

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PRISOPTIN®SR

verapamil hydrochloride sustained-release tablets
120 mg, 180 mg and 240 mg

Manufacturer's Standard

Antihypertensive Agent

BGP Pharma ULC
85 Advance Road
Etobicoke, Ontario
M8Z 2S6

Date of Initial Authorization:
December 18, 2014

Date of Revision:
December 7, 2021

Submission Control Number: 253349

RECENT MAJOR LABEL CHANGES

| | |
|---------------------------------|--------------|
| CONTRAINDICATIONS | October 2019 |
| WARNINGS AND PRECAUTIONS | |

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed .

| | |
|---|-----------|
| RECENT MAJOR LABEL CHANGES | 2 |
| TABLE OF CONTENTS | 2 |
| PART I: HEALTH PROFESSIONAL INFORMATION | 4 |
| INDICATIONS | 4 |
| 1.1 Pediatrics | 4 |
| 1.2 Geriatrics..... | 4 |
| CONTRAINDICATIONS | 4 |
| 4 DOSAGE AND ADMINISTRATION | 5 |
| 4.1 Dosing Considerations | 5 |
| 4.2 Recommended Dose and Dosage Adjustment..... | 6 |
| 4.4 Administration..... | 6 |
| 4.5 Missed Dose | 6 |
| 5 OVERDOSAGE | 7 |
| 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING | 8 |
| 7 WARNINGS AND PRECAUTIONS | 9 |
| 7.1 Special Populations..... | 13 |
| 7.1.1 Pregnant Women..... | 13 |
| 7.1.2 Breast-feeding..... | 13 |
| 7.1.3 Pediatrics..... | 13 |
| 7.1.4 Geriatrics | 13 |
| 8 ADVERSE REACTIONS | 14 |
| 8.1 Adverse Reaction Overview..... | 14 |

| | | |
|--|--|-----------|
| 8.2 | Clinical Trial Adverse Reactions | 14 |
| 8.3 | Less Common Clinical Trial Adverse Reactions | 15 |
| 8.4 | Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data | 16 |
| 8.5 | Post-Market Adverse Reactions..... | 16 |
| 9 | DRUG INTERACTIONS | 17 |
| 9.1 | Serious Drug Interactions..... | 17 |
| 9.2 | Drug Interactions Overview..... | 17 |
| 9.3 | Drug-Behavioural Interactions..... | 17 |
| 9.4 | Drug-Drug Interactions | 17 |
| 9.5 | Drug-Food Interactions | 26 |
| 9.6 | Drug-Herb Interactions | 26 |
| 9.7 | Drug-Laboratory Test Interactions | 26 |
| 10. | CLINICAL PHARMACOLOGY | 26 |
| 10.1 | Mechanism of Action..... | 26 |
| 10.2 | Pharmacodynamics | 27 |
| 10.3 | Pharmacokinetics..... | 27 |
| 11 | STORAGE, STABILITY AND DISPOSAL | 31 |
| PART II: SCIENTIFIC INFORMATION | | 32 |
| 13 | PHARMACEUTICAL INFORMATION..... | 32 |
| 14 | CLINICAL TRIALS..... | 33 |
| 16 | NON-CLINICAL TOXICOLOGY | 33 |
| | Acute Toxicity | 33 |
| | Subacute Toxicity | 33 |
| | Chronic Toxicity..... | 34 |
| PATIENT MEDICATION INFORMATION | | 36 |

PART I: HEALTH PROFESSIONAL INFORMATION

INDICATIONS

ISOPTIN® SR (verapamil hydrochloride) sustained-release tablets is indicated for:

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

ISOPTIN® 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 ISOPTIN® 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.

ISOPTIN® SR should not be used concurrently with beta-adrenoreceptor blockers in the treatment of hypertension. (see **9 DRUG INTERACTIONS, Table 5**).

1.1 Pediatrics

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

1.2 Geriatrics

Caution should be exercised when ISOPTIN® SR is administered to elderly patients. (see **7 WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics**).

CONTRAINDICATIONS

ISOPTIN® SR is contraindicated in the following situations:

- Patients who are hypersensitive to this drug 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, STRENGTH, COMPOSITION AND PACKAGING**.
- Complicated myocardial infarction (patients who have ventricular failure manifested by pulmonary congestion).
- Severe left ventricular dysfunction. (see **7 WARNINGS AND PRECAUTIONS, Cardiovascular, Heart Failure**)
- Cardiogenic shock.
- Severe hypotension.

- Second or third degree atrioventricular (A-V) block.
- Sick sinus syndrome. (see **7 WARNINGS AND PRECAUTIONS, Cardiovascular**).
- 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 **7 WARNINGS AND PRECAUTIONS, Cardiovascular, Accessory Bypass Tract**).
- ISOPTIN® SR is contraindicated with concomitant use of ivabradine as it may result in increased concentrations of ivabradine due to inhibition of CYP3A4 (see **9 DRUG INTERACTIONS**).
- ISOPTIN® SR 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, Cardiovascular, Hypotension**).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

The antihypertensive effects of ISOPTIN® 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: ISOPTIN® 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 overdose. ISOPTIN® SR should not be used in severe hepatic dysfunction. (see **7 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 ISOPTIN® Tablets to ISOPTIN® SR Tablets: When switching from ISOPTIN® (verapamil hydrochloride) immediate-release tablets to ISOPTIN® SR (verapamil hydrochloride) sustained-release tablets, the total daily dose in milligrams may remain the same.

4.2 Recommended Dose and Dosage Adjustment

Mild to Moderate Essential Hypertension

The dosage should be individualized by titration depending on patient tolerance and responsiveness to ISOPTIN® 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 180 to 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** below.

Table 1. Recommended Dosing Intervals for Specific Daily Dosages

| Total Daily ISOPTIN® 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 ISOPTIN® SR, i.e. 120 mg a day, may be warranted in elderly patients (i.e. 65 years and older). (see **7 WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics**). The dosage should be carefully and gradually adjusted depending on patient tolerability and response.

4.4 Administration

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

ISOPTIN® SR tablets should be taken with food. (see **10 CLINICAL PHARMACOLOGY, Pharmacokinetics, Influence of Food**).

4.5 Missed Dose

If you forget to take one tablet, take another as soon as you remember, unless it is almost time for your next dose. If it is, do not take the missed tablet at all. Never double-up on a missed dose.

5 OVERDOSAGE

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, 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

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.

Overdose-related ARDS can result from noncardiogenic pulmonary edema, and has been reported up to 24 hours after initial hemodynamic stabilization is achieved.

In case of overdosage with large amounts of ISOPTIN® 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**).

Table 2. 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 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 3. Dosage Forms, Strengths, Composition and Packaging

| Route of Administration | Dosage Form / Strength/Composition | Non-medicinal Ingredients |
|-------------------------|--|--|
| Oral | sustained-release tablets/120 mg, 180 mg, 240 mg | hydroxypropyl methylcellulose, indigo carmine (240 mg tablet only), macrogol 400, macrogol 6000, magnesium stearate, microcrystalline cellulose, montan glycol wax, povidone, purified water, quinoline yellow (240 mg tablet only), red iron oxide (180 mg tablet only), sodium alginate, talc, titanium dioxide <i>This is a complete listing of non-medicinal ingredients.</i> |

ISOPTIN® 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.

ISOPTIN® SR 120 mg tablets are supplied as white, biconvex, film-coated tablet with “120 SR” embossed on one side and KNOLL on the other side and are available in bottles of 100 tablets.

ISOPTIN® SR 180 mg tablets are supplied as old rose, oval, film-coated tablet with KNOLL embossed on one side and “SR”; score; “180” on the other side and are available in bottles of 100 tablets.

ISOPTIN® SR 240 mg tablets are supplied as light green, oblong, film-coated tablet with 2x KNOLL logo (a triangle of arched sides) divided by a score embossed on one side, and a score on the other side and are available in bottles of 100 and 500 tablets.

7 WARNINGS AND PRECAUTIONS

General

In patients with angina or arrhythmias using antihypertensive drugs, the additional hypotensive effect of ISOPTIN® SR (verapamil hydrochloride) sustained-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. These doses correspond to approximately 2.3 and 2 times human exposure based on body surface area, respectively.

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 **16 NON CLINICAL TOXICOLOGY, Carcinogenicity, and Mutagenicity**).

Cardiovascular

Heart Failure

Because of the drug's negative inotropic effect, ISOPTIN® SR 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 ISOPTIN® SR treatment.

If ISOPTIN® SR is administered concomitantly with digoxin, reduce digoxin dosage. (see **9 DRUG INTERACTIONS, Table 5**). The use of ISOPTIN® SR 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 ISOPTIN® SR.

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 ISOPTIN® SR at least 2 weeks prior to starting flibanserin. Do not administer ISOPTIN® SR within 2 days of discontinuing flibanserin.

Conduction Disturbance

ISOPTIN® SR affects the A-V and sinoatrial (S-A) nodes. ISOPTIN® SR slows conduction across the A-V node. ISOPTIN® 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 ISOPTIN® SR, 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 **2 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 **8 ADVERSE REACTIONS** and **5 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 **2 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 **9 DRUG INTERACTIONS, Table 5**).

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.

ISOPTIN® SR 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 ISOPTIN® SR 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 **9 DRUG INTERACTIONS, Table 5**).

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 **9 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 ISOPTIN® SR 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 **10 CLINICAL PHARMACOLOGY, Pharmacokinetics** and **4 DOSAGE AND ADMINISTRATION**).

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 ISOPTIN® SR 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 ISOPTIN® SR's neuromuscular blocking action, ISOPTIN® SR 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 ISOPTIN® SR 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 **4 DOSAGE AND ADMINISTRATION, Dosing Considerations, 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, ISOPTIN® SR 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**).

Verapamil hydrochloride is not removed by hemodialysis.

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. ISOPTIN® SR 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 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 breast milk. Because of the potential for adverse reactions in nursing infants from verapamil hydrochloride, nursing should be discontinued while ISOPTIN® SR is administered.

7.1.3 Pediatrics

The safety and dosage regimen of ISOPTIN® SR 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

Caution should be exercised when ISOPTIN® SR 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**). 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 Reaction Overview

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

In controlled pivotal studies with 128 patients treated with ISOPTIN® SR (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 hydrochloride immediate release tablets and 4.7% of patients on ISOPTIN® SR.

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 the 4,954 (4,826 + 128) patient base.

Table 4. 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% |
| A-V Block | |
| Total (1 ^o , 2 ^o , 3 ^o) | 1.2% |
| 2 ^o and 3 ^o | 0.8% |

| | Verapamil Hydrochloride (N = 4,954) |
|---|--|
| 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% |

8.3 Less Common Clinical Trial Adverse Reactions

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, hyperkinesia, 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 Mediastinal Disorders: | bronchospasm, dyspnea |
| 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.

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: | 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 |
| Metabolism and Nutrition Disorders: | hyperkalaemia |
| 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 **9 DRUG INTERACTIONS**).

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Ivabradine: ISOPTIN® SR is contraindicated with concomitant use of ivabradine as it may result in increased concentrations of ivabradine due to inhibition of CYP3A4

Flibanserin: ISOPTIN® SR 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, Cardiovascular, Hypotension**).

9.2 Drug Interactions Overview

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. Co-administration of verapamil and a drug primarily metabolized by CYP3A4 or being a P-gp substrate may be associated with elevations in drug concentrations that could increase or prolong both therapeutic and adverse effects of the concomitant drug. 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 ISOPTIN® SR (verapamil hydrochloride) sustained-release tablets to maintain optimum therapeutic blood levels.

9.3 Drug-Behavioural 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.

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 5. 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 | | | |

| Concomitant Drug Class: Drug Name | Ref | Effect on Concentration of Verapamil Hydrochloride or Concomitant Drug | Clinical Comment |
|--|------------|---|--|
| Prazosin | T | ↑ prazosin C _{max} (~40%) with no effect on t _½ | 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 also have 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 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 | | | |

| Concomitant Drug Class: Drug Name | Ref | Effect on Concentration of Verapamil Hydrochloride or Concomitant Drug | Clinical Comment |
|--|------------|---|--|
| 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. |
| 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 may need to be reduced (see DOAC label for dosing instructions). |
| 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 administered 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%) | |
| Metformin | T | | Co-administration of verapamil with metformin may reduce the efficacy of metformin. |
| 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 increased exposure to colchicine. Combined use is not recommended. |

| Concomitant Drug Class: Drug Name | Ref | Effect on Concentration of Verapamil Hydrochloride or Concomitant Drug | Clinical Comment |
|-----------------------------------|-----|--|---|
| 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 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. |

| Concomitant Drug Class: Drug Name | Ref | Effect on Concentration of Verapamil Hydrochloride or Concomitant Drug | Clinical Comment |
|--|--------|--|--|
| 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 7 WARNINGS AND PRECAUTIONS). Verapamil hydrochloride should not be combined with beta-blockers for the treatment of hypertension. |
| Propranolol | T C | ↑ propranolol 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 |

| Concomitant Drug Class: Drug Name | Ref | Effect on Concentration of Verapamil Hydrochloride or Concomitant Drug | Clinical Comment |
|-----------------------------------|-----|--|--|
| Digoxin | C | <p>↑ digoxin levels ~50-75% during the first week of therapy</p> <p>↑ digoxin AUC (~32%), C_{max} (~98%) in hepatic cirrhosis patients</p> <p>↑ digoxin C_{max} (~44%), ↑ digoxin C_{12h} (~53%), ↑ C_{ss} (~44%) and ↑ AUC (~50%) in healthy subjects</p> | <p>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).</p> |

| Concomitant Drug Class: Drug Name | Ref | Effect on Concentration of Verapamil Hydrochloride or Concomitant Drug | Clinical Comment |
|--|-----|--|--|
| Cardiac I_f Current Inhibitor | | | |
| Ivabradine | CT | Given its moderate CYP3A4 inhibitory effect, verapamil (120 mg b.i.d.), when co-administered with ivabradine, increases the ivabradine plasma AUC by 2- to 3- fold. Both verapamil 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 ISOPTIN® SR with ivabradine is contraindicated (see 2 <u>CONTRAINDICATIONS</u>). |
| Diuretics | | | |
| | T | | Concomitant use with diuretics may cause a potentiation of the hypotensive effect. |
| Gynecologicals | | | |
| Flibanserin | T | Use of a moderate CYP3A4 inhibitor such as verapamil with flibanserin significantly increases flibanserin concentrations, which can lead to severe hypotension and syncope (see <u>CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Cardiovascular, Hypotension</u>). | Concomitant use of ISOPTIN® SR and flibanserin is contraindicated. Discontinue ISOPTIN® SR at least 2 weeks prior to starting flibanserin. Do not administer ISOPTIN® SR within 2 days of discontinuing flibanserin (see 2 <u>CONTRAINDICATIONS and 7 <u>WARNINGS AND PRECAUTIONS, Cardiovascular, Hypotension</u></u>). |
| H2-Receptor Antagonists | | | |
| Cimetidine | T | In healthy subjects, ↑ AUC of R-(~25%) and S-(~40%) verapamil with corresponding ↓ in R- and S-verapamil clearance | |

| Concomitant Drug Class: Drug Name | Ref | Effect on Concentration of Verapamil Hydrochloride or Concomitant Drug | Clinical Comment |
|---|--------|--|---|
| 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) | | | |
| 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 |
| Lovastatin | C | Possible ↑ lovastatin levels ↑ verapamil AUC (by ~63%) and C_{max} by (~32%) | |

| Concomitant Drug Class: Drug Name | Ref | Effect on Concentration of Verapamil Hydrochloride or Concomitant Drug | Clinical Comment |
|---|---------|--|---|
| Simvastatin | C | ↑ simvastatin AUC (~2.6-fold), C _{max} (~4.6 fold) in healthy subject | 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. The maximum daily dose of simvastatin and lovastatin coadministered with verapamil hydrochloride should not exceed 10 and 20 mg, respectively. Fluvastatin, pravastatin and rosuvastatin are not metabolized by CYP3A4 and are less likely to interact with verapamil hydrochloride. |
| 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 | | | |
| 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

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.

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 C_{max} .

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been evaluated.

10. CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

ISOPTIN® SR (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 A-V conduction. In another study using septal strips isolated from the left ventricle of five patients with mitral disease, the S-enantiomer was 8 times more potent than the R-enantiomer in reducing myocardial contractility.

Animal Pharmacology

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

In isolated cardiac tissues, at low to moderate concentrations, verapamil 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.

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. 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.

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 $t_{1/2}$ 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 $t_{1/2}$ 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 ISOPTIN® (verapamil hydrochloride) immediate-release tablets (fasting) and ISOPTIN® SR (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 6. Pharmacokinetic Data Comparing a Single-Dose of ISOPTIN® Immediate-Release Tablet vs. ISOPTIN® SR Sustained-Release Tablet

| Parameter | ISOPTIN® Immediate-Release Tablet (240 mg) | | ISOPTIN® SR 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 times daily at 8 hourly intervals for five days is summarized in the following table.

Table 7. Steady-State Pharmacokinetic Data Comparing ISOPTIN® Immediate-Release Tablet vs. ISOPTIN® SR Sustained-Release Tablet

| Parameters | ISOPTIN® Immediate-Release 120 mg Tablet** (360 mg daily) | ISOPTIN® SR Sustained-Release 240 mg Tablet** (360 mg daily) | ISOPTIN® SR 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-∞} (ng/mL/hr) | 1850 | 3466 | 4484 |
| AUC ₀₋₃₆ (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.

Influence of Food: Administration of ISOPTIN® SR 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.

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 t_{1/2} prolonged up to 14 to 16 hours.

Elimination:

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).

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 $t_{1/2}$.

- **Sex**

The effect of gender on verapamil hydrochloride, when administered as ISOPTIN[®] SR, has not been investigated.

- **Ethnic Origin**

The effect of different races on verapamil hydrochloride, when administered as ISOPTIN[®] 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 $t_{1/2}$ prolonged up to 14 to 16 hours. (see **7 WARNINGS AND PRECAUTIONS, Hepatic Biliary Pancreatic, Hepatic Insufficiency** and **4 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 **7 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.

11 STORAGE, STABILITY AND DISPOSAL

Store ISOPTIN® SR (verapamil hydrochloride) sustained-release tablets at 15 to 25°C. Do not use beyond the expiry date indicated on the label.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

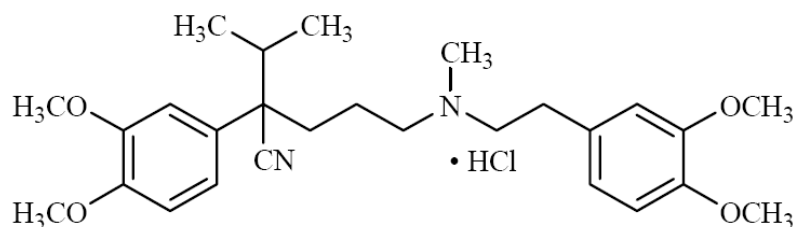
Drug Substance

Proper name: verapamil hydrochloride

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

Molecular formula and molecular mass: $C_{27}H_{38}N_2O_4 \cdot HCl$ 491.07

Structural formula:



Physicochemical properties: Verapamil, as the hydrochloride, is an almost white, bitter-tasting crystalline powder practically free from odour. It is 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.

14 CLINICAL TRIALS

The clinical trial data on which the original indication was authorized are not available.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute Toxicity

Table 8. Lethal Dose 50 (LD₅₀) (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 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. 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 at 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.

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 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:

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).

Reproductive and Developmental Toxicology:

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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrISOPTIN® SR

Verapamil Hydrochloride Sustained-Release Tablets

Read this carefully before you start taking **ISOPTIN® SR** 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 **ISOPTIN® SR**.

What is ISOPTIN® SR used for?

ISOPTIN® SR is used to treat high blood pressure (hypertension) in adults (18 years of age or older) that:

- cannot take diuretics (medicines used to increase the amount of water released in your urine),
- cannot take beta blockers (medicines used to treat high blood pressure), or
- experience serious side effects when taking diuretics or beta blockers.

How does ISOPTIN® SR work?

ISOPTIN® SR belongs to a group of medicines known as calcium channel blockers. Calcium channel blockers change the amount of calcium getting into the muscle cells of your heart and blood vessels. This can change the strength and speed at which your heart beats. It also opens up the blood vessels so that blood can be pumped around your body more easily. This helps to lower your blood pressure.

What are the ingredients in ISOPTIN® SR?

Medicinal ingredient: verapamil hydrochloride.

Non-medicinal ingredients: hydroxypropyl methylcellulose, indigo carmine (240 mg tablet only), macrogol 400, macrogol 6000, magnesium stearate, microcrystalline cellulose, montan glycol wax, povidone, purified water, quinoline yellow (240 mg tablet only), red iron oxide (180 mg tablet only), sodium alginate, talc, and titanium dioxide.

ISOPTIN® SR comes in the following dosage forms:

Sustained-release tablets: 120 mg, 180 mg, and 240 mg of verapamil hydrochloride.

Do not use ISOPTIN® SR if:

- you are allergic to verapamil hydrochloride or to any other ingredients in ISOPTIN® SR.
- you have any of the following heart conditions:
 - left ventricular dysfunction (a weakness to part of the heart that pumps oxygen-rich blood to the rest of the body);
 - cardiogenic shock (heart is not able to pump enough blood to the body);
 - second or third degree heart block (a type of irregular heart beat and rhythm);
 - sick sinus syndrome (heart's natural pacemaker is unable to create normal heartbeats at the normal rate);
 - bradycardia (abnormally slow heart beat); or
 - atrial flutter or atrial fibrillation (abnormal heart rhythm which is rapid and irregular), and you

also have an accessory bypass tract (e.g., Wolff-Parkinson-White and Lown-Ganong-Levine syndromes).

- you have had a heart attack, and you also have heart failure.
- you are taking ivabradine, medicine used to treat chronic heart failure by lowering the heart rate.
- you are taking or have recently taken (within the last 2 days) flibanserin, a medicine used to treat a condition known as hypoactive sexual desire disorder (HSDD) in women.

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

- are pregnant or planning to become pregnant. ISOPTIN® SR is not recommended during pregnancy.
- are breastfeeding or planning to breastfeed. ISOPTIN® SR can be passed in your breast milk and is not recommended during breastfeeding.
- have any heart problems.
- have kidney problems.
- have liver problems.
- are taking beta blockers. ISOPTIN® SR should not be taken with beta blockers as this can cause serious adverse effects.
- have neuromuscular disease (e.g. myasthenia gravis, Lambert-Eaton syndrome, or Duchenne muscular dystrophy).
- have high levels of calcium in your blood.
- are 65 years of age or older.

Other warnings you should know about:

Taking ISOPTIN® SR can cause the following:

- **Hypotension** (low blood pressure): This can occur after a single dose and even after several months of treatment. If you develop hypotension, your healthcare professional may reduce your dose of ISOPTIN® SR.
- **Heart problems:** This includes:
 - heart block (a type of irregular heartbeat and rhythm). ISOPTIN® SR may worsen a first-degree heart block to the second- or third-degree;
 - bradycardia (abnormally slow heartbeat); and
 - asystole (no electrical activity in the heart and the heart stops beating).

If you develop a heart problem, your healthcare professional may decide to reduce or stop your treatment with ISOPTIN® SR. A therapy may also be recommended by your healthcare professional to treat the heart problem.

- **Liver problems:** This includes an increase of certain liver enzymes that can result in the injury or death of liver cells. Your healthcare professional will monitor your liver enzyme levels throughout treatment. If you develop any liver problems, your healthcare professional may reduce your dose of ISOPTIN® SR.

See the **Serious side effects and what to do about them** table, below, for more information on these and other serious side effects.

Monitoring and testing: If you are prescribed ISOPTIN® SR, your healthcare professional may conduct various tests depending on your health and the other medicines you take. This includes blood tests, blood pressure checks, and electrocardiogram tests (used to evaluate your heart). Your healthcare professional will interpret your results and may adjust your dose or stop your treatment with ISOPTIN® SR.

Driving and using machines: ISOPTIN® SR may affect your ability to react. This may be more likely to occur at the start of your treatment and when your dose is raised. You should not drive or use machines until you know how ISOPTIN® SR affects you.

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 ISOPTIN® SR:

Serious Drug Interactions

Serious drug interactions with ISOPTIN® SR include:

- ivabradine, a medicine used to treat chronic heart failure by lowering the heart rate. Do not take ISOPTIN® SR if you are taking ivabradine.
- flibanserin, a medicine used to treat a condition known as hypoactive sexual desire disorder (HSDD) in women. Do not take ISOPTIN® SR if you are taking or have recent taken (within 2 days) discontinuing flibanserin. In addition, if you plan to start taking flibanserin, you must wait at least 2 weeks after your last dose of ISOPTIN® SR.

- alcohol.
- almotriptan, a medicine used to treat acute migraine headaches.
- anesthetics, medicines used to prevent pain during surgery.
- antiarrhythmics, medicines used to treat or prevent irregular heartbeats (e.g., disopyramide, flecainide, and quinidine).
- anticoagulants, medicines used to prevent blood clotting (e.g., dabigatran, rivaroxaban, apixaban, and edoxaban).
- anticonvulsants also known as antiepileptics, medicines used to prevent epilepsy or seizures (e.g., carbamazepine and phenytoin).
- antidepressants, medicines used to treat depression (e.g., tranquilizers, tricyclic antidepressants, and imipramine).
- antidiabetics, medicines used to treat diabetes (e.g., glibenclamide and metformin).
- anti-gout agents, medicines used to treat chronic gout (e.g., colchicine and sulfapyrazone).
- antihypertensive agents, medicines used to treat high blood pressure:
 - alpha blockers (e.g., terazosin and prazosin);
 - beta blockers (e.g., propranolol, metoprolol, atenolol, and timolol);
 - vasodilators;
 - angiotensin-converting enzyme (ACE) inhibitors; and
 - diuretics (e.g., hydrochlorothiazide).
- anti-infectives, medicines used to prevent or treat infections (e.g., clarithromycin, erythromycin,

rifampicin, and telithromycin).

- antineoplastics, medicines used to treat cancer (e.g., doxorubicin).
- anxiolytics, medicines typically used to treat anxiety, insomnia, and seizures (e.g., benzodiazepines, buspirone, and midazolam).
- aspirin (acetylsalicylic acid), a non-steroidal anti-inflammatory agents (NSAIDs) used to reduce pain and swelling.
- barbiturates, medicines used to relax the body and help with sleeping (e.g., phenobarbital)
- cardiac glycosides, medicines used to treat heart failure and certain heartbeats problems (e.g., digitoxin and digoxin).
- cimetidine, a medicine used to treat heartburn and certain types of stomach ulcers.
- grapefruit juice.
- HIV antiviral agents, medicines used to treat HIV infection (e.g., ritonavir).
- immunosuppressive agents, medicines used to treat autoimmune diseases (e.g., cyclosporine, everolimus, sirolimus, and tacrolimus).
- lipid metabolism regulators, medicines used to lower the amount of cholesterol in the blood and prevent coronary heart disease (e.g., atorvastatin, simvastatin, and lovastatin).
- lithium, a medicine used to treat bipolar disorder.
- neuromuscular blocking agents, medicines used to cause muscle relaxation (e.g., atracurium).
- St. John's wort, a herbal medicines commonly used to treat depression and mood disorders.
- theophylline, a medicine used to relieve symptoms of asthma.

How to take ISOPTIN® SR:

- Take ISOPTIN® SR exactly as directed by your healthcare professional.
- The ISOPTIN® SR tablets should be taken with food should be taken with sufficient liquid, preferably with or shortly after meals. Do not crush or chew the tablets.
- The ISOPTIN® SR 180 mg and 240 mg tablets are scored. However, only the 240 mg tablets may be cut in half without damaging the modified release formulation. Do not cut the 180 mg tablets.

Usual dose:

Your healthcare professional will decide how much ISOPTIN® SR you should take each day. This may depend on your condition and if you take other medications.

The usual starting adult dose for ISOPTIN® SR is 180 mg to 240 mg per day, taken at the same time every day. The maximum dose is 480 mg each day. This is usually taken as one ISOPTIN® SR 240 mg tablet in the morning and one in the evening, leaving a gap of about 12 hours between each dose.

Overdose:

If you think you, or a person you are caring for, have taken too much ISOPTIN® SR, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget or miss a dose of ISOPTIN® SR, take it as soon as you remember. If it is almost time for your next dose, then do not take the missed dose at all. Do not take a double dose to make up for a missed dose. If you are unsure what to do, ask your healthcare professional.

What are possible side effects from using ISOPTIN® SR?

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

Side effects of ISOPTIN® SR may include constipation and headaches. Check with your healthcare professional if you are concerned by any of the above side effects.

| 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 | | | |
| Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, or fatigue (may occur when you go from lying or sitting to standing up). | | √ | |
| Edema: unusual swelling of the arms, hands, legs, feet and ankles, face or airway passages. | | √ | |
| Heart failure (heart does not pump blood as well as it should): shortness of breath, difficult breathing, fatigue, weakness, swelling in ankles, legs and feet, cough, fluid retention, lack of appetite, nausea, rapid or irregular heartbeat, or reduced ability to exercise. | | | √ |
| Heart block (a type of irregular heartbeat and rhythm): feeling lightheaded, fainting, dizziness, shortness of breath, difficult breathing, nausea, or fatigue. | | | √ |
| Bradycardia (abnormally slow heartbeat) | | √ | |
| UNCOMMON | | | |
| Skin disorders: rash, painful red lumps, itchiness, sweating, redness, pain in joints, or pain in | | | √ |

| 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 | |
| muscles. | | | |
| Muscle problems: joint pain, muscle cramps, or muscle weakness. | | √ | |
| UNKNOWN FREQUENCY | | | |
| Liver problems: feeling of discomfort, fever, right upper abdominal pain, jaundice (yellowing of the skin or whites of eyes), dark urine, or light coloured stools. | | √ | |

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

Storage:

Store the ISOPTIN® SR tablets at 15°C to 25°C.

Do not take your tablets after the expiry date shown on the label.

It is important to keep the ISOPTIN® SR tablets in the original package.

Keep out of reach and sight of children.

If you want more information about ISOPTIN® SR:

- 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>); the manufacturer's website www.mylan.ca, or by calling 1-844-596-9526.

This information is current up to the time of the last revision date shown below, but more current information may be available from the manufacturer.

This leaflet was prepared by BGP Pharma ULC.

Last Revised: December 7, 2021