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IKACOR®

TABLETS

Composition

Ikacor Tablets 40 mg

Each tablet contains:

Active Ingredient

Verapamil HCl	40 mg

Others Ingredients

Lactose monohydrate, starch, microcrystalline cellulose, gelatin, talc, sodium starch glycolate, magnesium stearate, HPMC 2910, titanium dioxide, polyethylene glycol, erythrosine aluminium lake.

Each tablet contains: 40.0 mg lactose, 0.08 mg sodium.

Ikacor Tablets 80 mg

Each tablet contains:

Active Ingredient

Verapamil HCl	80 mg

Others Ingredients

Lactose monohydrate, starch, microcrystalline cellulose, gelatin, talc, sodium starch glycolate, magnesium stearate, polydextrose FCC, titanium dioxide, HPMC 2910, macrogol/PEG 4000, polyethylene glycol, erythrosine aluminium lake, brilliant blue FCF aluminium lake FD&C Blue No.1.

Each tablet contains 80.0 mg lactose, 0.16 mg sodium.

Ikacor Tablets 120 mg

Each tablet contains:

Active Ingredient

Verapamil HCl	120 mg

Others Ingredients

Lactose monohydrate, starch, microcrystalline cellulose, gelatin, talc, sodium starch glycolate, magnesium stearate, HPMC 2910, titanium dioxide, polyethylene glycol, brilliant blue FCF aluminium lake FD&C Blue No.1.

Each tablet contains 120.0 mg lactose, 0.24 mg sodium.

Action

Pharmacotherapeutic group: Selective calcium channel blockers with direct cardiac effects, phenylalkylamine derivatives.

ATC-Code: C08DA01

Verapamil is a calcium antagonist which blocks the inward movement of calcium in cardiac muscle cells, in smooth muscle cells of the coronary and systemic arteries and in the cells of the intracardiac conduction system. The decrease in systemic and coronary vascular resistance and the sparing effect on intracellular oxygen consumption appear to explain the anti-anginal properties of the product.

Because of its effect on the movement of calcium in the intracardiac conduction system, Verapamil reduces automaticity, decreases conduction velocity and increases the refractory period.

Ikacor lowers peripheral vascular resistance with little or no reflex tachycardia. Its efficacy in reducing both raised systolic and diastolic blood pressures is thought to be primarily due to this mode of action.

Pharmacokinetic properties

Verapamil hydrochloride is a racemic mixture consisting of equal portions of the R-enantiomer and the S-enantiomer. Verapamil is extensively metabolized. Norverapamil is one of 12 metabolites identified in urine, has 10 to 20% of the pharmacologic activity of verapamil and accounts for 6% of excreted drug. The steady-state plasma concentrations of norverapamil and verapamil are similar. Steady state after multiple once daily dosing is reached after three to four days.

Absorption

Greater than 90% of verapamil is rapidly absorbed from the small intestine after oral administration. Mean systemic availability of the unchanged compound after a single dose of verapamil is 22% owing to an extensive hepatic first-pass metabolism. Bioavailability is about two times higher with repeated administration. Peak verapamil plasma levels are reached one to two hours after administration. The peak plasma concentration of norverapamil is attained approximately one hour after administration. The presence of food has no effect on the bioavailability of verapamil.

Distribution

Verapamil is widely distributed throughout the body tissues, the volume of distribution ranging from 1.8–6.8 L/kg in healthy subjects. Plasma protein binding of verapamil is approximately 90%.

Metabolism

Verapamil is extensively metabolized. *In vitro* metabolic studies indicate that verapamil is metabolized by cytochrome P450 CYP3A4, CYP1A2, CYP2C8, CYP2C9 and CYP2C18. In healthy men, orally administered verapamil hydrochloride undergoes extensive metabolism in the liver, with 12 metabolites having been identified, most in only trace amounts. The major metabolites have been identified as various N and O-dealkylated products of verapamil. Of these metabolites, only norverapamil has any appreciable pharmacological effect (approximately 20% that of the parent compound), which was observed in a study with dogs.

Elimination

Following intravenous infusion, verapamil is eliminated bi-exponentially, with a rapid early distribution phase (half-life about four minutes) and a slower terminal elimination phase (half-life two to five hours). Following oral administration, the elimination half-life is three to seven hours. Approximately 50% of an administered dose is eliminated renally within 24 hours, 70% within five days. Up to 16% of a dose is excreted in the feces. About 3% to 4% of renally excreted drug is excreted as unchanged drug. The total clearance of verapamil is nearly as high as the hepatic blood
flow, approximately 1 L/h/kg (range: 0.7-1.3 L/h/kg).

Special Populations

Pediatric: Limited information on the pharmacokinetics in the paediatric population is available. After intravenous dosing, the mean half-life of verapamil was 9.17 hours and the mean clearance was 30 L/h, whereas it is around 70 L/h for a 70-kg adult. Steady-state plasma concentrations appear to be somewhat lower in the paediatric population after oral dosing compared to those observed in adults.

Geriatrics: Aging may affect the pharmacokinetics of verapamil given to hypertensive patients. Elimination half-life may be prolonged in the elderly. The antihypertensive effect of verapamil was found not to be age-related.

Renal insufficiency: Impaired renal function has no effect on verapamil pharmacokinetics, as shown by comparative studies in patients with end-stage renal failure and subjects with healthy kidneys.
Verapamil and norverapamil are not significantly removed by hemodialysis.

Hepatic insufficiency: The half-life of verapamil is prolonged in patients with impaired liver function owing to lower oral clearance and a higher volume of distribution.

Indications

Antianginal
.Angina at rest including vasospastic (Prinzmetal's variant) angina and unstable (crescendo, pre-infarction) angina.
.Chronic stable angina (classic effort-associated angina).

Antiarrhythmic
Ikacor is indicated for the treatment of supraventricular tachyarrhythmias, including:
.Rapid conversion to sinus rhythm of paroxysmal supraventricular tachycardias, including those associated with accessory bypass tracts (Wolff-Parkinson-White and Lown-Ganong-Levine syndrome).
.Temporary control of rapid ventricular rate in atrial flutter or atrial fibrillation.

Hypertension
Ikacor is indicated in the treatment of mild to moderate hypertension, alone or in conjunction with other antihypertensive drugs.

Contraindications

Known hypersensitivity to verapamil hydrochloride or to any other ingredient of the preparation.
Heart failure with reduced ejection fraction of less than 35%, and/or pulmonary wedge pressure above 20 mm Hg (unless secondary to a supraventricular tachycardia amenable to verapamil therapy).
Severe left ventricular dysfunction (see Warnings).
Hypotension (less than 90 mm Hg systolic pressure) or cardiogenic shock.
Sick sinus syndrome (except in patients with a functioning artificial ventricular pacemaker).
Second- or third-degree AV block (except in patients with a functioning artificial ventricular pacemaker).
Patients with atrial flutter or atrial fibrillation in the presence of an accessory bypass tract (e.g. Wolff-Parkinson-White, Lown-Ganong-Levine syndromes). These patients are at risk to develop ventricular tachyarrhythmia including ventricular fibrillation if verapamil hydrochloride is administered (See Warnings).

Warnings

Acute Myocardial infarction
Use with caution in acute myocardial infarction complicated by bradycardia, marked hypotension, or left ventricular dysfunction.

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 severe left ventricular dysfunction 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, if possible, be controlled with optimum doses of digitalis and/or diuretics before verapamil treatment (see Drug Interactions).

Heart failure patients with ejection fraction higher than 35% should be compensated before starting verapamil treatment and should be adequately treated throughout.

Hypotension

Occasionally, the pharmacological action of verapamil may produce a decrease in blood pressure below normal levels which may result in dizziness or symptomatic hypotension. Hypotensive is usually asymptomatic, orthostatic, mild and can be controlled by a decrease in the Ikacor dose.

HMG-CoA Reductase Inhibitors ("Statins")

See Drug Interactions.

Elevated Liver Enzymes

Occasional elevations of transaminases and alkaline phosphatases have been reported. Patients receiving verapamil should have liver enzymes monitored periodically. Use verapamil with caution in patients with severe hepatic impairment.

Atrial Flutter/Fibrillation with Accessory Bypass Tract

Patients with atrial flutter or fibrillation and an accessory AV pathway (e.g. Wolff-Parkinson-White or Lown-Ganong-Levine syndromes) may develop increased antegrade conduction across the aberrant pathway bypassing the AV node, producing a very rapid ventricular response after receiving intravenous verapamil (or digitalis). 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. Treatment is usually direct current cardioversion. Cardioversion has been used safely and effectively after oral verapamil.

Heart Block/ 1st Degree AV block/Bradycardia/Asystole

Verapamil hydrochloride affects the AV and SA nodes and prolongs AV conduction time. Use with caution as development of second-or third-degree AV block (contraindication) or unifascicular, bifascicular or trifascicular bundle branch block requires discontinuation in subsequent doses of verapamil hydrochloride and institution of appropriate therapy, if needed.

Verapamil hydrochloride affects the AV and SA nodes and rarely may produce second- or third degree AV block, bradycardia, and, in extreme cases, asystole. This is more likely to occur in patients with a sick sinus syndrome (SA nodal disease), which is more common in older patients.

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 Adverse Reactions.

Patients with Hypertrophic Cardiomyopathy (IHSS)

In a total of 120 patients referred to the National Institute of Health (USA) because of hypertrophic cardiomyopathy (most of them refractory or intolerant to propranolol) a variety of serious adverse effects were observed following therapy with verapamil at doses up to 720 mg/day. 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 (over 20 mm Hg) capillary 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 have to be discontinued.

Antiarrhythmics, Beta-blockers

Mutual potentiation of cardiovascular effects (higher-grade AV block, higher-grade lowering of heart rate, induction of heart failure and potentiated hypotension). Asymptomatic bradycardia (36 beats/minute) with a wandering atrial pacemaker has been observed in a patient receiving concomitant timolol (a beta-adrenergic blocker) eye drops and oral verapamil hydrochloride.

Digoxin

If verapamil is administered concomitantly with digoxin, reduce digoxin dosage. See Drug Interactions

Other Neuromuscular transmission disorders

Verapamil should be used with caution in patients with diseases in which neuromuscular transmission is affected (myasthenia gravis, Lambert-Eaton syndrome, advanced Duchenne muscular dystrophy).

Use in Pregnancy

There are no adequate and well-controlled studies in pregnant women. Verapamil crosses the placenta and has been measured in umbilical cord blood. This drug should be used during pregnancy only if clearly needed.

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

Use in Breastfeeding

Verapamil is excreted in human milk. Limited human data from oral administration has shown that the infant relative dose of verapamil is low (0.1 –1%of the mother's oral dose) and that verapamil use may be compatible with breastfeeding. Due to the potential for serious adverse reactions in nursing infants, verapamil should only be used during lactation if it is essential for the welfare of the mother.

<u>Special Populations</u>

Renal impairment

Although impaired renal function has been shown in robust comparator studies to have no effect on verapamil pharmacokinetics in patients with end-stage renal failure, several case reports suggest that verapamil should be used cautiously and with close monitoring in patients with impaired renal function.

Verapamil cannot be removed by hemodialysis.

Liver impairment
Use with caution in patients with severely impaired liver function (see Dosage)

Preclinical safety data
Reproduction studies have been performed in rabbits and rats at oral verapamil 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. 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.
There are, however, no adequate and well-controlled studies in pregnant women.

Adverse Reactions

The following adverse reactions have been reported with verapamil from clinical studies, postmarketing surveillance or Phase IV clinical trials and are listed below by system organ class. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

The most commonly reported ADRs were headache, dizziness, gastrointestinal disorders: nausea, constipation and abdominal pain, as well as bradycardia, tachycardia, palpitations, hypotension, flushing, edema peripheral and fatigue.

Adverse reactions reported from clinical studies with verapamil and post-marketing surveillance activities

MedDRA System Organ Class	**Common**	**Uncommon**	**Rare**	**Unknown**
Immune system disorders				Hypersensitivity
Nervous system disorders	Dizziness, Headache		Paresthesia Tremor	Extrapyramidal disorder, paralysis (tetraparesis)[1], Seizures
Psychiatric disorders			Somnolence	
Ear and labyrinth disorders			Tinnitus	vertigo
Cardiac disorders	Bradycardia	Palpitations, Tachycardia		Atrioventricular block (1°, 2°, 3°), Cardiac failure, Sinus arrest, Sinus bradycardia; asystole
Vascular disorders	Flushing, Hypotension			

MedDRA System Organ Class	Common	Uncommon	Rare	Unknown
Respiratory, thoracic and mediastinal disorders				Bronchospasm
Gastrointestinal disorders	Constipation, Nausea	Abdominal pain	vomiting	Abdominal discomfort, Gingival hyperplasia, Ileus
Skin and subcutaneous tissue disorders			Hyperhidrosis	Angioedema, Stevens-Johnson syndrome, Erythema multiforme, Alopecia, Itching, Pruritus, Purpura, Rash maculopapular, Urticaria
Musculoskeletal and connective tissue disorders				Arthralgia, Muscular weakness, Myalgia
Reproductive system and breast disorders				Erectile dysfunction, Galactorrhea, Gynecomastia
General disorders and administration site conditions	Edema peripheral	Fatigue		
Investigations				Blood prolactin increased, Hepatic enzymes increased

[1] There has been a single postmarketing report of paralysis (tetraparesis) associated with the combined use of verapamil and colchicine. This may have been caused by colchicine crossing the blood-brain barrier due to CYP3A4 and P-gp inhibition by verapamil. See Drug Interactions

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions is an important way to gather more information to continuously monitor the benefit/risk balance of the medicinal product.

Precautions

Treatment of Acute Cardiovascular Adverse Reactions

The frequency of cardiovascular adverse reactions which require therapy is rare; hence, experience with their treatment is limited. Whenever severe hypotension or complete AV block occurs following oral administration of verapamil, the appropriate emergency measures should be applied immediately, e.g. intravenously administered isoproterenol HCl; levarterenol bitartrate, atropine (all in the usual doses), or calcium gluconate (10% solution). In patients with hypertrophic cardiomyopathy (IHSS), alpha-adrenergic agents (phenylephrine, metaraminol bitartrate or methoxamine) should be used to maintain blood pressure and isoproterenol and levarterenol should be avoided. If further support is necessary, inotropic agents (dopamine or dobutamine) may be administered. Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

Use in Patients with Impaired Hepatic Function

Since verapamil is highly metabolized by the liver, it should be administered cautiously to patients with impaired hepatic function. Severe liver dysfunction prolongs the elimination half-life of verapamil to about 14 to 16 hours; hence, approximately 30% of the dose given to patients with normal liver function should be administered to these patients. Careful monitoring for abnormal prolongation of the PR interval or other signs of excessive pharmacologic effects (see Overdosage) should be carried out.

Use in Patients with Impaired Renal Function

About 70% of an administered dose of verapamil is excreted as metabolites in the urine. Verapamil is not removed by hemodialysis. 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).

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.

Drug Interactions

In vitro metabolic studies indicate that verapamil hydrochloride is metabolized by cytochrome P450 CYP3A4, CYP1A2, CYP2C8, CYP2C9 and CYP2C18. Verapamil has been shown to be an inhibitor of CYP3A4 enzymes and P-glycoprotein (P-gp).

Clinically significant interactions have been reported with inhibitors of CYP3A4 causing elevation of plasma levels of verapamil hydrochloride while inducers of CYP3A4 have caused a lowering of plasma levels of verapamil hydrochloride, therefore, patients should be monitored for drug interactions.

Potential drug interactions

Verapamil/Prazosin/Terazosin (Alpha Blockers):

Prazosin: Increase of about 40% in Cmax with no effect on half-life.

Terazosin: Increase of about 24% in AUC and 25% in Cmax.

In both cases there is additive hypotensive effect.

Verapamil/Colchicine:
Colchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (Pgp). Verapamil is known to inhibit CYP3A and P-gp. When verapamil and colchicine are administered together, inhibition of P-gp and/or CYP3A by verapamil may lead to increased exposure to colchicine. Colchicine levels may rise , AUC (approximately 2 fold) as well as C_{max} (approximately 1.3 fold). Reduce colchicine dose.
Verapamil/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. Effect on flecainide plasma clearance is minimal; no effect on verapamil clearance.
Verapamil/Quinidine: Pulmonary edema may occur in patients with hypertrophic obstructive cardiomyopathy (IHSS). Elevation of quinidine plasma level may occur. In a small number of patients with IHSS, 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. Oral quinidine clearance decreases by about 35%.
Verapamil/Theophylline: Concomitant use of verapamil in patients receiving theophylline has resulted in decreased oral and systemic clearance of theophylline by about 20% , elevated serum theophylline concentrations, and a prolonged serum half-life of the bronchodilator.
In smokers, the reduction in theophylline clearance was lessened (about 11%). Patients receiving theophylline should be closely monitored for signs of theophylline toxicity when verapamil is administered concomitantly; serum theophylline levels should be monitored and dosage of the bronchodilator reduced if indicated.
Verapamil/Carbamazepine/Antiepileptics:((e.g. Phenytoin) Verapamil therapy may increase carbamazepine concentrations during combined therapy. This may produce carbamazepine side effects such as diplopia, headache, ataxia or dizziness
Carbamazepine AUC may increase by about 46% in refractory partial epilepsy patients. Verapamil plasma concentrations may be decreased upon combination with phenytoin.
Verapamil/Antidepressants: Imipramine AUC may increase by about 15%.There was no effect on the level of the active metabolite, desipramine.
Verapamil/Antidiabetics: Glibenclamide C_{max} increases by about 28%, and Glibenclamide AUC increases by about 26%.
Verapamil/Erythromycin: Verapamil levels may possibly rise.
Verapamil/Clarithromycin: Concomitant administration may lead to a possible rise in verapamil levels.
Verapamil/Rifampin: Therapy with rifampin may markedly reduce oral verapamil bioavailability by about 92%, verapamil AUC by about 97%, and verapamil C_{max} by about 94%.The blood pressure lowering effect may be reduced.
Verapamil/Telithromycin: Verapamil levels may possibly rise**.**
Verapamil/Doxorubicin: In patients with small cell lung cancer doxorubicin AUC rose by 104% and doxorubicin Cmax by 61% with oral verapamil administration. In patients with advanced neoplasma there was no significant change in doxorubicin PK with intravenous verapamil administration
Verapamil/Phenobarbital: Phenobarbital therapy may increase oral verapamil clearance by about 5 fold.
Verapamil/Buspirone: Buspirone AUC and C_{max} may increase by 3.4 fold.
Verapamil/Midazolam: Elevation of midazolam AUC by about 3 fold and its Cmax by about 2 fold.

Verapamil/Beta Blockers: Controlled studies in a small number of patients suggest that the concomitant use of Ikacor and oral beta- blocker agents may be beneficial in certain patients with chronic stable angina or hypertension but available information is not sufficient to predict with confidence the effects of concurrent treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities. Concomitant therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractibility. Induction of heart failure and potentiated hypotension may also occur.
Metoprolol AUC increased by about 32.5%, metoprolol Cmax increased by about 41% in angina patients.
Propranolol AUC increased by about 65% and propranolol Cmax increased by about 94% in angina patients.
Verapamil/Digoxin/Digitoxin: Clinical use of verapamil in digitalized patients has shown the combination to be well tolerated if digoxin doses are properly adjusted. Digoxin Cmax increases by about 44%, digoxin C_{12h} (about 53%) in healthy subjects, Css increases by about 44% and AUC increases by about 50%. In patients with hepatic cirrhosis the influence of verapamil on digoxin kinetics is magnified.
Digitoxin total body clearance and extrarenal clearance are reduced by about 27% and 29%, respectively.
Maintenance 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 digoxin should be reduced or the drug temporarily discontinued. Upon discontinuation of verapamil the patient should be monitored to avoid underdigitalization.
Verapamil/Cimetidine: Possible elevation of verapamil hydrochloride plasma levels AUC of R-verapamil increases by about 25%, that of the S-verapamil by about 40% with corresponding decrease in R-and S-verapamil clearance.
Verapamil/Immunologics/Immunosuppressives:

Verapamil/Cyclosporine: Verapamil therapy may increase serum levels of cyclosporine (AUC, C_{ss}, C_{max} by ~45%).

Verapamil/Sirolimus/Tacrolimus/Everolimus: Possible increase in sirolimus, tacrolimus, or everolimus levels.

Everolimus: AUC increase (about 3.5 fold), C_{max} (about 2.3 fold); verapamil: C_{trough} increases by about 2.3 fold). Concentration determinations and dose adjustments of everolimus may be necessary.

Sirolimus: increased sirolimus AUC (about 2.2 fold); S-verapamil AUC increases by about 1.5 fold). Concentration determinations and dose adjustments of sirolimus may be necessary.

Tacrolimus: possible increase in tacrolimus levels.

Verapamil/Lipid Lowering Agents (HMG Co-A Reductase Inhibitors, i.e. "Statins", e.g., Atorvastatin, Lovastatin, Simvastatin): Concomitant use of these agents with verapamil hydrochloride may increase the serum levels of atorvastatin (as well as increase in AUC of verapamil by about 43%), simvastatin or lovastatin. For simvastatin: a rise in AUC (about 2.6 fold), C_{max} (about 4.6 fold). Lovastatin levels may possibly rise; verapamil AUC may rise (63%), Cmax (32%)
Treatment with HMG CoA reductase inhibitors (e.g., simvastatin, atorvastatin, or lovastatin) in a patient taking verapamil should be started at the lowest possible dose and titrated upwards. If verapamil treatment is to be added to patients already taking an HMG CoA reductase inhibitor (e.g., simvastatin/atorvastatin/lovastatin), consider a reduction in the statin dose and retitrate against serum cholesterol concentrations. Fluvastatin, pravastatin and rosuvastatin are not metabolized by CYP3A4 and are less likely to interact with verapamil.

Verapamil/Almotriptan (Serotonin Receptor Agonist): There is an increase in almotriptan AUC by about 20%, and its Cmax about 24%.
Verapamil/Sulfinpyrazone (Uricosuric): Oral verapamil clearance increases by about 3 fold, with a decrease in of about 60% in its bioavailability. The blood pressure lowering effect may be reduced.
Verapamil/Grapefruit juice: Grapefruit juice may increase the plasma levels of verapamil hydrochloride (AUC for R-verapamil increases by about 49% and for S-verapamil by about 37% verapamil AUC. C_{max} for R-verapamil increases by about 75% and for the S-verapamil by about 51%. Elimination half-life and renal clearance not affected. Grapefruit juice should therefore not be ingested with verapamil
Verapamil/St.John's Wort: Verapamil AUC decreases: R-verapamil by about 78% and S-verapamil by about 80% with corresponding reductions in Cmax.

Other Drug Interactions and Additional Drug Interaction Information (see also Potential drug interactions.

Antiarrhythmics, beta-blockers
Mutual potentiation of cardiovascular effects (higher-grade AV block, higher-grade lowering of heart rate, induction of heart failure and potentiated hypotension).

HIV Antiviral Agents
Due to the metabolic inhibitory potential of some of the HIV antiviral agents, such as ritonavir, plasma concentrations of verapamil may increase. Caution should be used or dose of verapamil may be decreased.
***Verapamil Protein-Bound Drugs*:** As verapamil is highly bound to plasma proteins, it should be administered with caution to patients receiving other highly protein-bound drugs, such as oral anticoagulants.
Verapamil/Antihypertensive Agents: Verapamil administered concomitantly with oral antihypertensive agents (e.g., vasodilators, angiotensin-converting enzyme inhibitors, diuretics, beta blockers) will usually have an additive effect on lowering blood pressure. Patients receiving these combinations should be appropriately monitored.
Concomitant use of agents that attenuate α-adrenergic function with verapamil may result in a reduction in blood pressure, which may be excessive in some patients. Such an effect has been observed in one study following the concomitant administration of verapamil and prazosin.
Verapamil/Disopyramide: Until data on possible interactions between verapamil and disopyramide phosphate are obtained, disopyramide should not be administered within 48 hours before or 24 hours after verapamil administration.
Verapamil/Nitrates: Verapamil has been given concomitantly with short- and long-acting nitrates without any undesirable drug interactions. The pharmacologic profile of both drugs and the clinical experience suggest beneficial interactions.
Verapamil/Acetylsalicylic acid : Increased tendency to bleed
Verapamil/Ethanol (alcohol): Elevation of ethanol plasma levels
Verapami/ Lithium*:* Increased sensitivity to the effects of lithium (neurotoxicity) has been reported during concomitant verapamil hydrochloride-lithium therapy with either no change or an increase in serum lithium levels. The addition of verapamil hydrochloride, however, has also resulted in the lowering of the serum lithium levels in patients receiving chronic stable oral lithium. Patients receiving both drugs should be monitored carefully.
Verapamil/Inhalation Anesthetic Agents/ Neuromuscular Blocking Agents: Clinical data and animal studies suggest that verapamil may potentiate the activity of inhalation anesthetics and neuromuscular blocking agents (curare-like and depolarizing). It may be necessary to decrease the dose of verapamil hydrochloride and/or the dose of the neuromuscular blocking agent when the drugs are used concomitantly..

Effects on ability to drive and use machines

Due to its antihypertensive effect, depending on the individual response, verapamil hydrochloride may affect the ability to react to the point of impairing the ability to drive a vehicle, operate machinery or work under hazardous conditions. This applies all the more at the start of treatment, when the dose is raised, when switching from another drug and in conjunction with alcohol. Verapamil may increase the blood levels of alcohol and slow its elimination. Therefore, the effects of alcohol may be exaggerated.

Dosage and Administration

The dose of verapamil must be individualized by titration.

Ikacor should be administered with food.

Ikacor tablets should be taken whole. They should not be crushed, sucked, chewed, or divided.

Angina

120 mg, 3 times daily is recommended.

80 mg, 3 or 4 times daily may be satisfactory in some patients with angina of effort.

The total daily dosage ranges from 240 - 480 mg.

The optimum daily dosage for most patients ranges from 320 - 480 mg.

Dosage may be increased at daily (e.g., patients with unstable angina) or weekly intervals until optimum clinical response is obtained. In general, maximum effects of any given dosage would be apparent during the first 24 to 48 hours of therapy, but note that between 24 to 48 hours the half-life of verapamil increases, hence maximum response may be delayed.

Arrhythmia

40 -120 mg, 3 times daily according to the severity of the condition.

Hypertension

240 - 480 mg daily in divided doses.

Overdosage

Symptoms

Hypotension, bradycardia up to high degree AV block and sinus arrest, hyperglycemia, stupor, metabolic acidosis Fatalities have occurred as a result of overdose.

Treatment

Treatment of overdosage should be supportive.

Beta-adrenergic stimulation or parenteral administration of calcium solutions may increase calcium ion flux across the slow channel, and have been used effectively in treatment of deliberate overdosage with verapamil.

Verapamil cannot be removed by hemodialysis.

Clinically significant hypotensive reactions or high degree AV block should be treated with vasopressor agents or cardiac pacing, respectively. Asystole should be handled by the usual measures including beta adrenergic stimulation (e.g., isoproterenol hydrochloride), other vasopressor agents or cardiopulmonary resuscitation.

Storage
Store in a dark and dry place (under 25°C).

Registration Numbers
Ikacor 40 mg tablets : 025 25 2113 00.
Ikacor 80 mg tablets: 040 02 23155 00.
Ikacor 120 mg tablets: 039 47 21913 00.

Manufacturer
Teva Pharmaceutical Industries Ltd
P.O.B. 3190, Petach Tikva.