PRODUCT MONOGRAPH

VERELAN®

Verapamil HCl Sustained Release Capsules

120 mg, 180 mg and 240 mg

Antihypertensive Agent

Manufactured by:
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Gainesville, Georgia, USA

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ACTIONS AND CLINICAL PHARMACOLOGY

Verapamil is a calcium ion influx inhibitor (slow channel blocker or calcium ion antagonist) which exerts its pharmacologic effects by modulating the influx of ionic calcium across the cell membrane of the arterial smooth muscle as well as in conductile and contractile myocardial cells.

Mechanism of Action in Essential Hypertension:

Verapamil HCl exerts antihypertensive effects by inducing peripheral vasodilation and reducing peripheral vascular resistance usually without reflex tachycardia. These effects are mediated by inhibition of calcium ion influx into smooth muscle cells of the arteriolar wall. Verapamil does not blunt hemodynamic response to isometric or dynamic exercise. Compared to baseline verapamil administration did not affect electrolytes, glucose and creatinine. The hypotensive effect of verapamil is not blunted by an increase in sodium intake.

PHARMACOKINETICS

Immediate Release Formulations of verapamil:

With the immediate release formulations, more than 90% of the orally administered dose of verapamil is absorbed. Because of rapid biotransformation during its first pass through the portal circulation, bioavailability ranges from 20% to 35%. Peak plasma concentrations are reached between 1 and 2 hours after oral administration. Chronic oral administration of 120 mg of verapamil every 6 hours resulted in plasma levels of verapamil ranging from 125 ng/mL to 400 ng/mL, with higher values reported occasionally. A nonlinear correlation between the verapamil dose administered and

verapamil plasma levels does exist. In initial dose titration with verapamil a relationship exists between verapamil plasma concentration and prolongation of the PR interval. After repetitive dosing, less than 10 consecutive doses given 6 hours apart, the mean elimination half life ranged from 4.5 to 12.0 hours. Half life of verapamil increases during titration due to saturation of hepatic enzyme systems as plasma verapamil levels rise.

Aging affects the pharmacokinetics of verapamil. Elimination half-life is prolonged in the elderly.

In healthy men, orally administered verapamil undergoes extensive metabolism in the liver. Twelve metabolites have been identified in plasma; all except norverapamil are present in trace amounts only. Norverapamil can reach steady-state plasma concentration approximately equal to those of verapamil itself. The biologic activity of norverapamil appears to be approximately 20% that of verapamil. 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. Approximately 90% is bound to plasma proteins. In patients with hepatic insufficiency, metabolism is delayed and elimination half-life prolonged up to 14 to 16 hours (see WARNINGS and DOSAGE AND ADMINISTRATION).

After 4 weeks of oral dosing (120 mg q.i.d.) verapamil and norverapamil levels were noted in the cerebrospinal fluid with estimated partition coefficients of 0.06 for verapamil and 0.04 for norverapamil.

VERELAN Sustained Release Capsules

In a multiple dose pharmacokinetic study, peak concentrations for a single daily dose of VERELAN (verapamil HCl) sustained release capsule 240 mg were approximately 65% of those obtained with an 80 mg t.i.d. dose of the conventional immediate release tables, and the 24 hour post-dose concentrations were approximately 30% higher. The steady state pharmacokinetic data are summarized in Table 1.

Influence of Food: Food does not affect the extent are rate of the absorption of verapamil from the controlled release VERELAN capsule. The VERELAN 240 mg capsule when administered with food had a C_{max} of 77 ng/mL which occurred 9.0 hours after dosing and an AUC(0-inf) of 1387 ng.hr/mL. VERELAN 240 mg under fasting conditions had a C_{max} of 77 ng/mL which occurred 9.8 hours after dosing, and an AUC(0-inf) of 1541 ng.hr/mL.

The time to reach maximum verapamil concentrations (t_{max}) with VERELAN (verapamil HCl) sustained release capsules has been found to be approximately 7-9 hours in each of the single dose (fasting), single dose (fed), the multiple dose (steady state) studies and dose proportionally pharmacokinetic studies. Similarly the apparent half-life ($T_{1/2}$) has been found to be approximately 12 hours independent of dose.

TABLE 1

COMPARISON OF PHARMACOKINETIC PARAMETERS OF VERELAN VERSUS IMMEDIATE RELEASE FORMATIONS

PARAMETERS	IMMEDIATE RELEASE TABLETS t.i.d		VERELAN ONCE DAILY DOSE		
	80 mg tid 240 mg/day	120 mg tid 360 mg/day	120 mg	240 mg	360mg
Cmax ng/mL	170.5	289.4	39.4	107.7	173.9
Cmin ng/mL	25.5	80.1	10.8	32.8	61
Tmax h	0.96	1.4	8.2	7.9	7.1
T1/2 h	6.1	6.1	13.6	10.5	9.6
$AUC_{(0\text{-}24h)}$ $AUC_{(0\text{-}36h)}$ ng.h/mL	1569	1809	656	1660	2729

INDICATIONS AND CLINICAL USE

VERELAN (verapamil HCl) sustained release capsules is indicated in the treatment of mild to moderate essential hypertension. It should normally be used in those patients in whom treatment with diuretics or beta blockers has been associated with unacceptable adverse effects.

VERELAN (verapamil HCl) sustained release capsules 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.

Combination of verapamil with a diuretic has been found to be compatible and showed additive antihypertensive effect.

VERELAN (verapamil HCl) sustained release capsules should not be used concurrently with beta blockers in the treatment of hypertension (See PRECAUTIONS, DRUG INTERACTIONS).

Safety of concurrent use of VERELAN (verapamil HCl) sustained release capsules with other antihypertensive agents has not been established and such use cannot be recommended at this time.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see DOSAGE FORMS.
- Severe hypotension.
- Cardiogenic shock.
- Acute myocardial infarction.
- Severe congestive heart failure and/or severe left ventricular dysfunction (unless secondary to a supraventricular tachycardia amenable to oral verapamil therapy).
- Second or third degree AV block.

- Sick sinus syndrome (see WARNINGS).
- 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).
- Concomitant use of ivabradine (see DRUG INTERACTIONS).

WARNINGS

General: In patients with angina or arrhythmias using antihypertensive drugs, the additional hypotensive effect of verapamil should be taken into consideration.

Heart Failure: Because of verapamil's negative inotropic effect, the drug 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 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 administration (see DRUG INTERACTIONS).

The use of verapamil 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.

Conduction Distribution: Verapamil slows conduction across the AV node and rarely may produce second or third degree AV block, bradycardia and in extreme cases, asystole.

Verapamil causes dose-related suppression of the SA node. In some patients, sinus bradycardia may occur. Especially in patients with sick sinus syndrome (SA nodal disease), which is more common in older patients (see CONTRAINDICATIONS).

Bradycardia: The total incidence of bradycardia (ventricular rate less than 50

beats/min) was 1.4% in controlled studies. Asystole in patients other than those with sick sinus syndrome is usually of short duration (few seconds or less), with spontaneous return to AV nodal or normal sinus rhythm. If this does not occur promptly, appropriate treatment should be initiated immediately, (see SYMPTOMS AND TREATMENT OF OVERDOSAGE).

Accessory Bypass Tract: 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 i.v. 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).

Concomitant therapy with beta-adrenergic blockers: Generally, oral verapamil should not be given to patients receiving beta-blockers since the depressant effects on myocardial contractility, heart rate and atrioventricular conduction may be additive.

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.

Patients with Hypertrophic Cardiomyopathy: In 120 patients with hypertrophic cardomyopathy who received therapy with verapamil at doses up to 720 mg/day, a variety of serious adverse effects was seen. Three patients died in pulmonary edema; all had severe left ventricular outflow obstruction and a past history of left ventricular dysfunction. Eight other patients had pulmonary edema and/or severe hypotension, abnormally high (greater than 20m 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 should be appreciated that this group of patients had a serious disease with high mortality rate. Most adverse effects responded well to dose reduction, but in some cases verapamil had to be discontinued.

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

Hepatic Insufficiency: Since verapamil is extensively metabolized by the liver, it should be administered cautiously to patients with impaired hepatic function. Impaired hepatic function prolongs the elimination half-life of immediate-release verapamil to about 14 to 16 hours. A decreased dosage should be used in patients with hepatic insufficiency and careful monitoring for abdominal prolongation of the PR interval or other signs of excessive pharmacologic effect should be carried out (see PHARMACOKENETICS 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 i.v. 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. Therefore, until further data are available, verapamil 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).

PRECAUTIONS

Atypical lens changes and cataracts were observed in beagle dog studies at high loses. This has been concluded to be species-specific for the beagle dog. (These ophthalmological changes were not seen in second study.) No similar changes have been observed in long-term prospective human ophthalmological trials.

Verapamil 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.

Patients with Attenuated (Decreased) Neuromuscular Transmission: It has been reported that verapamil decreases neuromuscular transmission in patients with Duchene'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.

Use in the Elderly: Caution should be exercised when verapamil is administered to elderly patients (≥ 65 years) especially those prone to developing hypotension or those with a history of cerebrovascular insufficiency. The incidence of adverse reactions occurring more frequently include dizziness and constipation.

Pregnancy: Teratology and reproduction studies have been performed with verapamil in rabbits and rats at oral does 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 weigh gains of the dams. This oral dose has also been shown to cause hypotension in rats.

There are no studies in pregnant women. Verapamil crosses the placental barrier and can be detected in umbilical vein blood at delivery. VERELAN (verapamil HCl) sustained release capsules is not recommended for use in pregnant women unless the anticipated benefits outweigh the potential risks to mother and fetus.

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

Nursing mothers: Verapamil is excreted in human milk. Because of the potential for adverse reactions in nursing infants from verapamil, nursing should be discontinued while the drug is administered.

Use in Children: The safety and dosage regimen of verapamil in children has not yet been established.

DRUG INTERACTIONS

Beta-Adrenergic Blockers: The concomitant administration of verapamil with beta-blockers can result in severe effects (see WARNINGS).

Digitalis: Verapamil treatment increase 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 nonrenal clearance of digitoxin by 27 and 29% respectively. Maintenance and digitalization doses should be reduced when verapamil is administered, and the patient should be carefully monitored to avoid over or underdigitalization. Whenever overdigitalization is suspected, the daily dose of digitals should be reduced or temporarily discontinued. On discontinuation of verapamil use, the patient should be reassessed to avoid underdigitalization.

Ivabradine: A clinical trial has shown that due to its moderate CYP3A4 inhibitory effect, verapamil (120 mg b.i.d.), when co-administered with ivabradine, increases the ivabradine plasma AUC by 2- to 3- fold. Moreover, both verapamil and ivabradine are heart rate lowering substances and hence, co-administration could lead to an exacerbated reduction in patient's heart rate. Concomitant use of VERELAN® with ivabradine is therefore contraindicated (see CONTRAINDICATIONS).

Antihypertensive Agents: Verapamil administered concomitantly with other antihypertensive agents may have an additive effect on lowering blood pressure. In patients with hypertension, combination with a diuretic has been found to be compatible; however, combination with other antihypertensive agents has not been established. Verapamil should not be combined with beta-blockers for the treatments of hypertension.

Antiarrhythmic Agents:

Disopyramide: 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, AV 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, concomitant use of verapamil and quinidine resulted in significant hypotension. Until further data are obtained, combined therapy of verapamil and quinidine in patients with hypertrophic cardiomyopathy should probably be avoided.

The electrophysiologic effects of quinidine and verapamil on AV conduction were studied in 8 patients. Verapamil significantly counteracted the effects of quinidine on AV

conduction. There has been a report of increased quinidine levels during verapamil therapy.

Nitrates, Diuretics: No cardiovascular adverse effects have been attributed to the concomitant use of verapamil and these agents.

Other:

Carbamazepine: The concomitant oral administration of verapamil and carbamazepine may potentiate the effects of carbamazepine neurotoxicity. Symptoms include nausea, diplopia, headache, ataxia or dizziness.

Cimetidine: The interaction between cimetidine and chronically administered verapamil has not been studied. Variable results on clearance have been obtained in acute studies of healthy volunteers; clearance of verapamil was either reduced or unchanged.

Lithium: Oral verapamil therapy may result in a lowering of serum lithium levels in patients receiving chronic, oral lithium therapy. A dose adjustment of the lithium may be necessary.

Rifampin: Therapy with rifampin may markedly reduce oral verapamil bioavailability.

Phenobarbital: Phenobarbital therapy may increase verapamil clearance.

Cyclosporine: Verapamil therapy may increase serum levels of cyclosporine.

Inhalation Anesthetics: When used concomitantly, inhalation anesthetics and calcium antagonists, such as verapamil, should be titrated carefully because additive hemodynamic depressive effects have been observed.

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.

Sulphinpyrazone: Oral clearance of verapamil following single and multiple doses in volunteers was increased, with an associated decrease in bioavailability, by sulphinpyrazone.

Theophylline: Increased plasma theophylline concentrations due to verapamil administration have been reported.

ADVERSE REACTIONS

In controlled clinical trials involving 289 hypertensive patients treated with VERELAN (verapamil HCl) sustained release capsules, the overall incidence of adverse events irrespective of causality was 26% and the rate of discontinuation from these trials due to adverse events was 2%. The following adverse reactions were reported in greater than 1% of the patients: constipation (7.4%), headache (5.3%), dizziness (4.2%), lethargy (3.2%), dyspepsia (2.5%), rash (1.4%), ankle edema (1.4%), sleep disturbance (1.4%) and myalgia (1.1%).

In clinical trials with other formulations of verapamil HCl, (N=4954), the following adverse reactions divided by body system have been reported. The most serious adverse reactions reported with verapamil are heart failure (1.8%), hypotension (2.5%), A-V-Block (1.2%) and rapid ventricular response (see WARNINGS).

Cardiovascular: Hypotension 2.5%; edema 2.1%; CHF/pulmonary edema 1.9%; bradycardia 1.4%; AV block, total (1°, 2°, 3°) 1.2% or 2° and 3° 0.8%.

Central Nervous System: Dizziness 3.2%, headache 2.2%, fatigue 1.7%.

Gastrointestinal: Constipation 7.3%, nausea 2.7%.

The following reactions were reported in 1% or less of patients:

Cardiovascular: Flushing, angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura, syncope, severe tachycardia, developing or worsening of heart failure, development of rhythm disturbances, ventricular dysrhythmias, painful coldness or numbness of extremities.

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

Gastrointestinal: Diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, vomiting.

Respiratory: Dyspnea, bronchospasm.

Urogenitial: Gynecomastia, increased frequency of urination, spotty menstruation, oligomenorrhea, impotence.

Hematologic and Lymphatic: Ecchymosis or bruising.

Skin: Arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson Syndrome, erythema multiforme, pruritus.

Special Senses: Blurred vision, diplopia.

Hepatotoxicity with elevated enzymes [AST (SGOT), ALT (SGPT), alkaline phosphatase] and bilirubin levels, jaundice and associated symptoms of hepatitis with cholestasis have been reported (see WARNINGS).

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.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms: Based on reports of intentional overdosage with verapamil, the following symptoms have been observed. Hypotension occurs, varying from transient to severe. Conduction disturbances seen included: prolonged AV conduction time, AV dissociation, nodal rhythm, ventricular fibrillation and ventricular asystole. In case of overdosage with VERELAN (verapamil HCl) sustained release capsules, it should be noted that the release rate and absorption of verapamil from VERELAN is prolonged (see Table 1) due to the sustained release characteristics of the formulation.

Treatment: Treatment of overdosage should be supportive (see TABLE 2). 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. AV 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 HCl. Verapamil is not removed by hemodialysis.

Suggested Treatment of Acute Cardiovascular Adverse Effects:

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

TABLE 2

Adverse Effects	Proven Effective Treatment	Treatment with Good Theoretical Rationale	Supportive Treatment
Shock, cardiac failure	Calcium salt e.g. calcium gluconate i.v. metaraminol* bitartrate i.v.	Dopamine HCl* i.v. dobutamine HCl* i.v.	Intravenous fluids Trendelenburg position
Bradycardia, A-V block, asystole	Isoproterenol HCl* i.v. atropine sulphate i.v. Cardiac pacing		Intravenous fluids (slow drip)
Rapid ventricular rate (due to antegrade conduction in flutter/fibrillation with W-P-W or L-G-L syndrome)	D.D. cardioversion (high energy may be required) procainamide i.v. lidocaine HCl i.v.		Intravenous fluids (slow drip)

DOSAGE AND ADMINISTRATION

Mild to Moderate Essential Hypertension: The dosage of VERELAN (verapamil HCl) sustained release capsules should be individualized by titration depending on patient tolerance and responsiveness to verapamil. 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 180-240 mg/day, taken once a day, in the morning. If adequate response is not obtained, the dose may be titrated upward to 360 mg or to 480 mg taken once a day in the morning. Optimal doses are usually lower in patients also receiving diuretics since additive antihypertensive effects can be expected.

The maximum daily dose of 480 mg should not be exceeded. The antihypertensive effects of VERELAN are evident within the first week of therapy.

Elderly: Initial doses of 120 mg a day may be warranted in patients who may have an increased response to verapamil (e.g. elderly, 65 years and older, and small people, See PRECAUTIONS). The dosage should be carefully and gradually adjusted depending on patient tolerability and response.

Patients with Impaired Liver or Renal Function: VERELAN (verapamil HCl) sustained release capsules should be administered cautiously to patients with impaired liver or renal function. The dosage should be adjusted gradually depending on patient tolerance and response. These patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. VERELAN should not be used in severe hepatic dysfunction (see WARNINGS).

PHARMACEUTICAL INFORMATION

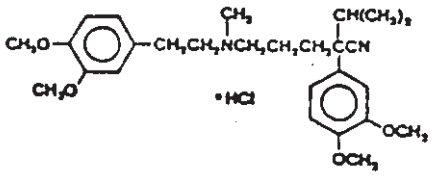
DRUG SUBSTANCE

Proper Name: Verapamil HCl USP

Chemical Name: Benzeneacetonitrile

α [3-[[2-(3m4-dimethoxyphenyl)-ethyl] methylamino]-3,4 dimethoxy- α (1methylethyl) monohydrochloride

Structural Formula:



Molecular Weight: 491.08

Molecular Formula: $C_{27}H_{38}N_2O_4HCl$

Physical Form: Almost white crystalline powder, practically free of odor with a bitter taste.

Solubility: Soluble in water, chloroform and methanol.

pH: 4.5 – 6.5

Melting Point: 140°C - 144°C

DOSAGE FORMS

Availability

VERELAN (verapamil HCl) is formulated as sustained release pellet filled capsules for oral administration.

120 mg – Size 2 – Yellow body – yellow cap

180 mg – Size 1 – Yellow body – gray cap

240 mg – Size 0 – Yellow body – blue cap

The capsules are packaged in high density polyethylene bottles, with 100 capsules/bottle.

Inactive ingredients: Fumaric acid, talc, sugar spheres, povidone, shellac, gelatin, FD&C red #40, yellow iron oxide, titanium dioxide, methylparaben, propylparaben, silicon dioxide, and sodium lauryl sulfate. The VERELAN 240 mg capsule also contains FD&C blue #1, and D&C red #28; and VERELAN 180 mg capsule contains black iron oxide.

Storage

Store at controlled room temperature, 15-25°C. Protect from moisture and light.

PHARMACOLOGY

VERELAN (verapamil HCl) is a calcium ion influx inhibitor which exerts its pharmacologic effects by modulating the influx of ionic calcium across the cell membrane of the arterial smooth muscle as well as in conductile and contractile myocardial cells.

Normal sinus rhythm is usually not affected by verapamil HCl. However, in patients with sick sinus syndrome, verapamil HCl may interfere with sinus node impulse generation and may induce sinus arrest or sinoatrial block. Atrioventricular block can occur in patients without preexisting condition defects (see WARNINGS). Verapamil HCl does not alter the normal atrial action potential or intraventricular conduction time, but depresses amplitude, velocity of depolarization and conduction in depressed atrial fibers. Verapamil HCl may shorten the antegrade effective refractory period of accessory bypass tracts. 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).

Although verapamil HCl has local anesthetic properties, in clinically relevant doses it does not affect the rate of either the depolarization or the repolarization phase of the cardiac action potential.

TOXICOLOGY

ACUTE TOXICITY

LD_{50} (mg/Kg)

	I.V	I.P	S.C.	Oral
Rat	16	67	107	114
Mouse	8	68	68	163
Guinea Pig				140
Juvenile Rats				93(M) 113(F)
Juvenile Rabbits				114(M) 129(F)

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

SUBACUTE AND CHRONIC ORAL TOXICITY

In the beagle dog emesis and depression were observed at oral doses of 50 to 400 mg/kg. In dog subacute and/or chronic oral studies, the minimum lethal dose of verapamil was about 60 mg/kg/day.

In the dog, behavioral and/or clinical effects of verapamil were observed at doses low as 10 mg/kg/day and included emesis, abnormal quietness, excessive salivation, scieral injection, papillary dilation, inhibition of papillary accommodation, lacrimation, hyperemia of the oral mucosa, and soft stools/diarrhea. These effects were more pronounced

and/or more frequently observed at doses of 60 mg/kg/day or higher; they also tended to occur more often early in the study and then to abate with continued dosing. Other effects observed at higher doses included photophobia at 62.5 mg/kg/day, gingival hypertrophy/hyperplasia at 40 mg/kg/day or greater, hair loss and a change in coat color (turned gray) at 60 mg/kg/day or greater. The gingival effects occurred after about 25 to 30 weeks of dosing; similar but less pronounced gum effects seen at lower doses (15-30 mg/kg/day) appeared to disappear despite continued dosing. The more pronounced gum effects as well as the hair loss and change in coat color were reversible when verapamil was discontinued. Body weight and food consumption were reduced at doses of 50 or 60 mg/kg/day and above. Lower dose only initially reduced food consumption and had little or no effect on body weight. Serum chemistries showed occasional, transient dose-related slight to moderate increases in SGPT at 40 mg/kg/day and above; increases in BUN at 62.5 mg/kg/day in one study and increases in SGOT at 10 to 62.5 mg/kg/day in another study were not confirmed in additional chronic studies.

In chronic animal toxicology studies, verapamil caused lenticular and/or suture line changes at 30 mg/kg/day or greater and frank cataracts at 62.6 mg/kg/day or greater in the beagle dog but not the rat. It was concluded that any changes caused by verapamil in lens transparency are specific to the beagle.

Heart rates in dogs counted before daily dosing showed a dose-related decline at 30 mg/kg/day and above. When the daily dose was fractionated into t.i.d. dose, heart rate usually increased after sub-doses of 20 to 23 mg/kg t.i.d. on the first day of treatment but decreased on subsequent days of dosing. Sub-doses of 30 mg/kg t.i.d. decreased heart rate. Heart rate decreases were sometimes marked, ranging from -60 to -118 beats/min, and in dogs that died heart rate reached levels of 30-40 beats/min. electrocardiographic effects of verapamil observed at doses of 62.5 to 85 mg/kg/day (fractionated0 included prolongation of the P-R interval, second degree AV block, loss of P-waves, A-V dissociation, nodal and ventricular rhythms, and abnormal T waves. Verapamil caused a dose-related decrease of systolic blood pressure at sub-doses of 20.84 mg/kg t.i.d. (62.5 mg/kg/day) to 30 mg/kg t.i.d. (90 mg/kg/day) which averaged -

21 mmHg to -71 mmHg. Blood pressure effects of the high dose tended to carry over to the next day.

Verapamil (2-64 mg/kg/day) administered orally to baboons for 4 weeks caused occasional emesis at 8 mg/kg/day and above and tended to reduce initial daily heart rates at doses of 16 mg/kg/day and above.

MUTAGENICITY

Verapamil was not mutagenic in the Ames test in 5 test strains at 3 mg per plate, with or without metabolic activation, not in other in vitro studies on chromosomal aberrations and sister chromatid exchanges (SCE) in human lymphocytes, in Chinese hamster, cells, nor in in vivo studies in Chinese hamster.

CARCINOGENICITY

There was no evidence of a carcinogenic potential of verapamil administered in the diet of rats for 2 years at doses of approximately 10, 35, & 110 mg/kg/day, or approximately 1x, 3.5x & 12x, respectively, the maximum recommended human daily dose (480 mg/day or 9.6 mg/kg/day). In the high dose group, drug related significant reductions in body weight and mortality, and cardiac lesions (dilation, atrial thrombi and myocardial metaplasia, combined with hydrothorax) were observed.

REPRODUCTION

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 maximum recommended human daily dose respectively, and have revealed no evidence of teratogenicity. In the 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.

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