

PRODUCT MONOGRAPH

**Pr<sup>phl</sup>-VERAPAMIL SR**

Verapamil hydrochloride Sustained-Release Tablets, USP

240 mg

Antihypertensive Agent

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**Pr phl-VERAPAMIL SR**  
Verapamil Hydrochloride Sustained-Release Tablets, USP

**PART I: HEALTH PROFESSIONAL INFORMATION**

**SUMMARY PRODUCT INFORMATION**

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>All Nonmedicinal Ingredients</b>
oral	Sustained-release tablets/ 240 mg	carnauba wax, D&C Yellow No. 10 lake, FD&C Blue No. 1 lake, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, sodium alginate, titanium dioxide.

**INDICATIONS AND CLINICAL USE**

phl-VERAPAMIL SR (verapamil hydrochloride) sustained-release tablets is indicated for:

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

phl-VERAPAMIL 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 verapamil hydrochloride with a diuretic or an angiotensin converting enzyme (ACE) inhibitor has been shown to be compatible and to have additive blood pressure lowering effects

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

**Geriatrics (≥ 65 years of age):**

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

**Pediatrics (< 18 years of age):**

phl-VERAPAMIL SR has not been studied in children and therefore use in this age group is not recommended.

## CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.
- Complicated myocardial infarction (patients who have ventricular failure manifested by pulmonary congestion).
- Severe congestive heart failure and/or severe left ventricular dysfunction (i.e. ejection fraction < 40%), unless secondary to a supraventricular tachycardia amenable to oral verapamil therapy.
- Cardiogenic shock.
- Severe hypotension.
- Second- or third-degree atrioventricular (A-V) block.
- Sick sinus syndrome. See (**WARNINGS AND PRECAUTIONS, Cardiovascular, Conduction Disturbance**).
- Marked bradycardia.
- Patients with atrial flutter or atrial fibrillation and an accessory bypass tract (e.g. Wolff-Parkinson-White, Lown-Ganong-Levine syndromes). See (**WARNINGS AND PRECAUTIONS, Cardiovascular, Accessory Bypass Tract**).

## WARNINGS AND PRECAUTIONS

### **General**

In patients with angina or arrhythmias using antihypertensive drugs, the additional hypotensive effect of verapamil 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.

### **Patients with Neuromuscular Diseases**

Due to verapamil hydrochloride neuromuscular blocking action, phl-VERAPAMIL 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 phl-VERAPAMIL 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 (**DRUG INTERACTIONS, Drug-Drug Interaction, Use in Patients with Attenuated (Decreased) Neuromuscular Transmission**).

### **Carcinogenesis and Mutagenesis**

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

*In vitro* mutagenicity tests showed that verapamil did not have mutagenic properties in five different strains of *Salmonella typhimurium*, nor in studies on chromosomal aberrations and sister chromatid exchanges (SCE) in human lymphocytes, nor in the hypoxanthine guanine phosphoribosyltransferase (HGPRT)-test with V-79 Chinese hamster cells, and also not in the cell transformation assay with Syrian hamster embryo cells. In addition, verapamil did not show any SCE-inducing activity *in vivo* (Chinese hamster). See (**TOXICOLOGY, Carcinogenicity and Mutagenicity**).

## **Cardiovascular**

### **Heart Failure:**

Because of the drug's negative inotropic effect, verapamil hydrochloride should not be used in patients with poorly compensated congestive heart failure, 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 (**DRUG INTERACTIONS, Table 2**). The use of verapamil hydrochloride in the treatment of hypertension is not recommended in patients with heart failure caused by systolic dysfunction.

### **Hypotension:**

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

### **Conduction Disturbance**

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

### **Bradycardia**

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

### **Patients with Hypertrophic Cardiomyopathy**

In 120 patients with hypertrophic cardiomyopathy who received therapy with verapamil hydrochloride at doses up to 720 mg/day, a variety of serious adverse effects were seen. Three patients died in pulmonary edema; all had severe left ventricular outflow obstruction and a past history of left ventricular dysfunction. Eight other patients had pulmonary edema and/or severe hypotension, abnormally high (greater than 20 mm Hg) pulmonary wedge pressure and a marked left ventricular outflow obstruction were present in most of these patients. Concomitant administration of quinidine (see **DRUG INTERACTIONS**) preceded the severe hypotension in 3 of the 8 patients (2 of whom developed pulmonary edema). Sinus bradycardia occurred in 11% of the patients, second-degree A-V block in 4%, and sinus arrest in 2%. It must be appreciated that this group of patients had a serious disease with a high mortality rate. Most adverse effects responded well to dose reduction, but in some cases, verapamil hydrochloride use had to be discontinued.

### **Elevated Liver Enzymes**

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

### **Hepatic Insufficiency**

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

### **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, *phl*-VERAPAMIL 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 (**DOSAGE AND ADMINISTRATION**).

Verapamil hydrochloride is not removed by hemodialysis.

### **Special Populations**

**Pregnant Women:** Teratology and reproduction studies have been performed in rabbits and rats at oral doses up to 1.5 (15 mg/kg/day) and 6 (60 mg/kg/day) times the human oral daily dose, respectively, and have revealed no evidence of teratogenicity or impaired fertility. In rat, however, this multiple of the human dose was embryocidal and retarded fetal growth and development, probably because of adverse maternal effects reflected in reduced weight gains of the dams. This oral dose has also been shown to cause hypotension in rats.

There are no studies in pregnant women. However, verapamil hydrochloride crosses the placental barrier and can be detected in umbilical vein blood at delivery. *phl*-VERAPAMIL SR

is not recommended for use in pregnant women unless the potential benefits outweigh potential risks to mother and fetus.

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

**Nursing Women:** Verapamil hydrochloride is excreted in human breast milk. Because of the potential for adverse reactions in nursing infants from verapamil hydrochloride, nursing should be discontinued while phl-VERAPAMIL SR is administered.

**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.

**Geriatrics (≥ 65 years of age):** Caution should be exercised when phl-VERAPAMIL SR is administered to elderly patients (≥ 65 years) especially those prone to developing hypotension or those with a history of cerebrovascular insufficiency. See (**DOSAGE AND ADMINISTRATION**). The incidence of adverse reactions is approximately 4% higher in the elderly. The adverse reactions occurring more frequently include dizziness and constipation. Serious adverse events associated with heart block have occurred in the elderly.

#### **Monitoring and Laboratory Tests**

Patients should be monitored by measuring the blood pressure response.

#### **Concomitant Use with Beta-Blockers**

In exceptional cases, when in the opinion of the physician concomitant use in angina and arrhythmias is considered essential, such use should be instituted gradually under careful supervision. If combined therapy is used, close surveillance of vital signs and clinical status should be carried out and the need for continued concomitant treatment periodically assessed.

#### **Elevated Liver Enzymes**

Periodic monitoring of liver function in patients receiving phl-VERAPAMIL 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



## ADVERSE REACTIONS

### Adverse Drug Reaction Overview

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

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

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

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

### Clinical Trial Adverse Drug Reactions

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

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

	<b>Verapamil Hydrochloride (N = 4,954)</b>
<b>Vasculars Disorders</b>	
Hypotension	2.5%
<b>Cardiac Disorders</b>	
Edema	2.1%
CHF/Pulmonary Edema	1.9%
Bradycardia	1.4%
A-V-Block	
Total ( 1°, 2°, 3°)	1.2%
2° and 3°	0.8%
<b>Nervouse System Disorders</b>	
Dizziness	3.2%
Headache	2.2
<b>General Disorders and Administration Site Conditions</b>	
Fatigue	1.7%
<b>Gastrointestinal Disorders</b>	
Constipation	7.3%
Nausea	2.7%

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

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

**Cardiac Disorders:** Angina pectoris, atrioventricular dissociation, cardiac failure, chest pain, claudication, development of rhythm disturbances, myocardial infarction, painful coldness and numbness of extremities, palpitations, syncope, severe tachycardia, ventricular dysrhythmias

**Ear and Labyrinth Disorders:** Vertigo

**Gastrointestinal Disorders:** Abdominal discomfort, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, vomiting

**Eye Disorders:** Blurred vision, diplopia

**Nervous System Disorders:** cerebrovascular accident, confusion, equilibrium disorders, excitation, extrapyramidal disorders, hyperkinesia, paresthesia, rotary nystagmus, shakiness, somnolence, and tremor

**Musculoskeletal and Connective Tissue Disorders:** Arthralgia, muscle cramps, muscle fatigue

**Psychiatric Disorders:** Depression, insomnia, psychotic symptoms

**Renal and Urinal 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:** Alopecia, ecchymosis or bruising, erythema multiforme, exanthema, hyperkeratosis, macules, pruritus, purpura, rash, Stevens-Johnson syndrome, sweating, urticaria

**Vascular Disorders:** Flushing

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

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

#### **Abnormal Hematologic and Clinical Chemistry Findings**

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

#### **Post-Market Adverse Drug Reactions**

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

**Cardiac Disorders:** Sinus arrest, sinus bradycardia

**Ear and Labyrinth Disorders:** Tinnitus

**Gastrointestinal Disorders:** Abdominal pain, ileus

**General Disorders and Administration Site Conditions:** Edema peripheral

**Immune System Disorders:** Hypersensitivity

**Musculoskeletal and Connective Tissue Disorders:** Muscle weakness, myalgia

**Skin and Subcutaneous System Disorders:** Rash maculopapular

**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.

## DRUG INTERACTIONS

### Drug-Drug Interactions

As with all drugs, care should be exercised when treating patients with multiple medications. Verapamil hydrochloride undergoes biotransformation by the CYP3A4, CYP1A2, CYP2C8, CYP2C9 and CYP2C18 isoenzymes of the cytochrome P450 system. Verapamil hydrochloride has also been shown to be an inhibitor of CYP3A4 enzymes and P-glycoprotein (P-gp). Co-administration of verapamil hydrochloride with other drugs which follow the same route of biotransformation or are inhibitors or inducers of these enzymes may result in altered bioavailability of verapamil hydrochloride or these drugs. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio, and especially in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered verapamil hydrochloride sustained-release tablets to maintain optimum therapeutic blood levels.

The following table provides a list of potential drug interactions:

**Table 2. Potential Drug Interactions Associated with Verapamil Hydrochloride**

Concomitant Drug Class: Drug Name	Ref	Effect on Concentration of Verapamil Hydrochloride or Concomitant Drug	Clinical Comment
<b>Alpha-Blockers</b>			
Prazosin	T	↑ prazosin $C_{max}$ (~40%) with no effect on $t_{1/2}$	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%)	
<b>Antiarrhythmics</b>			
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.

<b>Concomitant Drug Class: Drug Name</b>	<b>Ref</b>	<b>Effect on Concentration of Verapamil Hydrochloride or Concomitant Drug</b>	<b>Clinical Comment</b>
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.
<b>Antiasthmatics</b>			
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.
<b>Anticonvulsants</b>			
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
<b>Antidepressants</b>			
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.
<b>Antidiabetics</b>			
Glibenclamide (glyburide)	T	↑ glibenclamide C <sub>max</sub> (~28%), AUC (~26%)	
<b>Antihypertensive Agents</b>			
	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.

<b>Concomitant Drug Class: Drug Name</b>	<b>Ref</b>	<b>Effect on Concentration of Verapamil Hydrochloride or Concomitant Drug</b>	<b>Clinical Comment</b>
<b>Anti-Infectives</b>			
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	
Rifampin	T	↓ verapamil AUC (~97%), C <sub>max</sub> (~94%) oral bioavailability (~92%)	Blood pressure lowering effect of verapamil hydrochloride may be reduced when used concomitantly with rifampin
Telithromycin	T	Possible ↑ in verapamil when used in combination with telithromycin	
<b>Antimanic Agents</b>			
Lithium	T		Increased sensitivity to the effects of lithium (neurotoxicity) has been reported during concomitant verapamil hydrochloride-lithium therapy with either no change or an increase in serum lithium levels. 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.
<b>Antineoplastics</b>			
Doxorubicin	T	↑ doxorubicin AUC (89%) and C <sub>max</sub> (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 antineoplastic agents should be considered when verapamil hydrochloride is administered concomitantly.
<b>Barbiturates</b>			
Phenobarbital	T	↑ oral verapamil clearance (~5-fold)	
<b>Benzodiazepines and Other Anxiolytics</b>			
Buspirone	T	↑ buspirone AUC, C <sub>max</sub> by ~3.4-fold	
Midazolam	T C	↑ midazolam AUC (~3-fold) and, C <sub>max</sub> (~2-fold)	

<b>Concomitant Drug Class: Drug Name</b>	<b>Ref</b>	<b>Effect on Concentration of Verapamil Hydrochloride or Concomitant Drug</b>	<b>Clinical Comment</b>
<b>Beta-Blockers</b>			
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 <sub>max</sub> (~41%) in patients with angina pectoris	Concomitant therapy may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility. See <b>(WARNINGS AND PRECAUTIONS)</b> . Verapamil hydrochloride should not be combined with beta-blockers for the treatment of hypertension.
Propranolol	T C	↑ propranolol AUC (~65%), C <sub>max</sub> (~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.
<b>Cardiac Glycosides</b>			
Digitoxin	T	↓ digitoxin total body clearance (~27%) and extrarenal clearance (~29%)	The increase in digoxin levels can result in digoxin toxicity. Maintenance digoxin doses should be reduced when verapamil hydrochloride is administered, and the patient should be carefully monitored to avoid over or under-digitalization. Whenever over digitalization 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 under digitalization. See <b>(WARNINGS AND PRECAUTIONS)</b>
Digoxin	C	↑ digoxin levels -50-75% during the first week of therapy ↑ digoxin AUC (-32%), C <sub>max</sub> (-98%) in hepatic cirrhosis patients ↑ digoxin C <sub>max</sub> (~45 to 53%), ↑ C <sub>ss</sub> (~42%) and ↑ AUC (~52%) in healthy subjects	
<b>Diuretics</b>			
	T		Concomitant use with diuretics may cause a potentiation of the hypotensive effect.
<b>H2-Receptor Antagonists</b>			
Cimetidine	T	In healthy subjects, ↑ AUC of R-(~25%) and S-(~40%) verapamil with corresponding ↓ in R- and S-verapamil clearance	
<b>HIV Antiviral Agents</b>			
	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.

<b>Concomitant Drug Class: Drug Name</b>	<b>Ref</b>	<b>Effect on Concentration of Verapamil Hydrochloride or Concomitant Drug</b>	<b>Clinical Comment</b>
<b>Immunologics</b>			
Cyclosporine	T	↑ cyclosporine AUC, C <sub>ss</sub> , C <sub>max</sub> 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	Possible ↑ everolimus levels	
Sirolimus	T C	Possible ↑ sirolimus levels	
Tacrolimus	T	Possible ↑ tacrolimus levels	
<b>Inhalation Anesthetics</b>	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.
<b>Lipid Metabolism Regulators</b>			
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 an HMGCoA 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), C <sub>max</sub> (~4.6 fold) in healthy subject	
<b>Neuromuscular Blocking Agents</b>			
	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.
<b>Non-Steroidal Anti-Inflammatory Agents (NSAIDs)</b>			



<b>Concomitant Drug Class: Drug Name</b>	<b>Ref</b>	<b>Effect on Concentration of Verapamil Hydrochloride or Concomitant Drug</b>	<b>Clinical Comment</b>
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.
<b>Serotonin Receptor Agonists</b>			
Almotriptan	T	↑ almotriptan AUC (~20%) ↑ C <sub>max</sub> (~24%)	
<b>Uricosurics</b>			
Colchicine	C		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.
Sulfapyrazone	T	↑ verapamil oral clearance (~3-fold) ↓ bioavailability (~60%)	The blood pressure lowering effect of verapamil hydrochloride may be reduced
<b>Vasodilators</b>			
	T		Concomitant use with vasodilators may cause a potentiation of the hypotensive effect.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

### **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.

### **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<sub>max</sub> 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.

### **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<sub>max</sub>.

### **Drug-Laboratory Interactions**

Interactions with laboratory tests have not been evaluated

### **Drug-Lifestyle Interactions**

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

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

## **DOSAGE AND ADMINISTRATION**

### **Dosing Considerations**

The antihypertensive effects of phl-VERAPAMIL SR 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**

phl-VERAPAMIL SR should be administered cautiously to patients with liver or renal function impairment. The dosage should be carefully and gradually adjusted depending on patient tolerance and response. These patients should be monitored carefully for abnormal prolongation of the PR interval or other signs of overdosage. phl-VERAPAMIL SR should not be used in severe hepatic dysfunction. See (**WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Hepatic Insufficiency**). Verapamil hydrochloride is not removed by hemodialysis.

### **Switching from verapamil hydrochloride tablets to phl-VERAPAMIL SR Tablets**

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

### **Recommended Dose and Dosage Adjustment**

#### **Mild to Moderate Essential Hypertension**

The dosage should be individualized by titration depending on patient tolerance and responsiveness to phl-VERAPAMIL 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. (Note:

Pharmascienc provides only the 240 mg tablet strength (see **DOSAGE FORMS, COMPOSITION AND PACKAGING**).

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

**Table 3. Recommended Dosing Intervals for Specific Daily Dosages**

Total Daily Verapamil Hydrochloride 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 verapamil hydrochloride, i.e. 120 mg a day, may be warranted in elderly patients (i.e. 65 years and older). See (**WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics**). The dosage should be carefully and gradually adjusted depending on patient tolerability and response.

### **Administration**

Crushing or chewing phl-VERAPAMIL SR sustained-release tablets is not recommended since the sustained-release effect will be altered by damage to the tablet structure. The phl-VERAPAMIL SR 240 mg tablet may be split in half.

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

### **OVERDOSAGE**

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

Treatment of overdose 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 overdose 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.

In case of overdose with large amounts of verapamil hydrochloride sustained-release tablets, 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 functions as active drug depots. Extensive elimination measures are indicated, such as induced vomiting, removal of the contents of the stomach and the small intestine under endoscopy, intestinal lavage and high enemas.

Actual treatment and dosage should depend on the severity of the clinical situation and the judgement of the treating physician. Patients with hypertrophic cardiomyopathy treated with verapamil hydrochloride should not be administered positive inotropic agents marked by asterisks in **Table 4**).

**Table 4. Overdose 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 immediately.

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

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

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

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

Verapamil hydrochloride may shorten the antegrade effective refractory period of the accessory bypass tract. Acceleration of ventricular rate and/or ventricular fibrillation has been reported in patients with atrial flutter or atrial fibrillation and a coexisting accessory A-V pathway following administration of verapamil hydrochloride. See (**WARNINGS AND PRECAUTIONS, Cardiovascular, Conduction Disturbance**). Verapamil hydrochloride has a local anesthetic action that is 1.6 times that of procaine on an equimolar basis.

Verapamil hydrochloride is a potent smooth muscle relaxant with vasodilatory properties, as well as a depressant of myocardial contractility, and these effects are largely independent of autonomic influences

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

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

### **Pharmacodynamics**

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

### **Pharmacokinetics**

**Absorption:** Verapamil hydrochloride is a racemic mixture consisting of equal portions of the R-enantiomer and the S-enantiomer. More than 90% of the orally administered dose of verapamil hydrochloride is absorbed from the small intestine. Upon oral administration, there is rapid

stereoselective biotransformation during the first pass of verapamil hydrochloride through the portal circulation. The systemic concentrations of R- and S-enantiomers are dependent upon the route and the rate of administration and the rate and extent of release from the dosage forms.

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

In a study in five healthy volunteers with oral immediate-release verapamil hydrochloride, the systemic bioavailability varied from 33 to 65% for the R-enantiomer and from 13 to 34% for the S-enantiomer. The S-enantiomer is pharmacologically more active than the R-enantiomer. See (**ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics**) and (**DETAILED PHARMACOLOGY, Animal Pharmacology, Pharmacodynamics**).

There is a nonlinear correlation between the verapamil hydrochloride dose administered and verapamil hydrochloride plasma levels. In early dose titration with verapamil, a relationship exists between total verapamil hydrochloride (R-and S-enantiomer combined) plasma concentration and prolongation of the PR interval. The mean elimination  $t_{1/2}$  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.

**Distribution:** 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. 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. R-verapamil is 94% bound to plasma albumin, while

S-verapamil is 88% bound. In addition, R-verapamil is 92% and S-verapamil 86% bound to alpha-1 acid glycoprotein. The degree of biotransformation during the first pass of verapamil 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.

**Excretion:** Approximately 70% of an administered dose of verapamil hydrochloride is excreted as metabolites in the urine and 16% or more in the feces within 5 days. About 3 to 4% is excreted in the urine as unchanged drug.

### **Influence of Food**

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

### **Special Populations and Conditions**

**Geriatrics:** The pharmacokinetics of verapamil hydrochloride are significantly different in elderly ( $\geq 65$  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  $t_{1/2}$ .

**Gender:** The effect of gender on verapamil hydrochloride, when administered as verapamil hydrochloride sustained release tablets, has not been investigated

**Race:** The effect of different races on verapamil hydrochloride, when administered as verapamil hydrochloride sustained release tablets 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 (**WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Hepatic Insufficiency**) and (**DOSAGE AND ADMINISTRATION**).

**Renal Insufficiency:** About 70% of an administered dose of verapamil hydrochloride is excreted as metabolites in the urine. In one study in healthy volunteers, the total body clearance after intravenous administration of verapamil hydrochloride was 12.08 mL/min/kg, while in patients with advanced renal disease it was reduced to 5.33 mL/min/kg. This pharmacokinetic finding suggests that renal clearance of verapamil hydrochloride in patients with renal disease is decreased. In two studies with oral verapamil hydrochloride, no difference in pharmacokinetics could be demonstrated. See (**WARNINGS AND PRECAUTIONS, Renal, Renal Insufficiency**). Verapamil hydrochloride is not removed by hemodialysis.

**Genetic Polymorphism:** The effect of genetic polymorphism on verapamil hydrochloride pharmacokinetics has not been investigated

## STORAGE AND STABILITY

Store between 15°C and 30°C in airtight containers, protected from light and humidity.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

phl-VERAPAMIL SR tablets

**240 mg:** Each light-green, oblong, biconvex, film-coated tablet debossed with “SR” score “240” on one side and plain on the other side, contains 240 mg of verapamil hydrochloride and the following nonmedicinal ingredients: carnauba wax, D&C Yellow No. 10 lake, FD&C Blue No. 1 lake, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, sodium alginate, titanium dioxide. Available in bottles of 100 and 500 tablets.



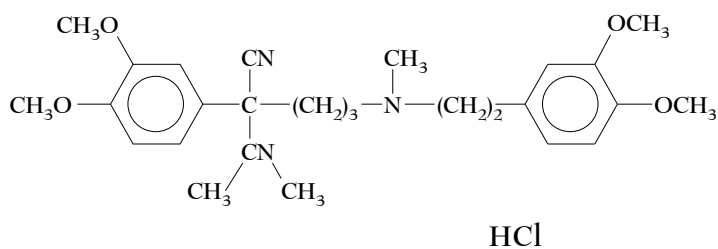
## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

Proper name Verapamil Hydrochloride

Structural formula:



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

Molecular mass: 491.08 g/mol

Chemical name:

- (1) Benzeneacetonitrile,  $\alpha$ -[3-[[2-(3,4-dimethoxyphenyl)-ethyl]-methylamino]propyl]-3,4-dimethoxy- $\alpha$ -(1-methylethyl)-monohydrochloride ((+/-))-.
- (2) 5-[(3,4-dimethoxyphenylethyl)-2-isopropylvaleronitrile monohydrochloride ((+/-))-.

Description: Verapamil, as the hydrochloride, is an almost white, bitter-tasting crystalline powder practically free from odour and readily soluble in chloroform and water (1 part in 20), but sparingly soluble in ethanol and practically insoluble in ether. It should be protected from light. Melting point: 140° to 144° C.

## CLINICAL TRIALS

### Comparative Bioavailability Studies

A single-dose bioavailability study conducted under fasting conditions was carried out to compare the pharmacokinetic parameters of phl-VERAPAMIL SR (verapamil hydrochloride) 240 mg sustained release tablets and ISOPTIN SR (verapamil hydrochloride) 240 mg tablets in 25 healthy male subjects. The pharmacokinetic results are summarized in the table below:

<b>Verapamil</b> <b>(1 x 240 mg, fast)</b> <b>From measured data</b>  <b>Geometric Mean</b> <b>Arithmetic Mean (CV %)</b>				
<b>Parameter</b>	<b>Test*</b>	<b>Reference†</b>	<b>% Ratio of Geometric Means</b>	<b>Confidence Interval 90%</b>
AUC <sub>T</sub> (ng·h/mL)	1079.88 1231.94 (48.42)	1139.79 1272.37 (40.79)	95	(84-106)
AUC <sub>I</sub> (ng·h/mL)	1167.71 1308.71 (45.36)	1232.50 1353.29 (38.01)	95	(85-106)
C <sub>max</sub> (ng·h/mL)	117.87 133.15 (46.97)	126.17 141.58 (46.21)	93	(82-107)
T <sub>max</sub> <sup>§</sup> (h)	3.96 (29.59)	4.40 (27.84)		
T <sub>1/2</sub> <sup>§</sup> (h)	6.89 (27.55)	7.27 (66.77)		

\* phl-VERAPAMIL SR 240 mg tablets (Pharmel Inc.)  
† ISOPTIN SR 240 mg Tablets (Searle Canada Inc.) purchased in Canada  
§ Expressed as the arithmetic mean (CV%) only.

A single-dose bioavailability study conducted under fed conditions was carried out to compare the pharmacokinetic parameters of phl-VERAPAMIL SR (verapamil hydrochloride) 240 mg sustained release tablets and ISOPTIN SR (verapamil hydrochloride) 240 mg tablets in 25 healthy male subjects. The pharmacokinetic results are summarized in the table below:

<b>Verapamil</b> <b>(1 x 240 mg, fed)</b> <b>From measured data</b>  <b>Geometric Mean</b> <b>Arithmetic Mean (CV %)</b>				
<b>Parameter</b>	<b>Test*</b>	<b>Reference†</b>	<b>% Ratio of Geometric Means</b>	<b>Confidence Interval 90%</b>
AUC <sub>T</sub> (ng·h/mL)	1112.09 1176.50 (34.47)	1175.21 1262.43 (38.52)	95	(86-104)
AUC <sub>I</sub> (ng·h/mL)	1194.64 1255.98 (32.20)	1255.77 1336.56 (36.50)	95	(88-103)
C <sub>max</sub> (ng·h/mL)	92.61 105.95 (57.12)	96.11 105.94 (45.34)	96	(79-119)
T <sub>max</sub> <sup>§</sup> (h)	8.24 (47.17)	8.56 (45.00)		
T <sub>1/2el</sub> <sup>§</sup> (h)	7.27 (33.43)	6.81 (31.13)		

\* phl-VERAPAMIL SR 240 mg tablets (Pharmel Inc.)

† ISOPTIN SR 240 mg Tablets (Searle Canada Inc.) purchased in Canada

§ Expressed as the arithmetic mean (CV%) only.

A multiple-dose bioavailability study conducted under fasting conditions was carried out to compare the pharmacokinetic parameters of phl-VERAPAMIL SR (verapamil hydrochloride) 240 mg sustained release tablets and ISOPTIN SR (verapamil hydrochloride) 240 mg tablets in 26 healthy male subjects. The pharmacokinetic results are summarized in the table below:

<b>Verapamil</b> <b>(6 daily doses of 240 mg)</b> <b>From measured data</b>  <b>Geometric Mean</b> <b>Arithmetic Mean (CV %)</b>				
<b>Parameter</b>	<b>Test*</b>	<b>Reference†</b>	<b>% Ratio of Geometric Means</b>	<b>Confidence Interval 90%</b>
AUC <sub>T</sub> (ng·h/mL)	1699.52 1863.80 (41.47)	1769.40 1885.39 (38.88)	96	(86-107)
AUC <sub>I</sub> (ng·h/mL)	2000.20 2203.77 (41.47)	2091.63 2273.70 (46.71)	96	(86-106)
C <sub>max</sub> (ng·h/mL)	160.58 179.81 (47.20)	173.56 186.50 (40.69)	93	(78-109)
T <sub>max</sub> § (h)	4.42 (37.38)	4.58 (26.34)		
T <sub>1/2el</sub> § (h)	8.02 (39.49)	8.52 (29.54)		

\* phl-VERAPAMIL SR 240 mg tablets (Pharmel Inc.)

† ISOPTIN SR 240 mg Tablets (Searle Canada Inc.) purchased in Canada

§ Expressed as the arithmetic mean (CV%) only.

The results presented show that no statistically significant difference could be detected between the Test and Reference formulation for any of the pharmacokinetic parameters under study.

## **DETAILED PHARMACOLOGY**

### **Animal Pharmacology**

#### **Pharmacodynamics**

Verapamil hydrochloride was initially investigated in experimental animals as a smooth muscle relaxant, with vasodilator properties. Subsequent studies have demonstrated that verapamil hydrochloride has significant anti arrhythmic 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.

## TOXICOLOGY

### Acute Toxicity

**Table 7. Lethal Dose 50 (LD<sub>50</sub>) (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-attributed 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.

## **Mutagenicity and Carcinogenicity**

### **Mutagenicity**

*In vitro* mutagenicity tests showed that verapamil did not have mutagenic properties in five different strains of *Salmonella typhimurium*, nor in studies on chromosomal aberrations and sister chromatid exchanges (SCE) in human lymphocytes, nor in the hypoxanthine guanine phosphoribosyltransferase (HGPRT)-test with V-79 Chinese hamster cells, and also not in the cell transformation assay with Syrian hamster embryo cells. In addition, verapamil did not show any SCE-inducing activity *in vivo* (Chinese hamster).

### **Carcinogenicity**

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

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

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

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

### **Reproduction and Teratology**

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

There was no evidence of teratogenicity in either species and no embryotoxic effects observed in the rats dosed via food, or with doses up to 12.5 mg/kg body weight given by gastric tube, or with doses up to 10 mg/kg three times a day. The single daily dose of 25 mg/kg body weight or more, caused a higher resorption rate in the rat. The dose of 20 mg/kg three times a day was embryocidal and retarded fetal growth and development, probably because of adverse maternal effects reflected in reduced weight gains of the dams. This oral dose has also been shown to cause hypotension in rats. There was no difference in resorption rates observed in the rabbit and no effect on peri- and post-natal development or fertility in the rat.



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**PART III: CONSUMER INFORMATION****Pr** **phl-VERAPAMIL SR****Verapamil Hydrochloride Sustained-Release Tablet, USP**

This leaflet is part III of a three-part "Product Monograph" published when phl-VERAPAMIL SR was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about phl-VERAPAMIL SR. Contact your doctor or pharmacist if you have any questions about the drug.

**ABOUT THIS MEDICATION****What the medication is used for:**

phl-VERAPAMIL SR is used to treat hypertension (high blood pressure).

**What it does:**

phl-VERAPAMIL SR is a calcium channel blocker. 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.

**When it should not be used:**

phl-VERAPAMIL SR should not be used if:

- you are allergic to any component of phl-VERAPAMIL SR including the active ingredient or the nonmedicinal ingredients. See **(What the nonmedicinal ingredients are)**.
- you have certain serious heart disease or problems.
- you feel faint when you get up.
- you have symptoms such as rapid pulse and breathing, anxiety, weakness, decreased urine production, cool hands and feet and loss of alertness. See your doctor immediately.
- you have had a heart attack.
- you have slow heartbeat or irregular heartbeat.
- you are breast-feeding while taking this medication.

**What the medicinal ingredient is:**

Verapamil hydrochloride.

**What the nonmedicinal ingredients are:**

Carnauba wax, D&C Yellow No. 10 lake, FD&C Blue No. 1 lake, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, sodium alginate, titanium dioxide.

**What dosage forms it comes in:**

Tablets: 240 mg

**WARNINGS AND PRECAUTIONS**

**BEFORE you use phl-VERAPAMIL SR talk to your doctor or pharmacist if:**

- you are pregnant or planning to become pregnant

- you have any heart disease.
- you have kidney disease.
- you have liver disease.
- you are taking beta-blockers. See **(Interactions With This Medication)**.
- you have neuromuscular disease (i.e. myasthenia gravis or Duchenne muscular dystrophy).

**INTERACTIONS WITH THIS MEDICATION**

**Drugs that may interact with phl-VERAPAMIL SR include:**

- beta-blockers (e.g. propranolol, metoprolol, atenolol, timolol);
- any other treatment for hypertension (high blood pressure) or an arrhythmia (abnormal heart beat) (e.g. hydrochlorothiazide, disopyramide, flecainide, quinidine, prazosin, terazosin);
- digoxin, digitoxin, cimetidine, lithium, rifampin, theophylline, sulfapyrazone, clarithromycin, erythromycin, telithromycin, glyburide, almotriptan, colchicine;
- carbamazepine and phenobarbital;
- any of the group of medicines known as major tranquilizers, or an antidepressant of the tricyclic group (e.g. imipramine);
- any of the group of medicines known as benzodiazepines or other anti-anxiety treatment (e.g. buspirone, midazolam);
- any of the group of medicines known as non-steroidal anti-inflammatory drugs (e.g. acetylsalicylic acid);
- anti-cancer medication (e.g. doxorubicin);
- some medication that can affect your immune system (e.g. cyclosporine, sirolimus, tacrolimus, everolimus);
- any neuromuscular blocking agent (e.g. atracurium);
- some anti-cholesterol products (e.g. simvastatin, atorvastatin, lovastatin);
- some HIV-antiviral medication (e.g. ritonavir);
- grapefruit juice;
- alcohol;
- St John's Wort.

**PROPER USE OF THIS MEDICATION****Usual dose:**

Always take your tablets exactly as your doctor has told you. The usual starting adult dose for phl-VERAPAMIL SR is 180 to 240 mg per day, taken at the same time every day. Dosage is individualized and your doctor will adjust your dose as needed. The maximum dose to treat high blood pressure is 480 mg each day. This is usually taken as one phl-VERAPAMIL SR 240 mg tablet in the morning and one in the evening, leaving a gap of about 12 hours between each dose.

Tablets should be taken with sufficient liquid, preferably with or shortly after meals. Do not crush or chew the tablets

The phl-VERAPAMIL SR 240 mg tablets are scored. It may be cut in half without damaging the modified release formulation

**Overdose:**

In case of drug overdose, contact a health care practitioner (doctor), hospital emergency department or regional Poison Control Centre even if there are no symptoms. Bring your pack of tablets with you.

If you or someone you know accidentally takes more than stated dose, contact your doctor immediately or go to the nearest hospital with the tablets.

In case of accidental drug overdose, contact a health care practitioner, hospital emergency department or regional poison control centre immediately, even if there are no symptoms. Tell your doctor or hospital how much was taken. Treat even small overdoses seriously.

**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.

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

Along with its needed effects, a medicine may cause some unwanted effects. These are referred to as “side effects”. Although not all of these side effects may occur, if they do occur they may need medical attention.

The most common side effects with phl-VERAPAMIL SR are constipation, dizziness and feeling sick (nausea). Other less common side effects may include headache and tiredness.

Check your physician or pharmacist *if you experience any unexpected effects, or are concerned by the above side effects*

**SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
Common	Feeling dizzy and faint or your blood pressure is too low		✓	
	Difficulty breathing		✓	
	Swelling in the arms or legs		✓	
Uncommon	Feeling an irregular heart beat		✓	

**SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
	Only if severe	In all cases	
Rash or other skin irritation		✓	
Muscle Weakness		✓	

*This is not a complete list of side effects. For any unexpected effects while taking phl-VERAPAMIL SR, contact your doctor or pharmacist.*

**HOW TO STORE IT**

- Keep phl-VERAPAMIL SR and all other medicines out of reach of children
- phl-VERAPAMIL SR tablets should be stored between 15°C and 30°C, in airtight containers. Protect from light and moisture.
- Do not take your tablets after the expiry date shown on the label

**REPORTING SUSPECTED SIDE EFFECTS**

**You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:**

- Report online at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program  
Health Canada  
Postal Locator 0701E  
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect).

**NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.**

**MORE INFORMATION**

This document plus the full product monograph, prepared for health professionals, can be obtained by contacting Pharmel Inc. at 1-888-550-6060.

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