

1 NAME OF THE MEDICINE

Verapamil hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Verapamil hydrochloride is a calcium ion influx inhibitor (slow channel blocker or calcium ion antagonist).

Each ISOPTIN SR film-coated tablet contains 180 mg or 240 mg of verapamil hydrochloride as the active ingredient.

Each ISOPTIN (immediate release formulation) tablet contains 40 mg or 80 mg of verapamil hydrochloride as the active ingredient.

Excipients with known effect in ISOPTIN SR 180 mg and 240 mg tablets: Trace quantities of sulfites.

Excipients with known effect in ISOPTIN 40 mg and 80 mg tablets: None.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

ISOPTIN SR is available for oral administration as light green, oblong shaped, scored, film-coated tablets (score and 2 logos on one face and score on the other face) containing 240 mg verapamil hydrochloride and as old rose, oval shaped, scored, film-coated tablets ('KNOLL' on one face and 'SR'; score; '180' on the other face) containing 180 mg verapamil hydrochloride. The tablets are designed for sustained release of the drug in the gastrointestinal tract; sustained release characteristics are not altered when the tablet is divided in half.

ISOPTIN 40 mg tablets are available for oral administration as white, biconvex, film coated tablets, embossed "40" on one side and the Knoll triangle on the other side.

ISOPTIN 80 mg tablets are available for oral administration as white, biconvex, film coated tablets, embossed "ISOPTIN 80" on the front and "Knoll" above the score on the back.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ISOPTIN SR is indicated for the management of hypertension and angina pectoris.

ISOPTIN Tablets 40 mg or 80 mg (immediate release) are indicated for:

- Hypertension
- Angina of effort
- Angina at rest
- Vasospastic angina (including Prinzmetal's variant angina)
- Tachyarrhythmias including paroxysmal supra-ventricular tachycardia
- Atrial fibrillation with rapid ventricular response
- Atrial flutter with rapid ventricular response

4.2 DOSE AND METHOD OF ADMINISTRATION

ISOPTIN SR

Hypertension

The dose of ISOPTIN SR should be individualised by titration and the drug should be administered with food. The usual daily dose of sustained release verapamil, ISOPTIN SR, in clinical trials has been 240 mg given by mouth once daily in the morning. Some patients may respond to initial therapy of one 180 mg tablet once daily. However, initial doses of 120 mg (½ 240 mg tablet) a day may be warranted in patients who may have an increased response to verapamil (e.g. elderly, small people etc.). Upward titration should be based on therapeutic efficacy and safety evaluated approximately 24 hours after dosing. The antihypertensive effects of ISOPTIN SR are evident within the first week of therapy.

If adequate response is not obtained, the dose may be titrated upward in the following manner:

- a) 240 mg each morning plus 120 mg (½ 240 mg tablet) each evening or 180 mg each morning plus 180 mg each evening.
- b) 240 mg every twelve hours.

Angina Pectoris

The usual dose is one 240 mg tablet once daily. In patients with an increased response to verapamil, (e.g. elderly, people with low body weight) an initial dose of one 180 mg tablet may be more appropriate. Depending on individual response the dosage can be increased to a total of 480 mg daily, given in two divided doses. Such dose titration can be carried out using the 180 mg or 240 mg strengths of ISOPTIN SR.

ISOPTIN SR is for use only in adults as its safety and efficacy in children has not yet been established.

ISOPTIN Tablets (immediate release)

All immediate release tablets of ISOPTIN (40 mg and 80 mg) are to be swallowed whole. The tablets are not designed to be broken.

The individual dose, and frequency of dosing, should be determined in accordance with the indication and individual patient response.

The usual starting dose is one 80 mg tablet two or three times a day. The maintenance dose may be adjusted to 160 mg two or three times a day. Usual maintenance dose 160 mg twice daily.

Paediatric:

Dose range 40 to 360 mg per day in two or three divided daily doses according to age and response.

Geriatric/Renal Failure:

The recommended daily dosage is usually well tolerated.

Hepatic Failure:

Caution should be exercised when initiating therapy since the pharmacological action of ISOPTIN may be increased or prolonged by hepatic insufficiency.

When switching from immediate release ISOPTIN to ISOPTIN SR (see above) the total daily dose in milligrams may remain the same.

4.3 CONTRAINDICATIONS

Verapamil hydrochloride is contraindicated in:

- Severe left ventricular dysfunction (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).
- Hypotension (less than 90 mmHg systolic pressure) or cardiogenic shock.
- Sick sinus syndrome (except in patients with a functioning artificial pacemaker).
- Second- or third-degree AV block (except in patients with a functioning artificial pacemaker).
- Patients with atrial flutter or atrial fibrillation and an accessory bypass tract (e.g. Wolff-Parkinson-White, Lown-Ganong-Levine syndromes) (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). These patients are at risk to develop ventricular tachyarrhythmia including ventricular fibrillation if verapamil hydrochloride is administered.
- Heart failure with reduced ejection fraction of less than 35%, and/or pulmonary wedge pressure above 20 mmHg.
- Patients concomitantly administered ivabradine (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).
- Simultaneous initiation of treatment with dabigatran etexilate and oral verapamil (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).
- Treatment initiation with oral verapamil in patients following major orthopaedic surgery who are already treated with dabigatran etexilate (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).
- Patients with known hypersensitivity to verapamil hydrochloride or any of the inactive ingredients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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. In clinical experience with 4,954 patients, 87 (1.8%) developed congestive heart failure or pulmonary oedema. Verapamil should be avoided in patients with severe left ventricular dysfunction (e.g. ejection fraction less than 30%, pulmonary wedge pressure above 20 mmHg, or severe symptoms of cardiac failure) and in patients with any degree of ventricular dysfunction if they are receiving a beta-adrenergic blocker (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Patients with milder ventricular dysfunction should, if possible, be controlled with optimum doses of digitalis and/or diuretics before verapamil treatment (Note interactions with digoxin under Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Acute Myocardial Infarction

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

Hypotension

Occasionally, the pharmacologic action of verapamil may produce a decrease in blood pressure below normal levels which may result in dizziness or symptomatic hypotension. The incidence of hypotension observed in 4,954 patients enrolled in clinical trials was 2.5%. In hypertensive patients, decreases in blood pressure below normal are unusual. Tilt table testing (60 degrees) was not able to induce orthostatic hypotension.

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 in the face of continued verapamil treatment. Several cases of hepatocellular injury related to verapamil have been proven by rechallenge. Half of these had clinical symptoms (malaise, fever, and/or right upper quadrant pain) in addition to elevations of SGOT, SGPT and alkaline phosphatase. Periodic monitoring of liver function in patients receiving verapamil is therefore prudent.

Accessory Bypass Tract (Wolff-Parkinson-White or Lown-Ganong-Levine)

Some patients with paroxysmal and/or chronic atrial fibrillation or atrial flutter and a co-existing accessory AV pathway have developed increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation 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 (see Section 4.3 CONTRAINDICATIONS).

Treatment is usually DC-cardioversion. Cardioversion has been used safely and effectively after oral ISOPTIN.

Atrioventricular Block

Verapamil 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 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.

In studies using ISOPTIN SR, prolongation of PR interval values of 0.21 to 0.22 sec occurred in 59 of 3,670 patients (=1.6%) and to 0.23 to 0.28 sec in 4 patients whose PR intervals had been normal before treatment (0.1 to 0.2 sec). Second or third degree AV block was not observed. Higher degrees of AV block, however, were infrequently (0.8%) observed.

Patients with Hypertrophic Cardiomyopathy (IHSS)

In 120 patients with hypertrophic cardiomyopathy (most of them refractory or intolerant to propranolol) 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 oedema; all had severe left ventricular outflow obstruction and a past history of left ventricular dysfunction. Eight other patients had pulmonary oedema and/or severe hypotension; abnormally high (over 20 mmHg) capillary wedge pressure and a marked left ventricular outflow obstruction were present in most of these patients. Concomitant administration of quinidine (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS) preceded the severe hypotension in 3 of the 8 patients (2 of whom developed pulmonary oedema). 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.

Use in Patients with Impaired Neuromuscular Transmission

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

Interchangeability of ISOPTIN SR with other Sustained Release Verapamil Products

Other sustained release capsule formulations of verapamil should not be considered interchangeable with equivalent doses of ISOPTIN SR.

Use in Hepatic Impairment

Since verapamil is highly metabolised by the liver, it should be administered cautiously to patients with impaired hepatic function. Severe liver dysfunction prolongs the elimination half-life of immediate release 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 Section 4.9 OVERDOSE) should be carried out.

Use in Renal Impairment

About 70% of an administered dose of verapamil is excreted as metabolites in the urine. Although impaired renal function has been shown to have no effect on verapamil pharmacokinetics in patients with end-stage renal failure, verapamil should be used cautiously and with close monitoring in patients with impaired renal function. These patients should be carefully monitored for abnormal prolongation of the PR interval or other signs of overdosage (see Section 4.9 OVERDOSE). Verapamil is not removed by haemodialysis.

Use in the Elderly

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.2 PHARMACOKINETIC PROPERTIES.

Paediatric Use

ISOPTIN SR

ISOPTIN SR is for use only in adults as its safety and efficacy in children has not yet been established.

ISOPTIN Tablets (immediate release)

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

In vitro metabolic studies indicate that verapamil hydrochloride is metabolised 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 while inducers of CYP3A4 have caused a lowering of plasma levels of verapamil, therefore, patients should be monitored for drug interactions. Coadministration of verapamil and a drug primarily metabolised by CYP3A4 or being a P-gp substrate may be associated with elevations in drug concentrations that could increase or prolong both therapeutic and adverse effects of the concomitant drug.

Beta Blockers

Concomitant therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction, and/or cardiac contractility. The combination of sustained release verapamil and beta-adrenergic blocking agents has not been studied. However, there have been reports of excessive bradycardia and AV block, including complete heart block, when the combination has been used for the treatment of hypertension. For hypertensive patients, the risks of combined therapy may outweigh the potential benefits. The combination should be used only with caution and close monitoring.

Asymptomatic bradycardia (36 beats/min) with a wandering atrial pacemaker has been observed in a patient receiving concomitant timolol (a beta-adrenergic blocker) eye drops and oral verapamil.

Atenolol, metoprolol and propranolol plasma levels may be increased by concomitant administration of verapamil.

Ivabradine

Concomitant administration of verapamil and ivabradine is contraindicated. Ivabradine use in combination with verapamil is associated with increased plasma concentrations of ivabradine and additional heart rate lowering effects (see Section 4.3 CONTRAINDICATIONS).

Digitalis

Clinical use of verapamil in digitalised patients has shown the combination to be well tolerated if digoxin doses are properly adjusted. Chronic verapamil treatment can 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 extrarenal clearance of digitoxin by 27% and 29%, respectively. Maintenance digitalis doses should be reduced when verapamil is administered, and the patient should be carefully monitored to avoid over or underdigitalisation. Whenever overdigitalisation is suspected, the daily dose of digitalis should be reduced or temporarily discontinued. Upon discontinuation of ISOPTIN (verapamil HCl), the patient should be reassessed to avoid underdigitalisation. In clinical trials related to the control of ventricular response in digitalised patients who had atrial fibrillation or atrial flutter, ventricular rates below 50/min at rest occurred in 15% of patients and asymptomatic hypotension occurred in 5% of patients.

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 alpha-adrenergic function with verapamil may result in a reduction in blood pressure that is excessive in some patients. Such an effect was observed in one study following the concomitant administration of verapamil and prazosin.

Antiarrhythmic Agents

When combined with antiarrhythmic drugs (e.g. disopyramide, flecainide, mexiletine, amiodarone) additive (depressant) effects on myocardial contractility and AV conduction may occur.

In a small number of patients with hypertrophic cardiomyopathy (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.

The electrophysiological 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

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.

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

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.

Prazosin, Terazosin

Additive hypotensive effect.

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 the dose of verapamil may be decreased.

Carbamazepine

Verapamil therapy may increase carbamazepine concentrations during combined therapy. This may produce carbamazepine side effects such as diplopia, headache, ataxia, or dizziness.

Erythromycin, Clarithromycin and Telithromycin

Erythromycin, clarithromycin and telithromycin therapy may increase serum levels of verapamil.

Rifampicin

Blood pressure lowering effect may be reduced.

Phenobarbital (Phenobarbitone)

Phenobarbital (phenobarbitone) therapy may increase verapamil clearance.

Ciclosporin

Verapamil therapy may increase serum levels of ciclosporin.

Everolimus, Sirolimus and Tacrolimus

Verapamil therapy may increase serum levels of everolimus, sirolimus and tacrolimus.

Buspirone

Verapamil therapy may increase plasma levels of buspirone.

Midazolam

Verapamil therapy may increase plasma levels of midazolam.

Theophylline

Verapamil therapy may inhibit the clearance and increase the plasma levels of theophylline.

Phenytoin

Verapamil therapy may alter plasma levels of phenytoin.

Alcohol

Verapamil therapy may inhibit metabolism of alcohol increasing its CNS depressant effects.

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 antagonists, such as verapamil, should be titrated carefully to avoid excessive cardiovascular depression.

Neuromuscular Blocking Agents

Clinical data and animal studies suggest that verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarising). 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.

Grapefruit Juice

Grapefruit juice has been shown to increase the plasma levels of verapamil, and therefore grapefruit and its juice should not be taken with ISOPTIN.

HMG-CoA Reductase Inhibitors

Treatment with HMG CoA reductase inhibitors (e.g. simvastatin or atorvastatin) 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 or atorvastatin), consider a reduction in the statin dose and retitrate against serum cholesterol concentrations.

Verapamil hydrochloride may increase the serum levels of HMG CoA reductase inhibitors primarily metabolised by CYP3A enzymes (e.g., atorvastatin and simvastatin). An interaction in healthy subjects demonstrated a 43% increase in verapamil AUC in combination with atorvastatin. Consider using caution when these HMG CoA reductase inhibitors and verapamil are concomitantly administered.

Fluvastatin, pravastatin and rosuvastatin are not metabolized by CYP3A4 and are less likely to interact with verapamil.

Metformin

Co-administration of verapamil with metformin may reduce the efficacy of metformin.

Sulfinpyrazone

Blood pressure lowering effect may be reduced.

Aspirin

Increased tendency to bleed.

Dabigatran

Use of dabigatran with verapamil may increase the bioavailability of dabigatran.

Verapamil immediate release: ↑dabigatran (C_{max} up to 180% and AUC up to 150%)

Verapamil sustained release: ↑dabigatran (C_{max} up to 90% and AUC up to 70%)

When co-administered with oral verapamil, the dose of dabigatran may need to be reduced (refer to dabigatran Product Information for dabigatran dosing instructions) as the risk of bleeding may increase.

No meaningful interaction was observed when verapamil was given 2 hours after dabigatran etexilate (increase of C_{max} by about 10% and AUC by about 20%).

Close clinical surveillance is recommended when verapamil is combined with dabigatran etexilate and particularly in the occurrence of bleeding, notably in patients having mild to moderate renal impairment.

Simultaneous initiation of treatment with dabigatran etexilate and oral verapamil is contraindicated (see Section 4.3 CONTRAINDICATIONS).

Treatment initiation with oral verapamil in patients following major orthopaedic surgery who are already treated with dabigatran etexilate is contraindicated (see Section 4.3 CONTRAINDICATIONS).

Other Direct Oral Anticoagulants (DOACs)

Use of DOACs with verapamil may increase the absorption of DOACs since they are P-glycoprotein (P-gp) substrates. If applicable, coadministration with verapamil may also reduce elimination of DOACs which are metabolised by CYP3A4, and this may increase the systemic bioavailability of DOACs.

When co-administered with oral verapamil, the dose of DOAC may need to be reduced (refer to DOAC Product Information for DOAC dosing instructions) as the risk of bleeding may increase especially in patients with further risk factors.

Doxorubicin

Caution should be used when oral verapamil is administered in combination with doxorubicin due to the potential for increased doxorubicin levels.

Colchicine

Colchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (P-gp). 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. Combined use is not recommended.

Imipramine

Verapamil therapy may increase serum levels of imipramine.

Glibenclamide

Verapamil therapy may increase serum levels of glibenclamide.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Studies in female rats at daily dietary doses up to 5.5 times (55 mg/kg/day) the maximum recommended human dose did not show impaired fertility. Effects on male fertility have not been determined.

Use in Pregnancy

Pregnancy Category: C

Verapamil carries the potential to produce fetal hypoxia associated with maternal hypotension.

Reproduction studies have been performed in rabbits and rats at oral doses up to 180 mg/m²/day and 360 mg/m²/day (compared to a maximum recommended human oral daily dose of 317 mg/m²) and have revealed no evidence of teratogenicity. In the rat, however, a dose similar to the clinical dose (360 mg/m²) was embryocidal and retarded fetal growth and development. These effects occurred in the presence of maternal toxicity (reflected by reduced food consumption and weight gain of dams). This oral dose has also been shown to cause hypotension in rats. There are, however, no adequate and well controlled studies in pregnant women.

Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. ISOPTIN (verapamil HCl) crosses the placental barrier and can be detected in umbilical vein blood at delivery.

Labour and Delivery

Verapamil crosses the placental barrier and can be detected in umbilical vein blood at delivery. It is not known whether the use of verapamil during labour or delivery has immediate or delayed adverse effects on the foetus or whether it prolongs the duration of labour or increases the need for forceps delivery or other obstetric intervention. Such adverse experiences have not been reported in the literature, despite a long history of use

of ISOPTIN in Europe in the treatment of cardiac side effects of beta-adrenergic agonist agents used to treat premature labour.

Use in Lactation

Verapamil is excreted in human milk. Limited human data from oral administration have shown that the estimated infant dose is low (0.01 – 1% of the mother's oral dose). Due to the potential for serious adverse reaction in nursing infants, ISOPTIN should only be used during lactation if it is essential for the welfare of the mother.

4.7 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.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

ISOPTIN is usually well tolerated.

Serious adverse reactions are uncommon when ISOPTIN therapy is initiated with upward dose titration within the recommended single and total daily dose. See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE for discussion of heart failure, hypotension, elevated liver enzymes, AV block and rapid ventricular response.

ISOPTIN SR

In 11 clinical trials with ISOPTIN SR including a phase IV multicentre trial, on a total of 4,538 patients, the following side effects occurred at rates of 1% or more which appeared to be drug-related:

Constipation	4.1%	Headaches	1.2%
Dizziness	2.6%	Nausea	1.2%
Flush	1.2%	Tiredness	1.0%

The following side effects occurred at rates of 0.25 to 0.99%:

Cardiovascular

Bradycardia, palpitations, oedema, orthostasis, abrupt BP fall.

Digestive System

Gastric complaints/discomfort.

Skin

Itching, urticaria, exanthema.

The following reactions, the majority at rates of 1% or less, occurred under ISOPTIN administration in general (all formulations) and most of them 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, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope.

Digestive System

Diarrhoea, dry mouth, gastrointestinal distress, abdominal discomfort/pain, gingival hyperplasia.

Haemic and Lymphatic

Ecchymosis or bruising.

Nervous System

Cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence.

Skin

Arthralgia and rash, exanthema, hair loss, hyperkeratosis, maculae, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme.

Special Senses

Blurred vision.

Ear and Labyrinth Disorders

Vertigo, tinnitus.

Urogenital

Gynaecomastia, impotence, increased urination, spotty menstruation.

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 occur following oral administration of verapamil, the appropriate emergency measures should be applied immediately, e.g. intravenously administered isoprenolol, noradrenaline (norepinephrine), atropine (all in the usual doses), or calcium gluconate monohydrate (10% solution). In patients with hypertrophic cardiomyopathy (IHSS), alpha-adrenergic agents (phenylephrine, metaraminol bitartrate or methoxamine) should be used to maintain blood pressure, and isoprenolol and noradrenaline (norepinephrine) 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 and the clinical situation and the judgement and experience of the treating physician.

ISOPTIN Tablets (immediate release)

The following reactions to orally administered verapamil occurred at rates greater than 1.0% or occurred at lower rates but appeared clearly drug related in clinical trials in 4,954 patients.

Constipation	7.3%	Fatigue	1.7%
Dizziness	3.3%	Dyspnea	1.4%
Nausea	2.7%	Bradycardia (HR < 50/min)	1.4%
Hypotension	2.5%	AV Block - total 10, 20, 30	1.2%
Headache	2.2%	20 and 30	0.8%
Oedema	1.9%	Rash	1.2%
CHF, Pulmonary Oedema	1.8%	Flushing	0.6%

Elevated Liver Enzymes (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

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

Adverse Effects from Post-Marketing Surveillance:

There has been a single post-marketing 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 CYP3A and P-gp inhibition by verapamil. Combined use of verapamil and colchicine is not recommended.

Other adverse effects reported from post-marketing surveillance include myalgia, vomiting, tachycardia, ileus, galactorrhea, increased blood prolactin extrapyramidal syndrome, hyperkalaemia, dyspnoea and renal failure.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms

Bradycardia, cardiac arrest, second and third degree AV block, hypotension, myocardial insufficiency and acute respiratory distress syndrome.

ISOPTIN SR: Symptoms and signs of overdose may be delayed due to the controlled release properties of these products, so patients should be kept under observation for at least 24 hours.

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 haemodialysis. Clinically significant hypotensive reactions or fixed high degree AV block should be treated with vasopressor agents or cardiac pacing, respectively. Asystole should be handled by the usual measures including cardiopulmonary resuscitation.

In poisoning with large quantities of the sustained release preparation one should bear in mind that the active drug substance may be released into and absorbed by the intestine over a period exceeding 48 hours after ingestion. Dependent upon the time of intake, agglomerates of puffed tablet residues are to be anticipated along the whole length of the G.I. tract, acting as depots.

Thus, in suspected ISOPTIN SR poisoning intensive measures for complete elimination of the drug are indicated: induced vomiting, endoscope-monitored aspiration of G.I. contents, purgation, high enemas.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

ISOPTIN 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

Hypertension

ISOPTIN exerts antihypertensive effects by decreasing systemic vascular resistance, usually without orthostatic decreases in blood pressure or reflex tachycardia; bradycardia (rate less than 50 beats/min) is uncommon (1.4%). During isometric or dynamic exercise ISOPTIN does not alter systolic cardiac function in patients with normal ventricular function.

Angina Pectoris

ISOPTIN (verapamil HCl) dilates the main coronary arteries and coronary arterioles, both in normal and ischaemic regions, and is a potent inhibitor of coronary artery spasm, whether spontaneous or ergonovine-induced. This property increases myocardial oxygen delivery in patients with coronary artery spasm, and is responsible for the effectiveness of ISOPTIN in vasospastic (Prinzmetal's or variant) as well as unstable angina at rest. Whether this effect plays any role in classical effort angina is not clear, but studies of exercise tolerance have not shown an increase in the maximum exercise rate-pressure product, a widely accepted measure of oxygen utilisation. This suggests that, in general, relief of spasm or dilation of coronary arteries is not an important factor in classical angina.

ISOPTIN regularly reduces the total systemic resistance (afterload) against which the heart works both at rest and at a given level of exercise by dilating peripheral arterioles.

ISOPTIN does not alter total serum calcium levels. However, one report suggested that calcium levels above the normal range may alter the therapeutic effect of ISOPTIN.

Other Pharmacological Actions of ISOPTIN Include The Following

Electrical activity through the AV node depends, to a significant degree, upon calcium influx through the slow channel. By decreasing the influx of calcium, ISOPTIN prolongs the effective refractory period within the AV node and slows AV conduction in a rate-related manner. Normal sinus rhythm is usually not affected, but in patients with sick sinus syndrome, ISOPTIN may interfere with sinus node impulse generation and may induce sinus arrest or sinoatrial block. Atrioventricular block can occur in patients without pre-existing conduction defects (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

ISOPTIN does not alter the normal atrial action potential or intraventricular conduction time, but depresses amplitude, velocity of depolarisation and conduction in depressed atrial fibres. ISOPTIN 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 co-existing accessory AV pathway following administration of verapamil (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

ISOPTIN has a local anaesthetic action that is 1.6 times that of procaine on an equimolar basis. It is not known whether this action is important at the doses used in humans.

Clinical Trials

See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).

5.2 PHARMACOKINETIC PROPERTIES

With the immediate release formulation, more than 90% of the orally administered dose of ISOPTIN is absorbed. Because of rapid biotransformation of verapamil 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 ISOPTIN every 6 hours resulted in plasma levels of verapamil ranging from 125 to 400 ng/mL with higher values reported occasionally. A nonlinear correlation between the verapamil dose administered and verapamil plasma levels does exist.

In early dose titration with verapamil a relationship exists between verapamil plasma concentrations and the prolongation of the PR interval. However, during chronic administration this relationship may disappear. The mean elimination half-life in single dose studies ranged from 2.8 to 7.4 hours. In these same studies, after repetitive dosing 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 may affect the pharmacokinetics of verapamil. Elimination half-life may be prolonged in the elderly.

In multiple dose studies under fasting conditions the bioavailability measured by AUC of ISOPTIN SR was similar to ISOPTIN immediate release; rates of absorption were, of course, different. In a randomised, single dose, crossover study using healthy volunteers, administration of 240 mg ISOPTIN SR with food produced peak plasma verapamil concentrations of 63 ng/mL, time to peak plasma verapamil concentration of about 12 hours, and AUC (0-∞) of 1,300 ng-hr/mL. When ISOPTIN SR was administered to fasting subjects, peak plasma verapamil concentration was 92 ng/mL, time to peak plasma verapamil concentration was about 7 hours, and AUC (0-∞) was 1,270 ng-hr/mL. Similar results were demonstrated for plasma norverapamil. Good correlation of dose and response is not available but controlled studies of ISOPTIN SR have shown effectiveness of doses similar to the effective doses of ISOPTIN (immediate release) in hypertensive patients. Plasma verapamil levels are not directly related to antihypertensive efficacy at the dosages usually administered (240 to 480 mg/day).

In healthy subjects, orally administered ISOPTIN undergoes extensive metabolism in the liver. Twelve metabolites have been identified in plasma. 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. Approximately 70% of an administered dose is excreted as metabolites in the urine and 16% or more in the faeces 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 of immediate release verapamil is delayed and elimination half-life prolonged up to 14 to 16 hours (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE); the volume of distribution is increased and plasma clearance reduced to about 30% of normal. Verapamil clearance values suggest that patients with liver dysfunction may attain therapeutic verapamil plasma concentrations with one-third of the oral daily dose required for patients with normal liver function.

Impaired renal function has no effect on verapamil hydrochloride pharmacokinetics in patients with end-stage renal failure and subjects with healthy kidneys.

After four weeks of oral dosing (120 mg q.i.d.), verapamil and norverapamil levels were noted in the cerebrospinal fluid. Estimated partition coefficient of 0.06 for verapamil and 0.04 for norverapamil.

Haemodynamics and Myocardial Metabolism

ISOPTIN reduces afterload and myocardial contractility. Improved left ventricular diastolic function in patients with hypertrophic cardiomyopathy (IHSS) and those with coronary heart disease has also been observed with ISOPTIN therapy. In most patients, including those with organic cardiac disease, the negative inotropic action of ISOPTIN is countered by reduction of afterload and cardiac index is usually not reduced. In patients with severe left ventricular dysfunction however, (eg pulmonary wedge pressure above 20 mmHg or ejection fraction lower than 30%), or in patients on beta-adrenergic blocking agents or other cardiodepressant drugs, deterioration of ventricular function may occur (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Pulmonary Function

ISOPTIN does not induce broncho-constriction and hence, does not impair ventilatory function.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Verapamil was not mutagenic in the Ames test in 5 test strains at 3 mg per plate, with or without metabolic activation.

Carcinogenicity

An 18-month toxicity study in rats, at a low multiple (6 fold) of the maximum recommended human dose, and not the maximum tolerated dose, did not suggest a tumorigenic potential. There was no evidence of a carcinogenic potential of verapamil administered in the diet of rats for two years at doses of 10, 35 and 120 mg/kg/day or approximately 1x, 3.5x and 12x, respectively, the maximum recommended human daily dose (480 mg/day or 9.6 mg/kg/day).

Animal Pharmacology and/or Animal Toxicology

In chronic animal toxicology studies verapamil caused lenticular and/or suture line changes at 30 mg/kg/day or greater and frank cataracts at 62.5 mg/kg/day or greater in the beagle dog but not the rat.

Development of cataracts due to verapamil has not been reported in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

ISOPTIN SR

ISOPTIN SR 180mg: Glycol/butylene glycol montanate, hypromellose, iron oxide red, macrogol 400, macrogol 6000, magnesium stearate, microcrystalline cellulose, povidone, purified talc, sodium alginate and titanium dioxide.

ISOPTIN SR 240mg: Glycol/butylene glycol montanate, hypromellose, indigo carmine, macrogol 400, macrogol 6000, magnesium stearate, povidone, powdered cellulose, purified talc, purified water, quinoline yellow, sodium alginate and titanium dioxide.

ISOPTIN (immediate release)

The excipients are: Calcium hydrogen phosphate dihydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, colloidal anhydrous silica, hypromellose, purified talc, sodium lauryl sulfate, macrogol 6000 and titanium dioxide.

6.2 INCOMPATIBILITIES

Refer to Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

ISOPTIN SR

Sustained release tablets, 180 mg – 7*, 15*, 30 tablets in PVC/PVDC/Al blister packs

Sustained release tablets, 240 mg – 7*, 15*, 30 tablets in PVC/PVDC/Al blister packs

*Not currently marketed

ISOPTIN (immediate release)

Tablets, 40 mg – 10*, 100* tablets in PVC/Al blister packs

Tablets, 80 mg – 10*, 100 tablets in PVC/Al blister packs or PVC/PVDC blister packs

*Not currently marketed

Australian Register of Therapeutic Goods (ARTG)

AUST R 54032 – ISOPTIN 180 SR 180mg verapamil hydrochloride tablet blister pack

AUST R 12801 – ISOPTIN SR 240mg verapamil hydrochloride tablet blister pack

AUST R 65502 – ISOPTIN verapamil hydrochloride 40mg tablet blister pack

AUST R 65503 – ISOPTIN verapamil hydrochloride 80mg tablet blister pack

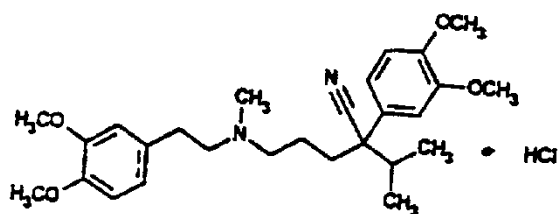
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Verapamil hydrochloride is present as a racemic mixture and different activities reside in the two enantiomers. Verapamil HCl is an almost white, crystalline powder, practically free of odour, with a bitter taste. It is soluble in water, sparingly soluble in alcohol, and practically insoluble in ether. Verapamil HCl is not chemically related to other cardioactive drugs.

Chemical Structure



CAS Number

152-11-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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8/10/1991

10 DATE OF REVISION

03/05/2022

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes
2	Update S1 declaration

ISOPTIN® is a Viatrix company trade mark

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