NEW ZEALAND DATA SHEET

ISOPTIN® AND ISOPTIN SR®

1. Product Name

ISOPTIN SR 120 mg and 240 mg sustained release tablets.

ISOPTIN 40 mg and 80 mg tablets.

2. Qualitative and Quantitative Composition

Each ISOPTIN SR tablet contains 120 mg or 240 mg of verapamil hydrochloride.

Each ISOPTIN tablet contains 40 mg or 80 mg of verapamil hydrochloride.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

ISOPTIN SR 240 mg sustained release tablets are light green, capsule shaped, scored and film coated with dimensions 6.5 x 18.5mm. The tablet is embossed with a double Knoll triangle on one side.

ISOPTIN SR 120 mg sustained release tablets are white, biconvex and film coated with dimensions 5mm x 10mm. The tablet is embossed with “120 SR” on one side and “KNOLL” on the other side.

ISOPTIN 40 mg tablets are white, film coated, marked “40” on one side and with “Knoll-triangle” on reverse side and have a diameter of about 7mm.

ISOPTIN 80 mg tablets are white, film coated, marked with “ISOPTIN 80” on one side and “Knoll” on reverse side above the score and have a diameter of about 9mm.

ISOPTIN SR 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.

ISOPTION 40 mg and 80 mg tablets cannot be divided into equal doses.

4. Clinical Particulars

4.1 Therapeutic indications

ISOPTIN SR

- Essential hypertension
- Secondary prevention post myocardial infarction - for secondary prevention after acute myocardial infarction, especially where β blocking agents are not tolerated such as in patients with asthma, diabetes, peripheral vascular disease with intermittent claudication, etc.
- Angina pectoris - for the prophylaxis and treatment of coronary insufficiency: chronic stable angina pectoris; angina at rest including vasospastic (Prinzmetal’s, variant angina) and

unstable angina (crescendo, pre-infarction angina); angina pectoris post myocardial infarction.

ISOPTIN 40 mg or 80 mg (immediate release)

- Essential hypertension
- Secondary prevention post myocardial infarction - long-term treatment after myocardial infarction.
- Angina pectoris - as for ISOPTIN SR
- Tachycardias, such as paroxysmal supraventricular tachycardia, atrial fibrillation with rapid ventricular response (except in WPW syndrome, see section 4.4), atrial flutter with rapid conduction, extrasystoles
- In patients with chronic atrial fibrillation for the medicamentous induction and maintenance of the sinus rhythm in combination with quinidine, as well as for the prophylaxis of relapses after electrocardioversion.

4.2 Dose and method of administration

Dose

ISOPTIN SR

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

The doses of ISOPTIN SR as prescribed by the physician are to be taken regularly, preferably with or shortly after meals with some liquid.

Children

ISOPTIN SR is not intended for use in children.

Adults

Hypertension

One tablet ISOPTIN SR 240 mg daily. For elderly patients and patients new to verapamil therapy, doctors should consider an initial daily dose of ISOPTIN SR 120 mg.

Maximum dose: one tablet ISOPTIN SR 240 mg twice daily (any single dose should not exceed 240 mg).

Secondary prevention of myocardial infarction

Data from studies available suggest that treatment with ISOPTIN SR can be initiated from 7 days post myocardial infarction.

Generally, doses will be 240 mg – 480 mg ISOPTIN SR daily in 1-2 divided doses. The average daily dose is 360 mg. It is advised that any single dose should not exceed 240 mg.

Angina pectoris

Generally, doses will be 120 – 480 mg ISOPTIN SR daily in 1-2 divided doses. The average daily dose is 360 mg. It is advised that any single dose should not exceed 240 mg.

ISOPTIN 40 mg, 80 mg (immediate release tablets)

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

Generally, doses will be:

Adults: Dose range 240 – 480 mg daily in 2 or 3 divided doses

Children: Dose range 40 – 360 mg daily in 2 or 3 divided doses

It is advised that any single dose should not exceed 160 mg in adults and 120 mg in children.

The doses of ISOPTIN prescribed by the physician are to be taken regularly preferably with or shortly after meals together with some liquid.

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).
- 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). 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 (unless secondary to a supraventricular tachycardia amenable to verapamil therapy).
- Patients concomitantly administered ivabradine (see section 4.5).
- Patients with known hypersensitivity to verapamil hydrochloride or any of the inactive ingredients (see section 6.1).

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).

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).

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

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 re-challenge. 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).

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 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. 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 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) 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 hepatic function

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)

should be carried out.

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.

Use in patients with impaired renal function

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). Verapamil is not removed by haemodialysis.

Digoxin

If verapamil is administered concomitantly with digoxin, reduce digoxin dosage (see section 4.5)

Digitoxin

Verapamil therapy may decrease digitoxin clearance.

4.5 Interaction with other medicines and other forms of interaction

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 hydrochloride while inducers of CYP3A4 have caused a lowering of plasma levels of verapamil hydrochloride, therefore, patients should be monitored for drug interactions. Coadministration of verapamil and a drug primarily metabolized 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.

Antiarrhythmics, 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.

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

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).

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.

Other

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 hydrochloride-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

Phenobarbital 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

Phenytoin may decrease verapamil plasma levels.

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 hydrochloride may potentiate the activity of neuromuscular blocking agents (curare-like and depolarising). 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.

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, 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 or lovastatin), consider a reduction in statin dose and retitrate against serum cholesterol concentrations.

Verapamil hydrochloride may increase the serum levels of HMG CoA reductase inhibitors primarily metabolized by CYP3A enzymes (e.g. atorvastatin and simvastatin). Similarly, verapamil AUC may increase by approximately 42.8% 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.

Sulfinpyrazone

Blood pressure lowering effect may be reduced.

Aspirin

Increased tendency to bleed.

Anticoagulants

Use of dabigatran with verapamil may increase dabigatran plasma concentrations. 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%).

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

Verapamil therapy increases absorption of other direct oral anticoagulants (DOACs) and may also reduce elimination leading to increased systemic bioavailability of DOACs. The dose of DOACs with verapamil may need to be reduced as risk of bleeding may increase.

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 colchicines 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.

Almotriptan

Verapamil therapy may increase serum levels of almotriptan.

St John's Wort

St John's Wort may decrease serum levels of verapamil.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category C

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

There are no adequate and well-controlled study data in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed (see section 5.3).

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.

Lactation

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

Verapamil hydrochloride and its metabolites are 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 ISOPTIN use may be compatible with breastfeeding. A risk to the newborns / infants cannot be excluded. Due to the potential for serious adverse reactions in nursing infants, ISOPTIN should only be used during lactation if it is essential for the welfare of the mother.

Fertility

No data available. For pre-clinical fertility data refer to section 5.3.

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 even 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 Undesirable effects

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, oedema peripheral and fatigue.

Table 1: 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
Metabolism and nutrition disorders				Hyperkalaemia
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			
Respiratory, thoracic and mediastinal disorders				Bronchospasm Dyspnoea
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
Renal and urinary disorders				Renal failure
Reproductive system and breast disorders				Erectile dysfunction, Galactorrhea, Gynecomastia
General disorders and administration site conditions	Oedema 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 section 4.5).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Symptoms

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

Treatment

Treatment of verapamil hydrochloride overdose should be mainly supportive and individualized. Beta-adrenergic stimulation and/or parenteral administration of calcium injection (calcium chloride) solutions may increase calcium ion flux across the slow channel, and have been used effectively in treatment of deliberate overdosage with oral verapamil hydrochloride. 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.

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. Due to the potential for delayed absorption of the sustained release product, patients may require observation and hospitalization for up to 48 hours.

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, intestinal lavage, purgation, high enemas.

Verapamil cannot be removed by haemodialysis.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: selective calcium channel blocker with direct cardiac effects, phenylalkylamine derivatives. ATC code: C08DA01.

Mechanism of action and pharmacodynamic effects

Verapamil inhibits the calcium ion (and possibly sodium ion) influx through slow channels into conductile and contractile myocardial cells and vascular smooth muscle cells. The antiarrhythmic effect of verapamil appears to be due to its effect on the slow channel in cells of the cardiac conductile system. Electrical activity through the sinoatrial (SA) and atrioventricular (AV) nodes depends, to a significant degree, upon calcium influx through the slow channel. By inhibiting this influx, verapamil slows AV conduction and prolongs the effective refractory period within the AV node in a rate-related manner. This effect results in a reduction of the ventricular rate in patients with atrial flutter and/or atrial fibrillation and a rapid ventricular response. By interrupting reentry at the AV node, verapamil

can restore normal sinus rhythm in patients with paroxysmal supraventricular tachycardias (PSVT), including Wolff-Parkinson-White (W-P-W) syndrome. Verapamil has no effect on conduction across accessory bypass tracts.

Clinical efficacy and safety

Verapamil does not alter the normal atrial action potential or intraventricular conduction time, but depresses amplitude, velocity of depolarization and conduction in depressed atrial fibers.

In the isolated rabbit heart, concentrations of verapamil that markedly affect SA nodal fibers or fibers in the upper and middle regions of the AV node have very little effect on fibers in the lower AV node (NH region) and no effect on atrial action potentials or His bundle fibers.

Verapamil does not include peripheral arterial spasm nor does it alter total serum calcium levels.

Verapamil reduces afterload and myocardial contractility. In most patients, including those with organic cardiac disease, the negative inotropic action of verapamil is countered by reduction of afterload and cardiac index is usually not reduced, but in patients with moderately severe to severe cardiac dysfunction (pulmonary wedge pressure above 20 mm Hg, ejection fraction less than 30%), acute worsening of heart failure may be seen. Peak therapeutic effects occur within three to five minutes after a bolus injection of verapamil.

The commonly used intravenous doses of 5 to 10 mg verapamil hydrochloride produce transient, usually asymptomatic, reduction in normal systemic arterial pressure, systemic vascular resistance and contractility; left ventricular filling pressure is slightly increased.

5.2 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 IR verapamil is 23% and that of SR verapamil approximately 32%, 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 IR administration, and four to five hours after SR administration. The peak plasma concentration of norverapamil is attained approximately one and five hours after IR or SR administration, respectively. 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%.

Biotransformation

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 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).

Linearity/non-linearity

A nonlinear correlation between the verapamil dose administered and verapamil plasma levels does exist.

Pharmacokinetic/pharmacodynamic relationship

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 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.

Special populations

Paediatric

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.

Elderly

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.

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.

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 haemodialysis.

5.3 Preclinical safety data

Reproduction studies have been performed in rabbits and rats at oral verapamil doses up to 180 mg/m^2/day and 360 mg/m^2/day (compared to a maximum recommended human oral daily dose of 300 mg/m^2) and have revealed no evidence of teratogenicity. In the rat, however, a dose similar to the clinical dose (360 mg/m^2) was embryocidal and retarded foetal 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.

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 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 120 mg & 240 mg also contains:

- Microcrystalline cellulose
- Sodium alginate
- Povidone
- Magnesium stearate
- Hypromellose
- Macrogol 400
- Macrogol 6000
- Purified talc
- Titanium dioxide
- Glycol montanite

In addition, ISOPTIN SR 240 mg also contains:

- Quinoline yellow (CI47005)
- Indigo carmine (CI 73015)

ISOPTIN 40 mg, 80 mg (immediate release)

- Calcium hydrogen phosphate
- Microcrystalline cellulose
- Croscarmellose sodium
- Magnesium stearate
- Colloidal silica dioxide
- Hypromellose
- Purified talc
- Sodium lauryl sulfate
- Macrogol 6000
- Titanium dioxide

ISOPTIN AND ISOPTIN SR are lactose, gluten and sugar free.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

ISOPTIN 40 mg & ISOPTIN 80 mg

3 years.

ISOPTIN SR 120 mg

3 years.

ISOPTIN SR 240 mg

3 years for products manufactured by Famar SA.

4 years for products manufactured by AbbVie Deutschland GmbH & Co. KG

6.4 Special precautions for storage

Store at or below 25°C

6.5 Nature and contents of container

ISOPTIN SR 120 mg – blister pack of 100 tablets.

ISOPTIN SR 240 mg – blister pack of 7 or 30 tablets.

ISOPTIN 40 mg and 80 mg – blister pack of 10 or 100 tablets.

Not all strengths, pack types and sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Mylan New Zealand
PO Box 11183
Ellerslie
AUCKLAND
Telephone 09-579-2792

9. Date of First Approval

ISOPTIN	13 May 1999
ISOPTIN SR	28 Feb 1986

10. Date of Revision of the Text

18 February 2020

Sections	
5.3	Additional preclinical safety data