Tissue Disorders:	muscle weakness, myalgia
Skin and Subcutaneous System Disorders: maculopapular	hyperhidrosis, itching, rash
Reproductive System and Breast Disorders:	galactorrhea

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. Combined use of verapamil hydrochloride and colchicine is not recommended (see 9 DRUG INTERACTIONS, Drug-Drug Interactions).

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

Ivabradine: APO-VERAP is contraindicated with concomitant use of ivabradine as it may result in increased concentrations of ivabradine due to inhibition of CYP3A4

Flibanserin: APO-VERAP is contraindicated with co-adminstration of flibanserin as it may result in significantly increased concentrations of flibanserin, which can lead to severe hypotension and syncope (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Hypotension).

9.2 Drug Interactions Overview

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 hydrochloride with other drugs which follow the same route of biotransformation may result in altered bioavailability. 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.

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

Drugs known to be inducers of the cytochrome P450 system include phenobarbital, phenytoin and rifampin.
Drugs known to be biotransformed via P450 include benzodiazepines, flecainide, imipramine, propafenone and theophylline.

9.3 Drug-Behavioural Interactions

Alcohol

Verapamil hydrochloride may increase blood alcohol 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.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 4 - Established or Potential Drug-Drug Interactions associated with verapamil hydrochloride

Proper/Common name	Source of Evidence	Effect	Clinical comment
Alpha-Blockers			
Prazosin		↑ prazosin Cmax (~40%) with no effect on t½	Concomitant use of verapamil hydrochloride and alphaadrenoceptor 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		↑ terazosin AUC (~24%) and Cmax (~25%)	
Antiarrhythmics			

Proper/Common name	Source of Evidence	Effect	Clinical comment
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	Minimal effect on flecainide plasma clearance (~10%); no effect on verapamil hydrochloride clearance	The concomitant administration of flecainide and verapamil hydrochloride may have additive deleterious effects on myocardial contractility, A-V conduction, and repolarisation. May also have negative inotropic effect and prolongation of atrioventricular conduction.

Proper/Common name	Source of Evidence	Effect	Clinical comment
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 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			

Proper/Common name	Source of Evidence	Effect	Clinical comment
Dabigatran	CT	↑ dabigatran (Cmax up to 90%) and AUC (up to 70%)	To minimize potential interaction, dabigatran should be given at least 2 hours before verapamil hydrochloride. Close clinical surveillance is recommended when verapamil hydrochloride is combined with dabigatran etexilate and particularly in the occurrence of bleeding, notably in patients having a mild to moderate renal impairment"
Other direct oral anticoagulants (DOACs; e.g. rivaroxaban, apixaban, and edoxaban)	C	Increased absorption of DOACs since they are P-gp substrates and, if applicable, also reduced elimination of DOACs which are metabolized by CYP3A4, may increase the systemic bioavailability of DOACs	Some data suggest a possible increase of the risk of bleeding, especially in patients with further risk factors. The dose of DOAC with verapamil hydrochloride may need to be reduced (see DOAC label for dosing instructions).
Anticonvulsants/Antiepileptics			
Carbamazepine	C	↑ carbamazepine AUC (~46%) in refractory partial epilepsy patients.	The concomitant oral administration of verapamil hydrochloride and carbamazepine may potentiate the effects of carbamazepine neurotoxicity. Symptoms include nausea, diplopia, headache, ataxia or dizziness.
Phenytoin	C	↓ verapamil hydrochloride plasma concentrations	Verapamil hydrochloride plasma concentration may not achieve its therapeutic level when it is administrated concomitantly with phenytoin.

Proper/Common name	Source of Evidence	Effect	Clinical comment
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)	↑ glibenclamide Cmax (~28%), AUC (~26%)		
Metformin			Co-administration of verapamil hydrochloride with metformin may reduce the efficacy of metformin.
Antigout			
Colchicine	CT	↑ colchicine AUC (~ 2.0- fold) and Cmax (~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 increased exposure to colchicine. Combined use is not recommended.
Antihypertensive Agents			

Proper/Common name	Source of Evidence	Effect	Clinical comment
	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, Erthromycin, Telithromycin	C, T	Possible ↑ in verapamil hydrochloride when used in combination with clarithromycin	Severe hypotension and bradycardia have been observed in patients receiving concurrent clarithromycin.
Rifampin	T	↓ verapamil hydrochloride AUC (~97%), Cmax (~94%) oral bioavailability (~92%)	Blood pressure lowering effect of verapamil hydrochloride may be reduced when used concomitantly with rifampicin.
Antimanic Agents			

Proper/Common name	Source of Evidence	Effect	Clinical comment
Lithium	T	Oral verapamil hydrochloride therapy may result in a lowering of serum lithium levels in patients receiving chronic, oral lithium therapy.	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 increased. A dose adjustment of the lithium may be necessary.
Anti–neoplastic Agents			
Doxorubicin	T	↑ doxorubicin AUC (104%) and Cmax (61%) with oral verapamil hydrochloride administration in patients with small cell lung cancer. 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 adjustment of anti–neoplastic agents should be considered when verapamil hydrochloride is administered concomitantly.
Barbiturates			
Phenobarbital	T	↑ oral verapamil clearance (~5-fold)	
Beta–Adrenergic Blockers			

Proper/Common name	Source of Evidence	Effect	Clinical comment
Atenolol, metoprolol, propranolol	T, C	An increase in beta blocker plasma concentrations has been reported in patients with angina pectoris. .	Concomitant therapy may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility (see 7 WARNINGS AND PRECAUTIONS). Verapamil hydrochloride should not be combined with beta-blockers for the treatment of hypertension.
Timolol	T, C		Asymptomatic bradycardia (< 36 beats/min) with a wandering atrial pacemaker has been observed in a patient receiving concomitant timolol (a betaadrenergic 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

Proper/Common name	Source of Evidence	Effect	Clinical comment
Digoxin	C	Verapamil hydrochloride treatment increases serum digoxin levels by 50% and 75% during the first week of therapy, and this can result in digitalis toxicity. In patients with hepatic cirrhosis, the influence of verapamil hydrochloride on digoxin kinetics is magnified. Verapamil may reduce total body clearance and extrarenal clearance of digitoxin by 27% and 29% respectively.	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 7 WARNINGS AND PRECAUTIONS).
Cardiac I_f Current Inhibitor			
Ivabradine	CT	Given its moderate CYP3A4 inhibitory effect, verapamil hydrochloride (120 mg b.i.d.), when coadministered with ivabradine, increases the ivabradine plasma AUC by 2- to 3- fold. Both verapamil hydrochloride and ivabradine are heart rate lowering substances and hence, co-administration could lead to an exacerbated reduction in patient's heart rate.	Given the increase in ivabradine exposure and additive heart rate lowering effect, the concomitant use of APO-VERAP with ivabradine is contraindicated (see 2 CONTRAINDICATIONS).

Proper/Common name	Source of Evidence	Effect	Clinical comment
Diuretics			
	T	No cardiovascular adverse effects have been attributed to any interaction between these agents and verapamil hydrochloride.	
Gynecologicals			
Flibanserin	T	Use of a moderate CYP3A4 inhibitor such as verapamil hydrochloride with flibanserin significantly increases flibanserin concentrations, which can lead to severe hypotension and syncope (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Hypotension).	Concomitant use of APO-VERAP and flibanserin is contraindicated. Discontinue APO-VERAP at least 2 weeks prior to starting flibanserin. Do not administer APO-VERAP within 2 days of discontinuing flibanserin (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Hypotension).
H2-Receptor Antagonists			
Cimetidine	CT	In healthy subjects, ↑ AUC of R- (~25%) and S- (~40%) verapamil with corresponding ↓ in R- and S- verapamil clearance	
HIV antiviral agents			

Proper/Common name	Source of Evidence	Effect	Clinical comment
	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, Css, Cmax by 45% in renal transplant patients	The co-administration of verapamil hydrochloride 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 ↑ Cmax (~2.3-fold) Verapamil: ↑ Ctrough (~2.3- fold)	
Sirolimus	T, C	Sirolimus ↑ AUC (~2.2-fold); S-verapamil ↑ AUC (~1.5-fold)	
Tacrolimus	T		
Inhalation Anaesthetics			
	C		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.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Lipid metabolism regulators			
Atorvastatin	T	Possible ↑ atorvastatin levels ↑ verapamil AUC by ~42.8%	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 and 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	
Simvastatin	C	↑ simvastatin AUC (~2.6-fold), Cmax (~4.6-fold) in healthy subjects	
Neuromuscular Blocking Agents			
	CT	Clinical data and animal studies suggest that verapamil hydrochloride may potentiate the activity of neuromuscular blocking agents (curare–like and depolarizing).	It may be necessary to decrease the dose of verapamil hydrochloride and/or the dose of the neuromuscular blocking agent when the drugs are used concomitantly.
Nitrates			

Proper/Common name	Source of Evidence	Effect	Clinical comment
		No cardiovascular adverse effects have been attributed to any interaction between these agents and verapamil hydrochloride.	
NSAIDS			
Acetylsalicylic acid (ASA)	T		Potential adverse reactions in terms of bleeding due to synergistic antiplatelet of the two agents should be taken into consideration in patients taking ASA and verapamil hydrochloride concomitantly.
Serotonin Receptor Agonists			
Almotriptan	T	↑ almotriptan AUC (~20%) ↑ Cmax (~24%)	
Uricosurics			
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

9.5 Drug-Food Interactions

Interaction with Grapefruit Juice

Grapefruit juice can increase the plasma levels of verapamil hydrochloride.

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 Cmax 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 hydrochloride. see 2 CONTRAINDICATIONS.

9.6 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 Cmax.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been evaluated.

10 CLINICAL PHARMACOLOGY

10.1 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 (7 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.

10.2 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 AV 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.

10.3 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. 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 5 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 10 CLINICAL PHARMACOLOGY, Pharmacodynamics.

There is a nonlinear correlation between the verapamil dose administered and verapamil hydrochloride 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 hydrochloride 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 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 of 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 48-hour 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 Hydrochloride Sustained-Release Tablet

Parameter	Verapamil Hydrochloride Standard Release Tablet (240 mg)		Verapamil Hydrochloride Sustained Release Tablet (240 mg)	
	R-verapamil	S-verapamil	R-verapamil	S-verapamil
Cmax, ng/mL	258	59.0	60.1	11.3
Tmax, hr	1.46	1.58	10.8	11.8
AUC0-48 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)
Cmax (ng/mL)	289.4	250.5	298.4
Cmin (ng/mL)	80.1	110.7	152.0
Tmax (hr)	1.4	4.5	4.4
Tl/2 (hr)	6.1	8.2	8.7
AUC0-∞ (ng/mL/hr)	1850	3466	4484
AUC0-36 (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 hydrochloride 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.

Elimination

Approximately 50% of an administered dose of verapamil hydrochloride 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 hydrochloride 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 with food results in marked prolongation of Tmax (45 to 75%) and slight decreases in Cmax (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 t½. 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.
- **Sex:** The clinical trial data on which the indication was originally authorized is not available.

- **Pregnancy and Breast-feeding**: Verapamil hydrochloride crosses the placental barrier and can be detected in umbilical vein blood at delivery. Verapamil hydrochloride is excreted in human milk.
- **Genetic Polymorphism**: The effect of genetic polymorphism on verapamil hydrochloride pharmacokinetics has not been investigated.
- **Ethnic Origin**: The effect of different races on verapamil hydrochloride, when administered as APO-VERAP 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, metabolism is delayed and elimination half–life prolonged up to 14 to 16 hours. (see 4 DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment and 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).
- **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 7 WARNINGS AND PRECAUTIONS, Renal, Renal Insufficiency).
- **Obesity:** The clinical trial data on which the indication was originally authorized is not available.

11 STORAGE, STABILITY AND DISPOSAL

Store verapamil hydrochloride at controlled room temperature (15°C-30°C). Protect from light.

APO-VERAP should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

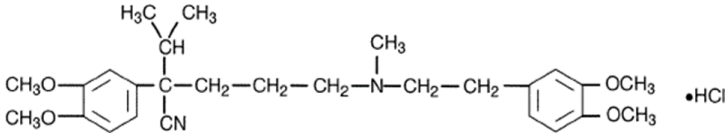
Drug Substance

Proper name: verapamil hydrochloride

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

Molecular formula and molecular mass: C27H38N2O4 •HCl and 491

Structural formula:



Physicochemical properties:

Description: 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.

14 CLINICAL TRIALS

14.3 Comparative Bioavailability Studies

A bioavailability study was performed using healthy human volunteers. The rate and extent of absorption of verapamil hydrochloride was measured and compared after a single oral dose of Isoptin 120 mg or Verapamil Hydrochloride 120 mg Tablets. The rate and extent of norverapamil formation was also measured and compared. The results can be summarized as follows:

Table 7. Summary of the rate and extent of absorption of a single dose of Isoptin 120 mg vs. Verapamil Hydrochloride 120 mg tables.

Verapamil Parameter	Isoptin (SD*)	Verapamil Hydrochloride Tablets (SD*)
AUC_{0-36} (ng.hr/mL)	537 (325)	537 (389)

C_{max} (ng/mL)	143 (77.9)	146 (127)
T_{max} (hr)	1.13 (0.35)	1.11 (0.43)
$t_{½}$ (hr)	3.32 (1.57)	3.39 (1.57)
Norverapamil Parameter		
AUC_{0-36} (ng.hr/mL)	843 (288)	843 (332)
C_{max} (ng/mL)	95.4 (29.5)	95.0 (34.9)
T_{max} (hr)	1.45 (0.53)	1.51 (0.54)
$t_{½}$ (hr)	7.79 (2.28)	7.92 (2.27)

*SD = Standard Deviation

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute Toxicity

Animal Species	Sex	LD_{50} (and 95% probability level exclusive of the 20% confidence limits) mg/kg
Albino mice*	F	186.5 (138.1 - 252.0)
	M	233.7 (224.2 - 243.7)
	Combined	224.3 (207.6 - 242.3)
Albino rats**	F	114.2 (75.3 - 173.1)
	M	159.4 (71.5 - 355.7)
	Combined	135.7 (103.5 - 178.1)

* 6 groups, each with 5 mice/sex were treated with the test article at logarithmically spaced doses.

** 8 groups, each with 5 rats/sex were treated with the test article at logarithmically spaced doses.

Mortality generally occurred over a 3–day period post–dosing in mice and a 2–day period in rats.

Toxicity was generally characterized by mild–to–severe decrease in motor activity, dyspnea, piloerection, lethargy and ptosis.

Necropsy of animals succumbing during the study generally demonstrated dark liver and reddened lungs with occasional dark spleen, dark and/or pale kidneys, reddened thymus and reddened duodenum or ileum in mice. Rats demonstrated dark liver, uncollapsed and/or reddened lungs with occasional hydrothorax. Those animals sacrificed upon completion of the study demonstrated no abnormal findings.

Subacute Toxicity

Oral Studies

Verapamil hydrochloride 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 were no drug–attributable histological changes. The baboons showed no drug related changes.

Intramuscular Studies

Dogs (beagles) 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 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 hydrochloride 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 dogs (beagles) at 0.1, 0.4 and 1.6 mg/kg levels (6 animals/group).

At the highest dose level in dogs, all 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 hydrochloride at 10, 15, 25, 30, 60 and 62.5 mg/kg/day (50 animals/group) and dogs (beagles) 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 hydrochloride 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 hydrochloride 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.

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.

Genotoxicity

Mutagenicity: In vitro mutagenicity tests showed that verapamil hydrochloride did not have mutagenic properties in five different strains of Salmonella typhimurium.

Reproductive and Developmental Toxicology:

Studies were carried out in rats and rabbits with verapamil hydrochloride 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, and the multiple daily dose of 25 mg/kg t.i.d, caused a higher resorption rate in the rat. There was no difference in resorption rates observed in the rabbit and no effect on peri and postnatal development or fertility in the rat.

Special Toxicology: information is not available.

Juvenile Toxicity: information is not available.

17 SUPPORTING PRODUCT MONOGRAPHS

1 ISOPTIN, verapamil hydrochloride tablets 80 mg and 120 mg, Submission Control number- 088765, Product Monograph, Abbott Laboratories, Limited, February 19, 2004.

2 ISOPTIN SR, verapamil hydrochloride sustained release tablets 120 mg, 180 mg and 240 mg. Submission Control number- 253349, Product Monograph, BGP Pharma ULC, December 7, 2021.

3 NOVO-VERAMIL (verapamil hydrochloride) 80 mg, 120 mg tablets; Submission Control number- 164741, Product Monograph, Teva Canada Limited, May 28, 2013.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]APO-VERAP

Verapamil Hydrochloride Tablets

Read this carefully before you start taking **APO-VERAP** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **APO-VERAP**.

What are APO-VERAP Tablets used for?

APO-VERAP tablets are used to treat:

- Chest pain (angina);
- Swelling of the heart muscles (obstructive hypertrophic cardiomyopathy);
- Irregular and rapid heart rate (atrial fibrillation or flutter);
- Abnormal heart rhythms (paroxysmal supraventricular tachycardia), as a follow-up treatment to injectable verapamil;
- High blood pressure (hypertension).

How does APO-VERAP work?

Verapamil hydrochloride belongs to a group of medicines called calcium channel blockers. Calcium channel blockers change the amount of calcium getting into the muscle cells in your heart and blood vessels. This can change the strength and speed with which your heart beats. It also opens up the blood vessels so blood can be pumped around the body more easily. This helps more oxygen to get to your heart muscle and can lower your blood pressure.

What are the ingredients in APO-VERAP?

Medicinal ingredients: Verapamil hydrochloride

Non-medicinal ingredients: carnauba wax, colloidal silicon dioxide, croscarmellose sodium, D&C yellow #10 aluminum lake 14-18% and FD&C yellow #6 aluminum lake (in 80 mg tablet only), hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol and titanium dioxide

APO-VERAP comes in the following dosage forms:

Tablets: 80 mg and 120 mg

Do not use APO-VERAP if:

- you are allergic to verapamil hydrochloride or any of the other ingredients of this medicine.
- you have recently had a severe heart attack.
- you have severe heart failure.
- you have low blood pressure (hypotension).
- You have severe problems with the impulses and rhythms of the heart (second or third degree atrioventricular block or sick sinus syndrome).
- you suffer from a slow heart rate (bradycardia).
- you have an irregular or rapid heartbeat (atrial fibrillation/flutter).
- you have an electrical abnormality of the heart causing periods of very fast heartbeat (Wolff-Parkinson-White syndrome, Lown-Ganong-Levine syndrome).
- you are breastfeeding.
- you are taking ivabradine, flibanserin or beta-blockers.
- you drink grapefruit juice.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take APO-VERAP. Talk about any health conditions or problems you may have, including if you:

- have angina or arrhythmia (irregular heartbeat) and taking other medicines for high blood pressure.
- have ever suffered from heart failure or heart attack.
- are taking beta blockers.
- have obstructive hypertrophic cardiomyopathy (swelling of the heart muscles).
- have a disorder that weakens your muscles (such as Myasthenia gravis, Lambert-Eaton syndrome or Duchenne's muscular dystrophy).
- have impaired liver function.
- have impaired kidney function.
- have low levels of calcium in your blood.
- have neuro-muscular disease (i.e. Duchenne's muscular dystrophy).
- are pregnant or planning to become pregnant.
- are breast feeding or planning to breastfeed. APO-VERAP can transfer to your baby through breastmilk. You should stop breastfeeding while taking APO-VERAP.

Other warnings you should know about:

Laboratory Testing:
Your doctor may order tests to help monitor your liver while you take APO-VERAP.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with APO-VERAP:

- Anti-cancer drugs used to treat cancer.
- Aspirin used to relieve pain and reduce fever or to prevent blood clots.
- Apixaban, edoxaban, rivaroxaban used to prevent blood clots.
- Atorvastatin, lovastatin, simvastatin used to reduce the risk of heart attack.
- Azole antifungals used to treat fungal infections.
- Beta blockers or other drugs used to treat high blood pressure.
- Cimetidine used to treat stomach ulcers.
- Clarithromycin, erthromycin, telithromycin used to treat infections.
- Colchicine used to treat gout.
- Cyclosporine used to prevent organ transplant rejection.
- Dabigatran used to treat blood clots and prevent stroke.
- Digoxin used to treat heart failure.
- Disopyramide, flecainide and quinidine used to treat abnormal heart rhythm.
- Erythromycin, rifampin used to treat infections.
- Everolimus, sirolimus, tacrolimus used to prevent organ transplant rejection.
- Terfenadine used for the treatment of allergic conditions.
- Inhalation anaesthetics used for general anaesthesia.
- Imipramine used to treat depression.
- Lithium used to treat depression.
- Phenytoin, carbamazepine and phenobarbital used to treat convulsions or seizures.
- Metformin used to treat diabetes.
- Neuromuscular blocking agents such as vecuronium used to relax the muscles.
- NSAIDS (Acetylsalicylic acid) used to treat pain and inflammation.
- Rifampin used to treat infections.
- Sulfinpyrazone used to treat gout.
- Theophylline used to treat asthma.
- Warfarin used to prevent the formation of blood clots.

Grapefruit juice can increase the amount of APO-VERAP in your blood. Do not drink grapefruit juice while taking APO-VERAP.

Drinking alcohol while taking APO-VERAP may cause the effects of alcohol to last longer. Do not drive a vehicle or operate heavy machinery if your ability to react is impaired.

How to take APO-VERAP:

- Follow the directions given to you by your healthcare professional. Your healthcare professional will decide your dose based on your current condition and health.
- Take APO-VERAP tablets by mouth.

- APO-VERAP tablets should be taken with food.
- Swallow the tablets whole with water, without chewing or crushing them.

Usual dose:

Angina Pectoris and Atrial fibrillation:

- The usual starting dose of APO-VERAP Tablets in adults is 80 mg 3-4 times daily. Your healthcare professional may increase the dose to 120 mg 3-4 times daily based on your health condition.
- The maximum dose should not exceed 480 mg per day.

Obstructive Hypertrophic Cardiomyopathy:

- The usual starting dose is 80 to 120 mg 3-4 times daily. If required, your healthcare professional may increase dose up to 600-720 mg/day.

Mild to Moderate Essential Hypertension

- Your healthcare professional will adjust your dosage based on how you respond to APO-VERAP.
- The usual initial adult dose is 80 mg 3 times per day. The maximum dose should not exceed 480 mg per day.

Overdose:

If you think you or your child, or a person you are caring for, have taken too much APO-VERAP, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take a dose, take it as soon as you remember. If it is nearly time for the next dose, skip the missed dose and take the next dose at the right time. Do NOT take a double dose to make up for a forgotten dose.

What are possible side effects from using APO-VERAP?

These are not all the possible side effects you may have when taking APO-VERAP. If you experience any side effects not listed here, tell your healthcare professional.

Side Effects Include:

- bruising
- claudication (pain in your thigh, calf, or buttocks that happens when you walk)
- confusion, dizziness, feeling like you are going to fall
- constipation

- diarrhea
- dry mouth
- flushing (reddening of the skin)
- frequent urination
- gynecomastia (enlargement of breast in men)
- hair loss
- hyperkeratosis (thickening of skin)
- hyperkinesis (a state of overactive restlessness)
- impotence
- macules (a flat, distinct, discolored area of skin less than a centimeter wide)
- muscle cramps or fatigue
- numbness of arms or legs
- oligomenorrhea (infrequent menstrual periods)
- pain or discomfort in the stomach
- paresthesia (pins and needles)
- purpura (purple-colored spots and patches that occur on the skin)
- painful coldness
- rotary nystagmus (involuntary, rapid, and repetitive movement of the eyes)
- sleepiness
- sleeping difficulties
- shakiness
- spotty menstruation
- sweating
- swelling of the gums
- vertigo (sudden dizziness)
- vomiting

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Atrial fibrillation / Rapid Ventricular Response (abnormal heart rhythm which is rapid and irregular): chest discomfort with unpleasant awareness of your heartbeat, fainting, shortness of breath, weakness			√
A-V Block (Heart Block): Fainting, dizziness, chest pain, feeling tired, shortness of			√

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
breath, heart palpitations, rapid breading, nausea.			
Heart failure (heart does not pump blood as well as it should)**:** shortness of breath, fatigue and weakness, swelling in ankles, legs and feet, cough, fluid retention, lack of appetite, nausea, rapid or irregular heartbeat, reduced ability to exercise			√
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up)			√
Pulmonary edema (excess fluid in the lungs): difficulty breathing that worsens with activity or when lying down, extreme shortness of breath, wheezing or gasping for breath, cold clammy skin, irregular heartbeat, cough that produces frothy sputum, blue-tinged lips			√
UNCOMMON			
Angina pectoris (chest pain or discomfort due to coronary heart disease)			√
Stroke (bleeding or blood clot in the brain)**:** sudden numbness, weakness or tingling of the face, arm, or leg, particularly on one side of the body, sudden headache, blurry vision, difficulty swallowing or speaking, or lethargy, dizziness, fainting, vomiting, trouble			√

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
understanding, trouble with walking and loss of balance			
Psychotic symptoms (mental illness): depression		√	
Stevens-Johnson syndrome (SJS) (severe skin rash): redness, blistering and/or peeling of the skin and/or inside of the lips, eyes, mouth, nasal passages or genitals, accompanied by fever, chills, headache, cough, body aches or swollen glands			√
Jaundice (build up of bilirubin in the blood): yellowing of the skin and eyes, dark urine, light coloured stool, itching all over your body		√	
RARE			
Allergic Reaction: difficulty swallowing or breathing, wheezing, nausea, vomiting, hives or rash, swelling of the face, lips, tongue or throat.			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at controlled room temperature (15°C-30°C).

Protect from light.

Keep out of reach and sight of children.

If you want more information about APO-VERAP:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html). Find the Patient Medication Information on the manufacturer's website (http://www.apotex.ca/products), or by calling 1-800-667-4708.

This leaflet was prepared by APOTEX INC., Toronto, Ontario, M9L 1T9.

Last Revised MAY 12, 2022