PRODUCT MONOGRAPH

[Pr]COVERA-HS*

(verapamil hydrochloride)
Controlled-Onset Extended Release Tablets

180 mg and 240 mg tablets

Antihypertensive and Anti-anginal Agent

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(verapamil hydrochloride)
Controlled-Onset Extended Release tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	tablet: 180 mg and 240 mg controlled onset, extended release	For a complete listing, see Dosage Forms, Composition and Packaging section.

INDICATIONS AND CLINICAL USE

COVERA-HS (verapamil hydrochloride) is indicated for:

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

  COVERA-HS 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.

  Verapamil should not be used concurrently with beta adrenoreceptor blockers in the treatment of hypertension (see **DRUG INTERACTIONS**).

- The treatment of chronic stable angina pectoris.

Pediatrics (< 18 years of age): The safety and effectiveness of verapamil in children have not been established.

Geriatrics (> 65 years of age): Caution should be exercised when verapamil is administered to elderly patients (see **WARNINGS AND PRECAUTIONS**, **Special Populations**).

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation. 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 systolic dysfunction (ie, ejection fraction <40%), unless secondary to a supraventricular tachycardia amenable to oral verapamil therapy.

- Cardiogenic shock.

- Hypotension (systolic blood pressure <90 mm Hg).

- Second- or third-degree A-V block (except in patients with a functioning artificial ventricular pacemaker) (see **WARNINGS AND PRECAUTIONS**, **Cardiovascular, Conduction Disturbance**).

- Sick Sinus Syndrome (except in patients with a functioning artificial ventricular pacemaker).

- Marked bradycardia.
- Patients with atrial flutter or atrial fibrillation and an accessory bypass tract (eg, Wolff-Parkinson-White, Lown-Ganong-Levine syndrome) (see **WARNINGS AND PRECAUTIONS, Cardiovascular, Accessory Bypass Tract**).

WARNINGS AND PRECAUTIONS

General

In hypertensive patients also using anti-anginal or anti-arrhythmic agents, the additional hypotensive effect of COVERA-HS (verapamil hydrochloride) should be taken into consideration.

Carcinogenesis and Mutagenesis:

Carcinogenicity tests were performed in rats. For details, refer to **Part II: TOXICOLOGY – Mutagenicity and Carcinogenicity** section.

Cardiovascular

Heart Failure

Verapamil has a negative inotropic effect, which in most patients is compensated by its afterload reduction (decreased systemic vascular resistance) properties without a net impairment of ventricular performance. Verapamil should be avoided in patients with moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-adrenergic blocker (see **DRUG INTERACTIONS**).

Patients with milder ventricular dysfunction should be controlled with optimum doses of digitalis and/or diuretics before verapamil treatment is started (see **DRUG INTERACTIONS**).

Hypotension

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

Conduction Disturbance

The effect of verapamil on AV conduction and the SA node may cause asymptomatic first-degree AV block and transient bradycardia, sometimes accompanied by nodal escape rhythms and in extreme cases, asystole. PR-interval prolongation is correlated with verapamil plasma concentrations, especially during the early titration phase of therapy. However, higher degrees of AV block have been observed infrequently. Marked first-degree block or progressive development to second- or third-degree AV block requires a reduction in dosage or, in rare instances, discontinuation of verapamil HCl and institution of appropriate therapy.

Bradycardia

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

Concomitant Use With Beta Blockers

Generally, oral verapamil should not be given to patients receiving beta blockers since the depressant effects on myocardial contractility, heart rate and A-V conduction may be additive (see **WARNINGS AND PRECAUTIONS**, **Heart Failure**). If combined therapy is used, close surveillance of vital signs and clinical status should be carried out and the need for continued concomitant treatment periodically assessed.

Verapamil gives no protection against the dangers of abrupt beta-blocker withdrawal and such

withdrawal should be done by the gradual reduction of the dose of beta-blocker. Then verapamil may be started with the usual dose.

Accessory Bypass Tract (Wolff-Parkinson-White or Lown-Ganong-Levine)
Verapamil may result in significant acceleration of ventricular response during atrial fibrillation or atrial flutter in the Wolff-Parkinson-White (WPW) or Lown-Ganong-Levine syndromes after receiving intravenous verapamil. Although a risk of this occurring with oral verapamil has not been established, such patients receiving oral verapamil may be at risk and its use in these patients is contraindicated (see **CONTRAINDICATIONS**).

Patients With Hypertrophic Cardiomyopathy
In 120 patients with hypertrophic cardiomyopathy who received therapy with verapamil at doses up to 720 mg/day, a variety of serious adverse effects 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 AV 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, and only rarely did verapamil use have to be discontinued.

Gastrointestinal

Patients with Pre-existing Gastrointestinal Narrowing or Transit Disorders
In patients with pre-existing gastrointestinal narrowing (pathologic or iatrogenic) or significant GI motility disorders the administration of COVERA-HS tablets, whose formulation contains a nondeformable material, should be avoided, as there have been rare reports of obstructive symptoms in patients with GI strictures associated with COVERA-HS tablet ingestion.

Hematologic

Verapamil Hydrochloride has been associated with platelet inhibitory effect which may increase bleeding time. (see **CLINICAL TRIALS ADVERSE DRUG REACTIONS)**

Hepatic/Biliary/Pancreatic

Hepatic Insufficiency
Because verapamil is extensively metabolized by the liver, it should be administered cautiously to patients with impaired hepatic function, since the elimination half-life of verapamil in these patients is prolonged 4-fold (from 3.7 to 14.2 hours). A decreased dosage should be used in

patients with hepatic insufficiency, and careful monitoring for abnormal prolongation of the PR interval or other signs of excessive pharmacologic effect should be carried out (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Neurologic

Use In Patients With Attenuated (Decreased) Neuromuscular Transmission

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

Renal

Renal Insufficiency

About 70% of an administered dose of verapamil is excreted as metabolites in the urine. In one study in healthy volunteers, the total body clearance after intravenous administration of verapamil was 12.08 mL/min/kg, while in patients with advanced renal disease it was reduced to 5.33 mL/min/kg. This pharmacokinetic finding suggests that renal clearance of verapamil in patients with renal disease is decreased. In two studies with oral verapamil no difference in pharmacokinetics could be demonstrated. Until further data are available, verapamil should be administered cautiously to patients with impaired renal function. These patients should be carefully monitored for abnormal prolongation of the PR interval or other signs of overdosage (see **OVERDOSAGE**).

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 crosses the placental barrier and can be detected in umbilical vein blood at delivery. COVERA-HS 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 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 is excreted in human milk. Because of the potential for adverse

reactions in nursing infants from verapamil, nursing should be discontinued while verapamil is administered.

Pediatrics (< 18 years of age): The safety and effectiveness of verapamil in children have not been established.

Geriatrics (> 65 years of age): Caution should be exercised when verapamil is administered to elderly patients, especially those prone to developing hypotension or those with a history of cerebrovascular insufficiency (see **DOSAGE AND ADMINISTRATION, ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**). Serious adverse events associated with heart block have occurred in the elderly.

Monitoring and Laboratory Tests

Elevated Liver Enzymes:
Elevations of transaminases with and without concomitant elevations in alkaline phosphatase and bilirubin have been reported. Such elevations have sometimes been transient and may disappear even with continued verapamil treatment. Several cases of hepatocellular injury related to verapamil have been proven by rechallenge. Clinical symptoms of hepatocellular injury (malaise, fever, and/or right upper quadrant pain) were also present, in addition to elevation of SGOT, SGPT, and alkaline phosphatase have been reported. Periodic monitoring of liver function in patients receiving verapamil is therefore prudent.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Verapamil therapy is usually well tolerated when therapy is initiated with upward dose titration within the recommended daily dose. However, when given in high doses or in the presence of previous myocardial damage, some cardiovascular effects of verapamil may occasionally be greater than therapeutically desired eg, bradycardic arrhythmias, such as sinus bradycardia, sinus arrest with asystole, secondand third degree AV block, bradyarrhythmis in atrial fibrillation, hypotension.and development or aggravation of heart failure.

Verapamil hydrochloride immediate release tablets have been studied in 4,826 patients in controlled and uncontrolled trials. The most common adverse reactions were: constipation, dizziness, and nausea. The most serious adverse reactions reported with verapamil are heart failure (1.8%), 2^o and 3^o A-V block (0.8%), hypotension (2.5%) 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 have been reported in controlled or uncontrolled clinical trials with immediate release verapamil.

Cardiovascular	**%**
Hypotension	2.5
Edema	2.1
CHF/Pulmonary Edema	1.9
Bradycardia (HR<50/min)	1.4
A-V Block	
Total (1 °, 2 °, 3 °)	1.2
2 ° and 3 °	0.8
Central Nervous System	
Dizziness	3.2
Headache	2.2
Fatigue	1.7
Gastrointestinal	
Constipation	7.3
Nausea	2.7
Other	
Rash	1.2

The following reactions to COVERA-HS occurred at rates greater than 2.0% or occurred at lower rates but appeared drug related in clinical trials in hypertension and angina:

	All doses studied n=572 %	**Placebo n=261 %**
Cardiovascular		
Edema	3	3.1
AV block (1°)	1.7	0
Bradycardia	1.4	0.4
Flushing	0.8	0.3
Hypotension	0.7	0
Postural hypotension	0.4	0.3

Central Nervous System		
Headache	6.6	7.3
Dizziness	4.7	2.7
Fatigue	4.5	3.8
Paraesthesia	1	0
Gastrointestinal		
Constipation	11.7*	2.7
Nausea	2.1	1.9
Other		
Upper respiratory infection	5.4	4.6
Elevated liver enzymes	1.4	0.8

*At a once daily dose of 240 mg, the observed incidence was 7.2%.

The Controlled Onset Verapamil Investigation of Cardiovascular end points (CONVINCE) trial was a randomized, double blind, active controlled, multi-centre clinical trial with a total of 16602 participants. There were 364 primary cardiovascular disease-related events that occurred in the COER-verapamil group versus 365 in atenolol or hydrochlorothiazide group (hazard ratio [HR]: 1.02; 95% confidence interval [CI] of 0.88-1.18; p = 0.77). There were 118 patients (1.4%) randomized to COER-verapamil vs. 79 patients (1.0%) randomized to atenolol or hydrochlorothiazide (p=0.003) who died or were hospitalized for "non-stroke related bleeding". The large majority of these patients were diagnosed with Gastro-intestinal bleeding. There was no difference in the incidence of death from bleeding (6 (0.1%) vs. 6 (0.1%); p=0.97.

The incidence of acute MI was about 18% lower with COER-verapamil (p=0.09) than with atenolol or hydrochlorothiazide group; this benefit was offset by a 15% higher risk of stroke (p=0.26). Although quite possibly due to chance, these trends are consistent with COER-verapamil's ability to inhibit platelet aggregation."

See **WARNINGS AND PRECAUTIONS** for discussion of heart failure, hypotension, elevated liver enzymes, AV block, and rapid ventricular response.

Reversible (upon discontinuation of verapamil) non-obstructive, paralytic ileus has been infrequently reported in association with the use of verapamil.

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

Post-Market Adverse Drug Reactions

The following reactions, reported with orally administered verapamil in 2% or less of patients, occurred under conditions (open trials, marketing experience) where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship:

Cardiovascular: angina pectoris, second or third degree atrioventricular (AV) block, AV dissociation, pulmonary edema, chest pain, claudication, myocardial infarction, palpitations, syncope and congestive heart failure.

Gastrointestinal System: diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, vomiting, hepatitis.

Hematologic: purpura, petechiae, ecchymosis or bruising.

Central Nervous System: cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence.

Dermatologic: arthralgia and rash, exanthema, hair loss, sweating, pruritus, urticaria, Stevens-Johnson syndrome, erythema multiforme, vasculitis, hyperkeratosis and macules.

Special senses: blurred vision.

Urogenital: gynecomastia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

Other: allergy aggravated, dyspnea, myalgia.

DRUG INTERACTIONS

Overview

As with all drugs, care should be exercised when treating patients with multiple medications.

In vitro metabolic studies indicate that verapamil is metabolized by cytochrome P450 CYP3A4, CYP1A2, and CYP2C. It is also an inhibitor of cytochrome P450. Coadministration of verapamil with other drugs that follow the same route of biotransformation may result in altered bioavailability. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio, and especially in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered verapamil to maintain optimum therapeutic blood levels.

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

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

Significant post-market drug interactions with itraconazole, clarithromycin and erythromycin have been reported.

Clinically significant interactions have been reported with inhibitors of CYP3A4 (eg, erythromycin, ritonavir) causing elevation of plasma levels.

Drug-Drug Interactions

Established or Potential Drug-Drug Interactions

Class or Proper name	Effect	Clinical comment
Alcohol	Verapamil may increase blood alcohol concentrations and prolong its effects.	--
Anti-neoplastic Agents	Verapamil inhibits P-glycoprotein mediated transport of anti-neoplastic agents out of tumour cells, resulting in their decreased metabolic clearance.	Dosage adjustments of anti-neoplastic agents should be considered when verapamil is administered concomitantly.
Antihypertensive Agents - beta-blockers - alpha adrenergic agents	Verapamil administered concomitantly with oral antihypertensive agents (eg, vasodilators, angiotensin-converting enzyme inhibitors, and diuretics) may have an additive effect on lowering blood pressure.	• Patients receiving these combinations should be appropriately monitored. • Verapamil should not be combined with beta blockers for the treatment of hypertension. • Concomitant administration with verapamil may result in additive negative effects on heart rate, AV conduction, and/or cardiac contractility. (see also **WARNINGS AND PRECAUTIONS**). • In a study following the concomitant administration of verapamil and prazosin a reduction in blood pressure that was excessive in some patients was observed.

- calcium channel blockers		• As calcium channel blockers are metabolized by the cytochrome P450 system, co-administration with verapamil may result in altered bioavailability.
- diuretics		• No cardiovascular adverse effects have been attributed to any interaction between these agents and verapamil.
Antiarrhythmic agents - disopyramide	The interaction has not been studied	Until data on possible interactions between verapamil and disopyramide are obtained, disopyramide should not be administered within 48 hours before or 24 hours after verapamil administration.
- flecainide	A study in healthy volunteers showed that the concomitant administration of flecainide and verapamil may have additive effects on myocardial contractility, A-V conduction, and repolarization.	Concomitant therapy with flecainide and verapamil may result in additive negative inotropic effect and prolongation of atrioventricular conduction.
- quinidine	In a small number of patients with hypertrophic cardiomyopathy (IHSS), concomitant use of verapamil and quinidine resulted in significant hypotension. The electrophysiologic effects of quinidine and verapamil on AV conduction were studied in 8 patients. Verapamil significantly counteracted the effects of quinidine and AV conduction. There has been a report of increased quinidine levels during verapamil therapy.	Until further data are obtained, combined therapy of verapamil and quinidine in patients with hypertrophic cardiomyopathy should probably be avoided. All patients should be monitored for quinidine toxicity.
Antiplatelet agents	Verapamil has been associated with antiplatelet effects which can increase the effects of antiplatelet agents.	
Aspirin	In a few reported cases, co-administration of verapamil with aspirin led to an increased bleeding time.	--
Carbamazepine	Verapamil may increase plasma concentrations of carbamazepine, and potentiate the effects of carbamazepine neurotoxicity.	Symptoms include diplopia, headache, ataxia or dizziness.

Cimetidine	Two clinical trials have shown a lack of significant verapamil interaction with cimetidine. A third study showed cimetidine reduced verapamil clearance and increased elimination half-life.	--
Cyclosporine	Verapamil therapy may increase plasma concentration of cyclosporine.	--
Digoxin	Verapamil treatment increases serum digoxin levels by 50% to 75% during the first week of therapy, and this can result in digitalis toxicity. In patients with hepatic cirrhosis the influence of verapamil on digoxin kinetics is magnified. Verapamil may reduce total body clearance and extrarenal clearance of digitoxin by 27% and 29%, respectively.	Maintenance and digitalization doses should be reduced when verapamil is administered and the patient should be reassessed to avoid over- or under-digitalization. Whenever over-digitalization is suspected, the daily dose of digitalis should be reduced or temporarily discontinued. On discontinuation of verapamil use, the patient should be reassessed to avoid under-digitalization.
Inhalation Anaesthetics	Animal experiments have shown that inhalation anaesthetics depress cardiovascular activity by decreasing the inward movement of calcium ions.	When used concomitantly, inhalation anaesthetics and calcium channel blocking agents, such as verapamil, should each be titrated carefully to avoid excessive cardiovascular depression.
Lithium	Increased sensitivity to the effects of lithium (neurotoxicity) has been reported during concomitant verapamil-lithium therapy with either no change or an increase in serum lithium levels. However, the addition of verapamil has also resulted in the lowering of serum lithium levels in patients receiving chronic stable oral lithium.	Patients receiving both drugs must be monitored carefully.
Neuromuscular Blocking Agents	Clinical data and animal studies suggest that verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing).	It may be necessary to decrease the dose of verapamil and/or the dose of the neuromuscular blocking agent when the drugs are used concomitantly.
Nitrates	No cardiovascular adverse effects have been attributed to any interaction between these agents and verapamil.	--

Phenobarbital	Phenobarbital therapy may increase verapamil clearance, decreasing plasma concentrations.	--
Rifampin	Therapy with rifampin may markedly reduce oral verapamil bioavailability and may decrease verapamil plasma concentration.	--
Sulfinpyrazone	Increased clearance and decreased bioavailability of verapamil may occur.	--
Theophylline	Verapamil may inhibit the clearance and increase the plasma concentrations of theophylline.	--

Drug-Food Interactions

Consumption of a high fat meal just prior to dosing at night had no significant effect on the pharmacokinetics of COVERA-HS.

Grapefruit juice may significantly increase concentrations of verapamil.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Dosing of COVERA-HS (verapamil hydrochloride) should be individualized by titration. COVERA-HS tablets should be swallowed whole and not chewed, broken or crushed. The active ingredient, verapamil, is released slowly through a white outer shell. The outer shell of the tablet remains intact during gastrointestinal transit, and is passed in the stool.

Recommended Dose and Dosing Adjustment

System Components and Performance

COVERA-HS (verapamil hydrochloride) is a formulation designed to initiate the release of verapamil approximately 4-5 hours after ingestion by means of a delay coating and thereafter to provide a constant rate of release over 12 hours. The tablet is comprised of a semi-permeable membrane surrounding a drug core that is osmotically active. The core itself is divided into 2 layers: an “active” layer containing the drug, and a “push” layer containing pharmacologically inert, but osmotically active, components.

Delay in release of verapamil after ingestion is accomplished by the introduction of a coating between the active drug core and outer semi-permeable membrane. As water from the

gastrointestinal tract enters the tablet, this delay coating is solubilized and released. As tablet hydration continues, the osmotic layer expands and pushes against the drug layer, releasing drug through precision laser-drilled orifices in the outer membrane at a constant rate. This controlled rate of drug delivery in the gastrointestinal lumen is independent of posture, pH, gastrointestinal motility, and fed or fasting conditions.

The biologically inert components of the delivery system remain intact during GI transit and are eliminated in the feces as an insoluble shell (see **WARNINGS AND PRECAUTIONS, Gastrointestinal: Patients With Pre-existing GI Narrowing or Transit Disorders**).

Dosage

Hypertension

Initiate therapy with 180 mg of COVERA-HS.

If an adequate response is not obtained with 180 mg of COVERA-HS, the dose may be titrated upward in the following manner:

a) 240 mg each evening
b) 360 mg each evening (2 x 180 mg)
c) 480 mg each evening (2 x 240 mg)

Chronic Stable Angina

Initiate therapy with 180 mg of COVERA-HS

If an adequate response is not obtained with 180 mg of COVERA-HS, the dose may be titrated upward in the following manner:

a) 240 mg each evening
b) 360 mg each evening (2 x 180 mg)

The majority of patients, who will respond to COVERA-HS therapy, will do so at a dosage of 180-360 mg once daily. However, some patients may respond to 480 mg once daily.

In general, bioavailability of COVERA-HS is higher in the elderly and they tend to respond at lower dosages than those under 65. Dosage should be carefully individualized by titration (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics** and **WARNINGS AND PRECAUTIONS, Geriatrics**).

Patients With Impaired Liver and Renal Function

Verapamil hydrochloride 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. Verapamil should not be used in severe hepatic dysfunction (see **WARNINGS AND PRECAUTIONS, Hepatic Insufficiency** and **Renal Insufficiency**).

Administration

COVERA-HS is a dosage form designed to deliver peak verapamil levels in the morning by a delayed-release mechanism. Accordingly, COVERA-HS should be administered once daily **at bedtime**.

When COVERA-HS is administered **at bedtime**, office evaluation of blood pressure during morning and early afternoon hours is essentially a measure of peak effect. The usual evaluation of trough effect, which might be needed to evaluate the appropriateness of any given dose of COVERA-HS, would be just prior to bedtime.

OVERDOSAGE

Based on reports of intentional overdosage of verapamil hydrochloride, the following symptoms have been observed: hypotension, varying from transient to severe; conduction disturbances, including prolongation of A-V conduction time, A-V dissociation, nodal rhythm, ventricular fibrillation and ventricular asystole.

Treatment of overdosage should be supportive. Gastric lavage should be undertaken, even later than 12 hours after ingestion, if no gastrointestinal motility is present. Beta-adrenergic stimulation or parenteral administration of calcium solutions may increase calcium ion influx across the slow channel.

These pharmacologic interventions have been effectively used in treatment of overdosage with verapamil. Clinically significant hypotensive reactions should be treated with vasopressor agents. A-V block is treated with atropine and cardiac pacing. Asystole should be handled by the usual Advanced Cardiac Life Support measures including the use of vasopressor agents, eg, isoproterenol hydrochloride. Verapamil is not removed by hemodialysis.

In case of overdosage with large amounts of COVERA-HS (verapamil hydrochloride), 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, capsules 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.

Suggested Treatment of Acute Cardiovascular Adverse Reactions

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

Adverse Reaction	Proven Effective Treatment	Treatment with Good Theoretical Rationale	Supportive Treatment
Shock, cardiac failure, severe hypotension	Calcium salt, eg, calcium gluconate IV; IV metaraminol bitartrate*	IV dopamine HCl*; IV dobutamine HCl*	IV fluids; Trendelenburg position
Bradycardia, A-V block, asystole	IV isoproterenol HCl*; IV atropine sulphate; Cardiac pacing		IV fluids (slow drip)
Rapid ventricular rate (due to antegrade conduction in atrial flutter/fibrillation with WPW or LGL syndrome)	D.C. cardioversion (high energy may be required); IV procainamide; IV lidocaine HCl		IV fluids (slow drip)

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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

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

Verapamil may shorten the antegrade effective refractory period of the accessory bypass tract. Acceleration of ventricular rate and/or ventricular fibrillation has been reported in patients with atrial flutter or atrial fibrillation and a coexisting accessory AV pathway following administration of verapamil (see **WARNINGS AND PRECAUTIONS, Cardiovascular,**

Accessory Bypass Tract). Verapamil has a local anaesthetic action that is 1.6 times that of procaine on an equimolar basis.

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

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

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

Pharmacodynamics

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

Pharmacokinetics

Summary of steady-state verapamil Pharmacokinetic Parameters in healthy humans

Steady-State Pharmacokinetics of Verapamil in Healthy Humans with COVERA-HS Administration

	Enantiomer	COVERA-HS Dose	
		180 mg	240 mg
Mean C_{max} (ng/mL)	R-verapamil	90.6	120
	S-verapamil	21.2	28.7
AUC (0-24h) (ng•hr/mL)	R-verapamil	1,223	1,470
	S-verapamil	266	322

Absorption: Upon oral administration of verapamil, rapid stereoselective biotransformation occurs during the first pass through the portal circulation. The systemic concentrations of R and S enantiomers are dependent upon the route of administration and the rate and extent of release from the dosage form.

Racemic verapamil is released from COVERA-HS at a constant rate following solubilization of the delay coat (see **DESCRIPTION, System Components and Performance**). This process produces a lag period in drug release of approximately 4-5 hours, followed by prolonged drug release over 12 hours. Peak plasma concentration (C_{max}) occurs in the morning hours approximately 11 hours after administration, to coincide with the normal circadian rise in blood pressure and heart rate, when COVERA-HS is administered at bedtime. Trough concentrations occur approximately 4 hours after bedtime dosing while the patient is sleeping.

The clinical benefit of presenting peak, rather than trough, plasma levels of verapamil in the morning has not been established.

Steady-state pharmacokinetics were reached by the third or fourth day of dosing, as determined in healthy volunteers.

The pharmacokinetics were not affected by whether the volunteers were supine or ambulatory for the 8 hours following dosing. Administering COVERA-HS in the morning led to a slower rate of absorption, but did not affect the extent of absorption.

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

In a study in 5 healthy volunteers with oral immediate-release verapamil, the systemic bioavailability varied from 33% to 65% for the R enantiomer and from 13% to 34% for the S enantiomer. The S enantiomer is pharmacologically more active than the R enantiomer (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics** and **DETAILED PHARMACOLOGY**).

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

Metabolism: In healthy men, orally administered verapamil undergoes extensive metabolism by the cytochrome P-450 system in the liver. The particular isoenzymes involved are CYP3A4, CYP1A2, and CYP2C family. Thirteen (13) 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.

Administering COVERA-HS in the morning did not affect the extent of metabolism to norverapamil

Excretion: Approximately 70% of an administered dose is excreted as metabolites in the urine and 16% or more in the feces within 5 days. About 3% to 4% is excreted in the urine as unchanged drug. R-verapamil is 94% bound to plasma albumin, while S-verapamil is 88% bound. In addition, R-verapamil is 92% and S-verapamil 86% bound to alpha-1 acid

glycoprotein. The degree of biotransformation during the first pass of verapamil may vary according to the status of the liver in different patient populations. In patients with hepatic insufficiency, metabolism is delayed and elimination half-life prolonged up to 14-16 hours (see **WARNINGS AND PRECAUTIONS, Hepatic Insufficiency** and **DOSAGE AND ADMINISTRATION**).

Administering COVERA-HS in the morning led to a slower rate of elimination.

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

Special Populations and Conditions

Pediatrics: The dosage regimen of verapamil in children has not been established.

Geriatrics: In older subjects (65-80 years), the Cmax for S-verapamil increased by 1.7 fold and for R-verapamil increased by 1.45 fold, in comparison to values in younger subjects (19-53 years) when studied at 180 mg. The AUC for S-verapamil increased by 2.0 fold and for R-verapamil increased by 1.65 fold.

Gender: No gender difference was observed to date with COVERA-HS.

Body Weight: Lean body weight affects its pharmacokinetics inversely.

Genetic Polymorphism: No data available.

Hepatic insufficiency: Because verapamil is extensively metabolized by the liver, it should be administered cautiously to patients with impaired hepatic function, since the elimination half-life of verapamil in these patients is prolonged 4-fold (from 3.7 to 14.2 hours). (see **WARNINGS AND PRECAUTIONS, Hepatic Insufficiency** and **DOSAGE AND ADMINISTRATION**).

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

verapamil should be administered cautiously to patients with impaired renal function. These patients should be carefully monitored for abnormal prolongation of the PR interval or other signs of overdosage (see **OVERDOSAGE**).

STORAGE AND STABILITY

Protect contents from light and high humidity. COVERA-HS 180 mg and COVERA-HS 240 mg, packaged in HDPE bottles to be stored at controlled room temperature (15°C - 25°C).

DOSAGE FORMS, COMPOSITION AND PACKAGING

Description:

COVERA-HS 240 mg tablets are greenish-yellow, round, film coated tablets with COVERA-HS 2021 printed on one side. COVERA-HS 240 mg tablets are available in bottles of 100.

COVERA-HS 180 mg tablets are lavender round, film coated, with COVERA-HS 2011 printed on one side. COVERA-HS 180 mg tablets are available in bottles of 100.

Special Instruction to Pharmacist

Tablets cannot be split in half, crushed or chewed. The outer shell of the tablet remains intact during gastrointestinal transit and is passed in the stool.

Active Ingredient: Each COVERA-HS 240 mg tablet contains 240 mg verapamil hydrochloride. Each COVERA-HS 180 mg tablet contains 180 mg verapamil hydrochloride.

Non-medicinal ingredients: Each COVERA-HS 240mg tablet contains black ferric oxide, butylated hydroxytoluene, cellulose acetate, hydroxyethyl cellulose, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, polyethylene glycol, polyethylene oxide, polysorbate 80, povidone, sodium chloride, titanium dioxide, FD&C Blue No. 2 Lake and D&C Yellow No. 10 Lake

Each COVERA-HS 180mg tablet contains black ferric oxide, butylated hydroxytoluene, cellulose acetate, hydroxyethyl cellulose, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, polyethylene glycol, polyethylene oxide, polysorbate 80, povidone, sodium chloride, titanium dioxide, FD & C Blue No. 2 Lake and D&C Red No. 30 Lake.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

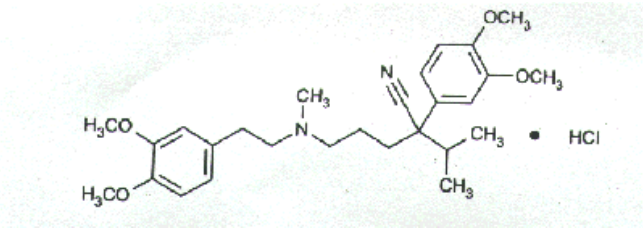
Proper Name: Verapamil hydrochloride

Chemical Name: (±) α - [3-[[2-(3, 4-dimethoxyphenyl) ethyl]-methylamino] propyl]-3, 4-dimethoxy-α- (1-methylethyl) Benzeneacetonitrile monohydrochloride

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

Molecular Weight: 491.07

Structural Formula:



Physicochemical Properties:

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 either. It melts at 140°C and should be protected from light.

CLINICAL TRIALS

Effects in hypertension:

Summary of patient demographics for clinical trials in hypertension

	Trial design	**Dosage, duration**	**Study subjects (n=number)**	**Mean age (Range)**	**Gender**
1.	Multicentre, double-blind, randomized, placebo-controlled parallel design, study. Blood pressure changes were measured with 36-hour ambulatory blood pressure monitoring (ABPM)	Placebo, 120 mg, 180 mg, 360 mg, or 540 mg COVERA-HS; given once daily at 10 pm. Treated for 8 w (the two higher doses were titrated from low doses and maintained for 6 and 4 w, respectively).	287 patients with mild to moderate hypertension ; 50-56/group completed	53.2 yrs (range 26-76 yrs)	62.0% male
2.	Multicentre, double-blind, randomized, placebo-controlled parallel design, study.	Placebo, 240 mg COVERA-HS; given once daily at 10 pm. Treated for 4 weeks	95 patients with mild to moderate hypertension; 44, 45/group completed	56.7 yrs (range 35-78 yrs)	67.4% male

Results of hypertension studies

Primary Endpoints	**Mean ABPM Diastolic Blood Pressure at Final Visit:** **COVERA-HS or placebo**	
Change from baseline in mean diastolic blood pressures (DBP) collected at the pre-dose (6-10 pm or trough) period through the use of ambulatory blood pressure monitoring (ABPM). Changes were deemed significant if - 1. The change was statistically significantly different from the change for placebo at the $p<0.05$ level (two-sided) 2. The observed change was at least 3.5 mmHg greater than that for the placebo.	Study 1. **mmHg change from baseline** placebo 98.3 +0.6 120 mg: 98.0 -0.6 180 mg: 93.1 -3.9** 360 mg: 91.3 -7.8** 540 mg: 87.2 -10.6**	Study 2. **mmHg change from baseline** placebo 97.4 + 1.0 120 mg: 91.4 -4.8**

** $P<0.001$

The results of these studies demonstrate that COVERA-HS (verapamil hydrochloride), at 180–540 mg, is a consistently and significantly more effective antihypertensive agent than placebo in reducing ambulatory blood pressures. Over this dose range, the placebo-subtracted net decreases in diastolic BP at trough (averaged over 6–10 pm) were dose-related, ranged from 4.5 to 11.2 mm Hg after 4–8 weeks of therapy, and correlated well with sitting cuff blood pressures.

The studies demonstrate that clinically and statistically significant blood pressure reductions are achieved with COVERA-HS throughout the 24-hour dosing period.
There were no significant treatment differences between patient subgroups of different age (older or younger than 65 years), sex, race (Caucasian and non-Caucasian) and severity of hypertension at baseline (cuff BP below and above
105 mm Hg).

Effect in chronic stable angina:

Summary of patient demographics for clinical trials in angina

Study #	Trial design	Dosage, duration	Study subjects (n=number)	Mean age (Range)	Gender
1	Multicentre, double-blind, randomized, placebo-controlled parallel design, study.	placebo, 180 mg, 360 mg, or 540 mg COVERA-HS; treated for 4 weeks (the two higher doses were titrated from low doses and maintained for 3 and 2 weeks, respectively)	277 patients randomized; 63-69/group completed	60.8 yrs (range 32-78 yrs)	84.1% male
2	Multicentre, double-blind, randomized, placebo-controlled parallel design, study.	single dose of 240 mg COVERA-HS or placebo	176 patients; 82, 88/group completed	61.3 yrs (range 36-83 yrs)	72.7% male

Results of angina studies:

Study 1

Primary Endpoints Measured during exercise tolerance testing (ETT) carried out pre-dose on trough (evening) and in the morning.	**Results at Endpoint (Evening)** Median (min) Change	**Results at Endpoint (Morning)** Median (min) Change
Symptom-limited ETT duration	Placebo: 6.4 0.5 180 mg: 6.2 1.0** 360 mg: 7.4 1.5** 540 mg: 7.0 1.5**	Placebo: 6.5 0.7 180 mg: 6.9 1.5** 360 mg: 8.2 1.8** 540 mg: 7.7 1.9**
Time to moderate angina on ETT	Placebo: 6.4 0.6 180 mg: 6.6 1.4** 360 mg: 7.8 1.9** 540 mg: 7.5 2.0**	Placebo: 6.6 0.9 180 mg: 7.0 1.8** 360 mg: 10.1 3.6** 540 mg: 9.3 2.9**
Time to ≥1 mm ST segment depression	Placebo: 4.9 0.9 180 mg: 5.0 1.0 360 mg: 6.4 2.0 540 mg: 6.0 1.5	Placebo: 5.5 0.9 180 mg: 6.0 2.2** 360 mg: 10.0 4.2** 540 mg: 8.8 3.3**

** P<0.001

Results from study 2 are consistent with those from Study 1. In these studies, COVERA-HS was significantly more effective than placebo in improvement of exercise tolerance. Placebo-adjusted net increases in median exercise times at the end of the dosing interval were 0.1 to 1.0 minute for symptom limited duration, 0.3 to 1.4 minutes for time to angina, and 0.1 to 1.1 minutes for time to ST change. Increases in exercise tolerance were in general greater at higher doses, but dose-response relationship was not well defined due to shorter treatment duration for high doses.

In addition, in the first study, 24 to 34% of patients treated with COVERA-HS did not experience exercise-limiting angina on exercise treadmill testing (ETT) versus 12% of patients on placebo.

DETAILED PHARMACOLOGY

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

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

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

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

TOXICOLOGY

Acute Toxicity

LD_{50} (mg/kg)				
	IV	IP	SC	oral
Rat	16	67	107	114
Mouse	8	68	68	163
Guinea Pig	-	-	-	140
Juvenile Rat	-	-	-	93 (M)
	-	-	-	113 (F)
Juvenile Rabbit	-	-	-	114.2 (M)
	-	-	-	129.8 (F)

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

Subacute Toxicity

Oral Studies: Verapamil was administered orally in doses of 12.5, 25 and 50 mg/kg per day, to rats via food for 14 weeks (29 animals/group) and to dogs for 6 days/week in capsules, for 15-16 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 25-50 mg/kg showed slight weight loss and a significant reduction in heart rate up to week 11, followed by a gradual return to normal. In one dog on 12.5 mg/kg, one on 25 mg/kg and in all animals on 50 mg/kg, there was emesis during the first two weeks of the study. SGPT was elevated for one dog on 25 mg/kg at week 9 and for two animals on 50 mg/kg at the end of the test. Macroscopic examinations at necropsy were negative and there was no drug-attributable histological changes. The baboons showed no drug-related changes.

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

Intravenous Studies: Verapamil was given to Sprague-Dawley rats at 0.2, 1 and 5.0 mg/kg

once daily for 4 weeks (30 animals/groups) and similarly to beagle dogs at 0.1, 0.4 and 1.6 mg/kg levels (6 animals/group).

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

Chronic Toxicity

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

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

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

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

Mutagenicity

In vitro mutagenicity tests showed that verapamil did not have mutagenic properties in 5 different strains of Salmonella typhimurium, nor in studies on chromosomal aberrations and sister chromatid exchanges (SCE) in human lymphocytes, nor in the HGPRT-test with V-79 Chinese hamster cells, and also not in the cell transformation assay with Syrian hamster embryo cells. Neither did verapamil show any SCE-inducing activity *in vivo* (Chinese hamster).

Carcinogenicity

In a 24-month carcinogenicity study, verapamil hydrochloride was administered orally to 50 male and 50 female rats in the diet as actual mean doses of 9.3/9.5 32.6/33.2, and 112.2/102.5 mg/kg/day, respectively. Two hundred (200) animals served as controls.

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

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

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

Reproduction

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

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

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PART III: CONSUMER INFORMATION

PrCOVERA-HS*
verapramil hydrochloride
(controlled-onset extended release tablets)

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

ABOUT THIS MEDICATION

What the medication is used for:
Your doctor has prescribed COVERA-HS to treat mild to moderate hypertension (high blood pressure) or chronic stable angina.

High blood pressure often produces no symptoms. Patients who do not get routine check-ups at the doctor's office often do not know that they have high blood pressure. If high blood pressure remains untreated, it may lead to stroke, heart attack, heart failure, kidney failure, and blindness.

If you have chronic stable angina, you sometimes experience chest pain. This happens when there is not enough blood supplied to the heart for it to carry out its normal functions.

What it does:
COVERA-HS belongs to a group of drugs called "calcium channel blockers". It affects the entry of calcium into the cells of the muscles of the arteries and the heart. This relaxes the arteries and affects the beating of the heart, thereby lowering blood pressure and supplying more blood to the heart.

When it should not be used:
COVERA-HS should generally not be used if you have the following:
1. Complicated myocardial infarction
2. Severe congestive heart failure
3. Cardiogenic shock
4. Hypotension
5. Heart conduction disturbances (eg. second- or third-degree A-V block, Sick Sinus Syndrome, atrial flutter or atrial fibrillation and an accessory bypass tract)
6. Noticeably slow heart rate (bradycardia)
7. Allergy to verapamil hydrochloride of any or the non-medicinal ingredients (see list below)

What the medicinal ingredient is:
COVERA-HS is the brand name for a once daily controlled-onset extended-release formulation of verapamil hydrochloride.

Each COVERA-HS 240 mg tablet contains 240 mg verapamil hydrochloride. Each COVERA-HS 180 mg tablet contains 180 mg verapamil hydrochloride.

What the important nonmedicinal ingredients are:
Each COVERA-HS 240 mg and 180 mg tablet contains black ferric oxide, butylated hydroxytoluene, cellulose acetate, hydroxyethyl cellulose, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, polyethylene glycol, polyethylene oxide, polysorbate 80, povidone, sodium chloride, and titanium dioxide, FD&C Blue No. 2 Lake, D&C Yellow No. 10 Lake (240 mg only) and D&C Red No. 30 Lake (180 mg only).

What dosage forms it comes in:
COVERA-HS is available as 180 mg and 240 mg tablets in bottles of 100.

WARNINGS AND PRECAUTIONS

BEFORE you use COVERA-HS talk to your doctor or pharmacist if:
- you take other medications, including those you can buy without prescription and herbal products, or if you drink alcohol;
- you have or have had heart or blood vessel diseases;
- you are also taking antianginal or antiarrythmic drugs (for heart problems);
- you have or have had kidney and liver disease;
- you have or have had stomach or intestinal problems;
- you suffer from muscular dystrophy or other neuromuscular disorder;
- you are pregnant or plan to become pregnant;
- you are breast-feeding;
- you are allergic to any of the ingredients of COVERA-HS.

If you drink alcohol the effects of the alcohol may be increased and prolonged. You should be aware of that and be more cautious with alcohol or you may wish to avoid alcohol altogether.

If you're seeing more than one doctor make sure that each knows about all the medicines you are taking.

Your doctor may perform occasional liver function tests while you are using COVERA-HS.

INTERACTIONS WITH THIS MEDICATION

The following list includes drugs that may interact with COVERA-HS. Talk to your doctor or pharmacist if you also take: alcohol, ACE-inhibitors, anti-neoplastic agents, anti-platelet agents, aspirin, triazole antifungals, benzodiazepines, beta-blockers, α_2-adrenergic agonists, carbamazepine, clarithromycin, cimetidine, cyclosporine, digoxin, disopyramide, diuretics, erythromycin, flecainide, imipramine, inhalation anesthetics, itraconazole, lithium, neuromuscular blocking agents (eg. curare), phenobarbital, phenytoin, propafenone, quinidine, rifampin, ritonavir, sulfinpyrazone theophylline, warfarin.

Avoid drinking grapefruit juice as it may increase the level of COVERA-HS in your system.

PROPER USE OF THIS MEDICATION

COVERA-HS should be taken once daily **at bedtime**. COVERA-HS can be taken with or without food. COVERA-HS tablets should be swallowed whole; do not break, crush, or chew. The medication in the COVERA-HS tablet is released slowly through a white outer shell that does not dissolve. Do not worry if you sometimes see this white outer shell in your stool.

If you miss a dose: If you miss a dose, as soon as you remember, you should still take the missed dose. However, if it is more than 6 hours since your scheduled dose, skip the missed dose and go back to your regular dosing schedule (ie, the next evening) as prescribed by your doctor. Do not take double doses to make up for missing a dose.

If you take too many tablets: If you take too many tablets by accident, call your doctor or pharmacist immediately.

How long to take COVERA-HS: You should take COVERA-HS as long as your doctor thinks it is necessary to control your blood pressure or your angina (chest pain).

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medications, some patients may experience side effects with COVERA-HS. The most common side effects are: constipation, headache, dizziness, nausea and fatigue. If you do have side effects or you experience anything out of the ordinary while taking COVERA-HS, talk to your doctor or pharmacist, they may have recommendations for managing these side effects.

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

If you notice any of the following potentially serious side effects, please stop taking COVERA-HS and contact your doctor immediately:

- Allergic reactions such as breathing difficulties, swelling of the face lips, and tongue
- slow, fast, or irregular heart rate; low blood pressure (hypotension); dizziness; weakness; or swelling.

This is not a complete list of side effects. If you have any unexpected effects after receiving COVERA-HS*, contact your doctor or pharmacist.*

HOW TO STORE IT

Store your tablets in a dry place at room temperature (15°C - 25°C).

Protect from light and moisture.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: http://www.pfizer.ca or by contacting Pfizer Canada Inc., at: 1-800-463-6001

TPD website:
http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/aboutus_e.html

BGTD website:
http://www.hc-sc.gc.ca/hpfb-dgpsa/bgtd-dpbtg/index_e.html

This leaflet was prepared by Pfizer Canada Inc.

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