AUSTRALIAN PRODUCT INFORMATION

ISOPTIN®

(verapamil hydrochloride) injection solution

1 NAME OF THE MEDICINE

Verapamil hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2 mL ampoule contains 5 mg of verapamil hydrochloride (equivalent to 4.6 mg of verapamil).

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

3 PHARMACEUTICAL FORM

Verapamil hydrochloride injection is a sterile, nonpyrogenic, clear colourless solution. The solution contains no bacteriostat or antimicrobial agent and is intended for single-dose intravenous administration.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

- Tachycardias, such as paroxysmal supraventricular tachycardia, atrial fibrillation with rapid ventricular response, (except in WPW syndrome, see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**)**, atrial flutter with rapid conduction, extrasystoles.
- For the prophylaxis and/or therapy of ectopic arrhythmias (predominantly ventricular extrasystoles).
- in halothane anaesthesia and in the application of adrenaline (epinephrine) in halothane anaesthesia, respectively.
- Acute hypertension.
- Acute coronary insufficiency.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults

5 mg slowly intravenously, in tachycardias and hypertensive crises repeated, if necessary, after 5 to 10 minutes. Drip infusion to maintain the therapeutic effect: 5-10 mg/hour in physiological saline, glucose, laevulose or similar solutions, on average up to a total dose of 100 mg/day.

Elderly

The dose should be administered over at least three minutes to minimise the risk of adverse effects (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Children

Newborn		0.75-1 mg (= 0.3-0.4 mL)
Infants		0.75-2 mg (= 0.3-0.8 mL)
Children	(aged 1-5 years)	2-3 mg (= 0.8-1.2 mL)

(aged 6-14 years)	2.5-5 mg (= 1-2 mL)

ISOPTIN should be given intravenously, depending on age and action. The injection should be made slowly under electrocardiographic control and only until onset of the effect. Intravenous infusion in hypertensive crises; initially 0.05-0.1 mg/kg/hour; if the effect proves to be insufficient, the dose is increased at 30-60 minute intervals until twice the dose or more is reached. Average total dose up to 1.5 mg/kg/day.

Method of Administration

For intravenous use only.

The medicine should be inspected visually for particulate matter and discolouration prior to administration. Any unused solution should be discarded immediately. Verapamil will precipitate in any solution with a pH above 6.0 (see Section 6.2 INCOMPATIBILITIES).

Do not dilute with Sodium Lactate Injection in polyvinyl chloride bags. For stability reasons, this product is not recommended for dilution with Sodium Lactate Injection USP in polyvinyl chloride bags.

Administering intravenous verapamil with albumin, amphotericin B, hydralazine HCl, and trimethoprim with sulfamethoxazole should be avoided.

4.3 CONTRAINDICATIONS

- Cardiogenic shock (except for arrhythmia induced shock), complicated acute myocardial infarction (bradycardia, hypotension, left ventricular failure), second- and third-degree AV block, sick sinus syndrome (bradycardia-tachycardia syndrome), manifest heart failure.

- In the presence of first-degree AV block, sinus bradycardia and hypotension the use of ISOPTIN should be given critical consideration. In acute coronary insufficiency intravenous administration is only admissible with careful indication and continuous monitoring of the patient. Where heart failure is present, full compensation with cardiac glycosides must be achieved before the administration of ISOPTIN.

- Patients with atrial flutter or atrial fibrillation and 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 is administered.

- Patients with ventricular tachycardia. Administration of intravenous verapamil to patients with wide-complex ventricular tachycardia (QRS > 0.12 sec) can result in marked haemodynamic deterioration and ventricular fibrillation. Proper diagnosis and differentiation from wide-complex supraventricular tachycardia is imperative in the emergency room setting.

- Severe hypotension.

- ISOPTIN injection should not be administered intravenously to patients on beta-blockers (except in an intensive care setting).

- In patients with diminished hepatic function (parenchymal loss/reduced blood supply) the effect of ISOPTIN is intensified and prolonged depending on the severity of the disease due to impaired drug metabolism. In these cases, dosage should be adjusted with special care.

- Concomitant administration of verapamil and ivabradine is contraindicated (See Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

- Known hypersensitivity to verapamil hydrochloride or any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Verapamil should be given as a slow intravenous injection over at least 2 minutes under continuous ECG and blood pressure monitoring (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Intravenous injection should only be given by the physician.

In atrial fibrillation and simultaneous WPW syndrome there is a risk of inducing ventricular fibrillation.

Some patients treated with verapamil responded with life-threatening adverse responses including rapid ventricular rate (in atrial flutter/fibrillation in the presence of an accessary bypass tract), marked hypotension or extreme bradycardia/asystole.

Hypotension

Severe hypotension has occasionally occurred following intravenous administration of the drug. On rare occasions this has been followed by a loss of consciousness. If severe hypotension develops, verapamil should be promptly discontinued, and vasoconstrictor substances used.

In patients using antihypertensive drugs, the additional hypotensive effect should be taken into consideration.

Acute Myocardial Infarction

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

Ventricular Fibrillation

Intravenous administration may precipitate ventricular fibrillation. Patients with atrial flutter/fibrillation and an accessory AV pathway may develop increased antegrade conduction across the aberrant pathway bypassing the AV node, producing a very rapid ventricular response after receiving intravenous verapamil. Its use in these patients is contraindicated (see Section 4.3 CONTRAINDICATIONS).

Bradycardia/Asystole

ISOPTIN slows conduction across the AV node 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). Asystole in patients other than those with sick sinus syndrome is usually of short duration (a 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 Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS), Treatment of Acute Cardiovascular Side Effects).

Heart Failure

Because of the drug's negative inotropic effect, verapamil should not be used in patients with poorly compensated congestive heart failure, unless the failure is complicated by or caused by an arrhythmia. If verapamil is used in such patients, they must be digitalized prior to treatment. Continuous monitoring is mandatory when intravenous verapamil is used in digitalized patients. It has been reported that digoxin plasma levels may increase with chronic oral administration.

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).

Intravenous verapamil can precipitate respiratory muscle failure in patients with progressive muscular dystrophy and should, therefore, be used with caution.

Increased Intracranial Pressure

Intravenous verapamil has been seen to increase intracranial pressure in patients with supratentorial tumors at the time of anaesthesia induction. Caution should be taken and appropriate monitoring performed.

Sick Sinus Syndrome

Precaution should be taken when treating any supraventricular arrhythmia on an emergency basis as it may be caused by an undiagnosed Sick Sinus Syndrome (see Section 4.3 CONTRAINDICATIONS).

Heart Block

Development of second- or third-degree AV block or unifascicular, bifascicular or trifascicular bundle branch block requires reduction in subsequent doses or discontinuation of verapamil and institution of appropriate therapy, if needed (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS), Treatment of Acute Cardiovascular Side Effects).

Use in Hepatic Impairment

Verapamil should be used with caution in patients with hepatic impairment.

Use in Renal Impairment

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. Verapamil cannot be removed by haemodialysis.

These patients should be monitored carefully for abnormal prolongation of the PR interval or other signs of excessive pharmacological effects.

Use in the Elderly

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Paediatric Use

There have been rare cases of severe haemodynamic events – some fatal – after intravenous administration of verapamil to neonates and infants. Intravenous verapamil should not be administered to this group of patients unless it is absolutely necessary and there is no alternative.

Effects on Laboratory Tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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.

Almotriptan

Verapamil therapy may increase serum levels of almotriptan.

Antihypertensives, diuretics, vasodilators

Potentiation of the hypotensive effect.

Aspirin

Increased tendency to bleed.

Beta Blockers

During the simultaneous administration of ISOPTIN and drugs with cardiodepressive action and/or inhibitory effect on AV conduction watch should be kept for additive effects. Above all ISOPTIN should not be administered intravenously without compelling reason if the patient is on β-adrenergic blockers.

The concomitant administration of intravenous beta blockers and intravenous verapamil has resulted in serious adverse reactions, especially in patients with severe cardiomyopathy, congestive heart failure or recent myocardial infarction. Intravenous beta-blockers should not be given to patients under treatment with verapamil (see Section 4.3 CONTRAINDICATIONS).

The additional hypotensive effect of ISOPTIN should be borne in mind particularly in patients on antihypertensive drugs.

Verapamil may increase the plasma concentrations of propranolol, atenolol and metoprolol which may lead to additive cardiovascular effects (e.g. AV block, bradycardia, hypotension, heart failure).

Buspirone

Verapamil therapy may increase plasma levels of buspirone.

Carbamazepine

Potentiation of carbamazepine effect, enhanced neurotoxicity.

Cardiac glycosides

Verapamil has been shown to increase the serum concentration of digoxin and digitoxin and caution should be exercised with regard to digitalis toxicity. The digitalis level should be determined and the glycoside dose reduced, if required.

Digitoxin

Reduction in total body clearance and extrarenal clearance of digitoxin.

Digoxin

Elevation of digoxin plasma levels because of diminished renal excretion. However, since both drugs slow AV conduction, patients should be monitored for AV block or excessive bradycardia.

Ciclosporin

Elevation of ciclosporin plasma levels.

Cimetidine

Cimetidine reduces verapamil clearance following intravenous verapamil administration.

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.

Dantrolene

Animal studies suggest that concomitant use of IV verapamil and IV dantrolene may result in cardiovascular collapse.

Disopyramide

Possible additive effects and impairment of left ventricular function. Pending further accumulation of data, disopyramide should be discontinued 48 hours prior to initiating verapamil therapy and should not be reinstituted until 24 hours after verapamil has been discontinued.

Doxorubicin

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

Ethanol (alcohol)

Delayed ethanol breakdown and elevation of ethanol plasma levels, resulting in enhancement of the alcoholic effect through verapamil.

Erythromycin, Clarithromycin and Telithromycin

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

Flecainide

Verapamil may slightly decrease the plasma clearance of flecainide whereas flecainide has no effect on the verapamil plasma clearance.

May result in an additive negative inotropic effect and prolongation of atrioventricular conduction and repolarisation.

Glibenclamide

Verapamil therapy may increase serum levels of glibenclamide.

Grapefruit Juice

Increase in verapamil serum level has been reported. Therefore, grapefruit and its juice should not be taken with verapamil.

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.

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 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 metabolised by CYP3A4 and are less likely to interact with verapamil.

Imipramine

Verapamil therapy may increase serum levels of imipramine.

Immunosuppressants

Verapamil therapy may increase serum levels of everolimus, sirolimus and tacrolimus. Concentration determinations and dose adjustments of everolimus and sirolimus may be necessary.

Inhalation Anaesthetics

Mutual potentiation of cardiovascular effects (higher-grade AV block, higher-grade lowering of heart rate, induction of heart failure, enhanced blood pressure lowering).

When used concomitantly, inhalation anaesthetics and calcium antagonists, such as verapamil injection, should each be titrated carefully to avoid excessive cardiovascular effects (e.g. AV block, bradycardia, hypotension, heart failure).

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).

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. The addition of verapamil, 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.

Metformin

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

Midazolam

Elevation of midazolam.

Muscle Relaxants

Possible potentiation by verapamil.

Neuromuscular Blocking Agents

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.

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.

Phenytoin, Phenobarbital

Lowering of the plasma level and attenuation of the effects of verapamil.

Prazosin, Terazosin

Additive hypotensive effect.

Protein Bound Drugs

As verapamil is highly protein bound, it should be administered with caution to patients receiving other highly protein bound drugs.

Quinidine

Elevation of quinidine plasma level.

Enhanced blood pressure lowering is possible. Caution should be exercised when administering intravenous verapamil to patients receiving oral quinidine due to the risk of hypotension. Pulmonary oedema may occur in patients with hypertrophic obstructive cardiomyopathy.

Rifampicin

Blood pressure lowering effect may be reduced.

St John's Wort

May decrease plasma levels of verapamil.

Sulfinpyrazone

Blood pressure lowering effect may be reduced.

Theophylline

Elevation of theophylline plasma levels.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

No data available.

Use in Pregnancy

Pregnancy category: C

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

Verapamil should not be administered intravenously during the first six months of pregnancy. There are no data on use in the first and second trimester. Verapamil should not be used in the final trimester unless the benefits clearly outweigh the risks.

Reproduction studies have been performed in rabbits and rats at oral doses up to 180 mg/m^2/day and 360 mg/m^2/day (compared to a maximum recommended human oral daily dose of 317 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 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 crosses the placental barrier and can be detected in umbilical vein blood at delivery.

Use in Lactation

Verapamil is excreted in human breast milk. There are currently no reports of verapamil injection or infusion use during breastfeeding. Due to the potential for serious adverse reactions in nursing infants, intravenous verapamil is not recommended during lactation.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

As with all drugs which inhibit AV conduction, ISOPTIN can produce first- or second-degree AV block; in extreme cases there may be complete block with or without subsequent asystole. Occasionally, heart failure may develop or existing heart failure may be exacerbated.

The risk of inducing ventricular fibrillation is minute, as ISOPTIN has no effect on the conduction velocity and refractory period in either atria or ventricles. By diminishing the peripheral resistance, the intravenous administration of ISOPTIN may lead to a slight and transient decrease of blood pressure even in normotensive patients. If the heart is no longer able to increase cardiac output for maintaining normal blood pressure, a critical blood pressure fall may occur. There are rare reports of symptoms such as palpitations and rapid heart beat (tachycardia) in patients receiving verapamil.

Elevation of the pacing and sensing threshold cannot be ruled out in pacemaker wearers on verapamil.

Bradycardia has been observed commonly.

Frequently, nausea (rarely, vomiting), bloating or constipation - in isolated cases to the point of ileus, abdominal discomfort and pain.

Occasionally, there may be headache, nervousness, dizziness or lightheadedness, fatigue, sensory disturbances such as tingling, numbness (paraesthesia, neuropathy), shakiness (tremor), and vertigo.

Flushing has been observed commonly.

Occasionally, allergic reactions such as erythema, pruritus, urticaria, maculopapular exanthema and erythromelalgia may occur. Rarely bronchospasm may occur.

Rarely – tinnitus. Peripheral oedema may occur as a result of local arteriole dilation.

Rarely, reversible elevation of liver enzymes has been observed, probably as a manifestation of allergic hepatitis.

Relevant lowering of glucose tolerance is rare.

There are rare reports of impotence.

Gynaecomastia has been observed very rarely in elderly patients on long term treatment. In the cases reported to date, the condition was reversible upon discontinuation of the drug. Elevated prolactin levels has been described, with isolated cases of milk (galactorrhoea).

Very rarely, there have been cases of purpura in the skin or mucous. There are isolated reports of photodermatitis.

Very rarely, muscular weakness or muscle and joint pain may occur.

There are isolated reports of angioneurotic oedema and Stevens-Johnson syndrome.

There may be isolated cases of gingival hyperplasia which is reversible when the drug is discontinued.

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 erythema multiforme, extrapyramidal syndrome, hyperkalaemia, dyspnoea, seizures, somnolence, hyperhidrosis and renal failure.

Investigations: A reversible impairment of liver function characterised by an increase of transaminase and/or alkaline phosphatase may occur on very rare occasions during verapamil treatment and is most probably a hypersensitivity reaction.

Cardiac disorders/vascular disorders: decreased myocardial contractility has been reported. On rare occasions, 2nd and 3rd block may occur and in extreme cases, this may lead to asystole. The asystole is usually of short duration and cardiac action returns spontaneously after a few seconds, usually in the form of sinus rhythm. If necessary, the procedures for the treatment of overdosage should be followed as described below. Flushing has been reported commonly.

Treatment of Acute Cardiovascular Side Effects

Cardiac Arrest

External cardiac massage, artificial respiration, ECG for differentiating between asystole and ventricular fibrillation; then appropriate intensive measures, such as defibrillation or pacemaker therapy, as required.

Second- or Third-Degree AV Block

Atropine, isoprenaline, if necessary, pacemaker therapy.

Development of Myocardial Insufficiency

Dopamine, dobutamine, cardiac glycosides or calcium.

Blood Pressure Fall

Proper positioning, dopamine, dobutamine, noradrenaline (norepinephrine).

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

Hypotension, bradycardia up to high-degree AV block and sinus arrest, hyperglycaemia, stupor, metabolic acidosis, acute respiratory distress syndrome, shock, loss of consciousness, first and second-degree AV block (frequently as Wenckebach's phenomenon with or without escape rhythms), total AV block with total AV dissociation, escape rhythm and asystole. Fatalities have occurred as a result of overdose.

Treatment

Treatment of overdosage should be supportive and individualised. Beta-adrenergic stimulation and/or parenteral administration of calcium injection (calcium chloride dihydrate) have been effectively used in treatment of deliberate overdosage with oral verapamil hydrochloride. Verapamil hydrochloride cannot be removed by haemodialysis. 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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia) or 0800 764 766 (New Zealand).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

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

Clinical Trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

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

Clinical Data

Verapamil has a pronounced antiarrhythmic action particularly in supraventricular cardiac arrhythmias. It prolongs impulse conduction in the AV node and thereby depending on the type of arrhythmia restores the sinus rhythm and/or normalises the ventricular rate.

The calcium antagonist verapamil reduces myocardial oxygen consumption directly by intervening in the energy consuming metabolic processes of the myocardial cell and indirectly by diminishing the peripheral resistance (afterload).

The decrease of the vascular smooth muscle tone moreover prevents coronary spasms and lowers raised blood pressure.

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

The injection contains sodium chloride (17 mg) and water for injections. It may contain hydrochloric acid for pH adjustment; pH is 4.5 to 6.0.

6.2 INCOMPATIBILITIES

ISOPTIN injection is incompatible with alkaline solutions.

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

Container type: Clear Type I glass ampoules

Pack size: 5 x 2 mL ampoules

Australian Register of Therapeutic Goods (ARTG)

AUST R 12796 – ISOPTIN verapamil hydrochloride 5mg/2mL injection ampoule

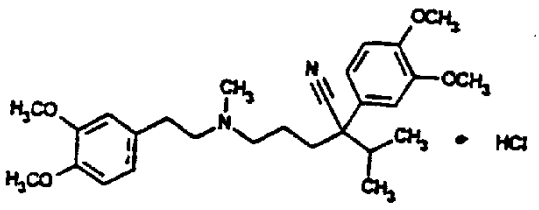
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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 a white or practically white crystalline powder. It is practically odourless and has a bitter taste. It is soluble in water, freely soluble in chloroform, sparingly soluble in alcohol and practically insoluble in ether.

Chemical Structure



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

Molecular weight: 491.07

Molecular formula: $C_{27}H_{38}N_2O_4 \bullet HCl$

CAS Number

152-11-4.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

8/10/1991

10 DATE OF REVISION

17/06/2025

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes.
8	Update to sponsor details

ISOPTIN® is a Viatris company trade mark

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