SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Isoptin 2.5mg/ml Solution for Injection or Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1ml of solution contains 2.5mg of Verapamil Hydrochloride.
Each ampoule contains 2ml of solution containing 5mg of verapamil hydrochloride.

Excipients with known effect: contains 17 mg of sodium under the sodium chloride form.

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Solution for injection or infusion.
A clear, colourless, sterile, aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Verapamil hydrochloride is indicated in adults, neonates, infants, children and adolescents for the treatment of tachycardias, such as paroxysmal supraventricular tachycardia, atrial fibrillation/flutter with tachyarrhythmia (except in WPW syndrome or LGL syndrome, see Section 4.3, Contra-indications), supraventricular extrasystoles, ventricular extrasystoles if due to myocardial ischaemia.
Severe angina not responsive to oral therapy.
Severe hypertension and hypertensive crisis.

4.2 Posology and method of administration

Adults:
The recommended intravenous doses of verapamil hydrochloride are as follows:
Initial dose: 5 mg initially, given slowly (over approximately 2 minutes), keeping the patient under constant observation and if possible under ECG and blood pressure monitoring.
Repeat dose: If the therapeutic effect is not achieved, a further 5 mg may be injected after 5 to 10 minutes. Drip infusion to maintain the therapeutic effect: 5-10 mg/hour in physiological saline, glucose, laevulose or similar solutions (pH≤ 6.5) on average up to a total dose of 100 mg/day.

Special Populations

Paediatric population
The safety and efficacy of verapamil hydrochloride injection have been established in neonates, infants, children and adolescents:

Newborn 0.75-1 mg (= 0.3-0.4 ml).
Infants 0.75-2 mg (= 0.3-0.8 ml).

If there are any signs of tachycardia-induced heart failure (energetic exhaustion of the myocardium), digitalisation is necessary before administering Isoptin intravenously.

Children aged 1-5 years, 2-3 mg (= 0.8-1.2 ml), aged 6-14 years, 2.5-5 mg (= 1-2 ml) of Isoptin. The injection should be given only until the onset of action.

Elderly patients:
The dose should be administered over at least 3 minutes to minimise the risk of untoward drug effects.

Intravenous infusion in hypertensive crisis:
Initial treatment with 0.05-0.1 mg/kg/hour and, if the effect proves to be insufficient, increase the dose 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.
Verapamil hydrochloride should be given as a slow intravenous injection over at least a two minute period of time under continuous electrocardiographic and blood pressure monitoring.
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
Verapamil hydrochloride is physically compatible and chemically stable for at least 24 hours at 25° C protected from light in most common large volume parenteral solutions. Use only if solution is clear and vial seal is intact.
Unused amount of solution should be discarded immediately following withdrawal of any portion of contents.
For stability reasons this product is not recommended for dilution with sodium lactate injection, USP in polyvinyl chloride bags.
Admixing intravenous verapamil hydrochloride with albumin, amphotericin B, hydralazine hydrochloride or trimethoprim and sulfamethoxazole should be avoided.
Verapamil hydrochloride will precipitate in any solution with a pH above 6.0.

Verapamil should not be taken with grapefruit juice (see Section 4.5, Interactions).

4.3 Contraindications

- Hypersensitivity to verapamil hydrochloride or to any of the inactive ingredients;
- Cardiogenic shock;
- Sick-sinus syndrome (bradycardia-tachycardia syndrome) (except in patients with a functioning artificial pacemaker);
- Second-or third-degree AV block (except in patients with a functioning artificial pacemaker;
- Heart failure with reduced ejection fraction of less than 35%, and/or pulmonary wedge pressure above 20 mm Hg (unless secondary to a supraventricular tachycardia amenable to verapamil therapy);
- Simultaneous intravenous administration of beta-adrenergic blockers;
- Atrial fibrillation/flutter in the presence of an accessory bypass tract (e.g., Wolff-Parkinson-White, Lown-Ganong-Levine syndromes). These patients are at risk to develop ventricular tachyarrhythmia including ventricular fibrillation if verapamil hydrochloride is administered.
- Use in pregnancy unless considered essential by the physician.
- Severe hypotension;
- Patients receiving intravenous beta-adrenergic blocking drugs (e.g., propranolol). Intravenous verapamil hydrochloride and intravenous beta-adrenergic blocking drugs, should not be administered in close proximity to each other (within a few hours), since both may have a depressant effect on myocardial contractility and AV conduction.
- Ventricular tachycardia: Administration of intravenous verapamil hydrochloride to patients with wide-complex ventricular tachycardia (QRS > 0.12 seconds) can result in marked hemodynamic deterioration and ventricular fibrillation. Proper pretherapy diagnosis and differentiation from wide-complex supraventricular tachycardia is imperative in the emergency room setting.

- Combination with ivabradine (see section Interactions with other medicinal products and other forms of interaction)

4.4 Special warnings and precautions for use

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

Heart Block/ 1st Degree AV block/Bradycardia/Asystole
Verapamil hydrochloride affects the AV and SA nodes and prolongs AV conduction time. Use with caution as development of second-or third-degree AV block (contraindication) or unifascicular, bifascicular or trifascicular bundle branch block requires discontinuation in subsequent doses of verapamil hydrochloride and institution of appropriate therapy, if needed.

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

Asystole in patients other than those with sick sinus syndrome is usually of short duration (few seconds or less), with spontaneous return to AV nodal or normal sinus rhythm. If this does not occur promptly, appropriate treatment should be initiated immediately. See Undesirable Effects Section.

Patients with heart failure or those who are susceptible to heart failure should be fully digitalised before verapamil therapy as it may aggravate or precipitate cardiac failure.

Great care should be taken in:

First degree AV block, bradycardia < 50 beats/min, hypotension < 90 mmHg systolic and ventricular tachycardias (QRS complex ≥ 0.12 sec).

If acute cardiovascular side effects arise, treat as for overdose (see Section 4.9, Overdose).

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

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

Hypotension
Intravenous verapamil hydrochloride often produces a decrease in blood pressure below baseline levels that is usually transient and asymptomatic but may result in dizziness.

HMG-CoA Reductase Inhibitors ("Statins") – *See Interaction with other medicinal products and other forms of interaction section*

Neuromuscular transmission disorders
Verapamil hydrochloride 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).
Respiratory standstill has been reported for one patient with progressive muscular dystrophy following administration of Isoptin.

Colchicine:
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. Combined use of verapamil and colchicine is not recommended. (see Section 4.5, Drug Interactions).

Digoxin
If verapamil is administered concomitantly with digoxin, reduce digoxin dosage. See Interactions with other medicinal drug products and other forms of interaction section.

Antiarrhythmics
Digitalis
Intravenous verapamil hydrochloride has been used concomitantly with digitalis preparations. Since both drugs slow AV conduction, patients should be monitored for AV block or excessive bradycardia.
Quinidine
Intravenous verapamil hydrochloride has been administered to a small number of patients receiving oral quinidine. A few cases of hypotension have been reported in patients taking oral quinidine who received intravenous verapamil hydrochloride. Caution should therefore be used when employing this combination of drugs.
Flecainide
A study in healthy volunteers showed that the concomitant administration of flecainide and verapamil hydrochloride may have additive effects reducing myocardial contractility, prolonging AV conduction and prolonging repolarization.
Disopyramide
Until data on possible interactions between verapamil hydrochloride and disopyramide are obtained, disopyramide should not be administered within 48 hours before or 24 hours after verapamil hydrochloride administration.
Beta-adrenergic blocking drugs
Intravenous verapamil hydrochloride has been administered to patients receiving oral beta-blockers. Since both drugs may depress myocardial contractility or AV conduction, the possibility of detrimental interactions should be considered. The concomitant administration of intravenous beta-blockers and intravenous verapamil hydrochloride has resulted in serious adverse reactions (see Contraindications), especially in patients with severe cardiomyopathy, congestive heart failure or recent myocardial infarction.

Other Special Populations
Renal impairment
Although impaired renal function has been shown in robust comparator studies to have no effect on verapamil pharmacokinetics in patients with endstage renal failure, several case reports suggest that verapamil should be used cautiously and with close monitoring in patients with impaired renal function.
Verapamil cannot be removed by hemodialysis.

Liver impairment
Use with caution in patients with severely impaired liver function (see also Posology section on liver impairment).

A small fraction of patients treated with verapamil hydrochloride respond with life-threatening adverse responses including rapid ventricular rate (in atrial flutter/fibrillation in the presence of an accessory bypass tract), marked hypotension or extreme bradycardia/asystole).

Sodium
This medicine contains less than 1 mmol sodium (23mg) per 2ml ampoule,
i.e. essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

In rare instances, including when patients with severe cardiomyopathy, congestive heart failure or recent myocardial infarction were given intravenous beta-adrenergic blocking agents or disopyramide concomitantly with intravenous verapamil hydrochloride, serious adverse effects have occurred.

Concomitant use of verapamil hydrochloride injection with agents that decrease adrenergic function may result in an exaggerated hypotensive response.

In vitro metabolic studies indicate that verapamil hydrochloride is metabolized by cytochrome P450 CYP3A4, CYP1A2, CYP2C8, CYP2C9 and CYP2C18. Verapamil has been shown to be an inhibitor of CYP3A4 enzymes and P-glycoprotein (P-gp). Clinically significant interactions have been reported with inhibitors of CYP3A4 causing elevation of plasma levels of verapamil hydrochloride while inducers of CYP3A4 have caused a lowering of plasma levels of verapamil hydrochloride, therefore, patients should be monitored for drug interactions. Coadministration of verapamil with a drug known to be primarily metabolized by CYP3A4 or known to be 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.

With the simultaneous administration of Isoptin and drugs with a cardiodepressive action and/or inhibitory effects on impulse generation or conduction, e.g. beta-receptor blockers, antiarrhythmics and inhalation anaesthetics, watch should be kept for possible additive effects (AV blockade, bradycardia, hypotension, heart failure).
Above all, Isoptin should not be administered intravenously if the patient is on beta-receptor blockers (except in intensive care).
The blood pressure lowering effect of Isoptin must be borne in mind in patients on antihypertensive drugs.

The following table provides a list of potential interactions with verapamil :
Potential Drug Interactions associated with Verapamil

Concomitant drug	**Potential effect on verapamil or concomitant drug**	**Comment**
Alpha blockers		
Prazosin	↑ prazosin Cmax (~40%) with no effect on half-life	Additive hypotensive effect.
Terazosin	↑ terazosin AUC (~24%) and Cmax (~25%)	
Antiarrhythmics		
Flecainide	Minimal effect on flecainide plasma clearance (<~10%); no effect on verapamil plasma clearance	See section 4.4
Quinidine	↓oral quinidine clearance (~35%)	Hypotension. Pulmonary edema may occur in patients with hypertrophic obstructive cardiomyopathy.
Antiasthmatics		
Theophylline	↓oral and systemic clearance by ~20%	Reduction of clearance was lessened in smokers (~11%)
Anticonvulsants/ Anti-epileptics		
Carbamazepine	↑ carbamazepine AUC (~46%) in refractory partial epilepsy patients	Increased carbamazepine levels. This may produce carbamazepine side effects such as diplopia, headache, ataxia or dizziness.

Phenytoin	↓ verapamil plasma concentrations	
Antidepressants		
Imipramine	↑ imipramine AUC (~15%)	No effect on level of active metabolite, desipramine
Antidiabetics		
Glyburide	↑ glyburide Cmax (~28%), AUC (~26%)	
Metformin	Co-administration of verapamil with metformin may reduce the efficacy of metformin.	
Anti-gout agents		
Colchicine	Possible ↑ colchicine levels ↑ colchicine AUC (~ 2.0fold) and Cmax (~1.3-fold)	Reduce colchicine dose (see colchicine label)
Anti-infectives		
Clarithromycin	Possible ↑ in verapamil levels	
Erythromycin	Possible ↑ in verapamil levels	
Rifampicin	↓ verapamil AUC (~97%), Cmax (~94%), oral bioavailability (~92%) with oral verapamil administration	Blood pressure lowering effect may be reduced.
Telithromycin	Possible ↑ in verapamil levels	
Antineoplastics		
Doxorubicin	↑ doxorubicin AUC (104%) and Cmax (61%) with oral verapamil administration	In patients with small cell lung cancer
	No significant change in doxorubicin PK with intravenous verapamil administration	In patients with advanced neoplasms
Barbiturates		
Phenobarbital	↑ oral verapamil clearance (~5-fold)	
Benzodiazepines and other anxiolytics		
Buspirone	↑ buspirone AUC, Cmax by ~3.4-fold	
Midazolam	↑ midazolam AUC (~3fold) and Cmax (~2-fold)	
Beta blockers		
Metoprolol	↑ metoprolol AUC (~32.5%) and Cmax (~41%) in angina patients	See Special warnings and precautions for use section
Propranolol	↑ propranolol AUC (~65%) and Cmax (~94%) in angina patients	
Cardiac glycosides		
Digitoxin	↓digitoxin total body clearance (~27%) and extrarenal clearance (~29%)	
Digoxin	Healthy subjects: ↑ Cmax (~44%) ↑ digoxin C12h (~53%) ↑ Css (~44%) and ↑ AUC (~50%)	Reduce digoxin dosage. Also see Special Warnings and Precautions for Use Section
H2 Receptor Antagonists		

Cimetidine	↑ AUC of R(~25%) and S(~40%) verapamil with corresponding ↓ in R-and Sverapamil clearance	Cimetidine reduces verapamil clearance following intravenous verapamil administration.
Immunologics/ Immuno-suppressives		
Ciclosporin	↑ ciclosporin AUC, Css, Cmax by ~45%	
Everolimus	Everolimus: ↑ AUC (~3.5fold) and ↑ Cmax (~2.3fold) Verapamil: ↑ Ctrough (~2.3-fold)	Concentration determinations and dose adjustments of everolimus may be necessary.
Sirolimus	Sirolimus ↑ AUC (~2.2-fold); Sverapamil ↑ AUC (~1.5-fold)	Concentration determinations and dose adjustments of sirolimus may be necessary.
Tacrolimus	Possible ↑ tacrolimus levels	
Lipid lowering agents (HMG COA reductase inhibitors)		
Atorvastatin	Possible ↑ atorvastatin levels Increase verapamil AUC (~43%)	Additional information follows
Lovastatin	Possible ↑ lovastatin levels ↑ verapamil AUC (~63%) and Cmax (~32%)	
Simvastatin	↑ simvastatin AUC (~2.6fold), Cmax(~4.6fold)	
Serotonin receptor agonists		
Almotriptan	↑ almotriptan AUC (~20%) ↑ Cmax (~24%)	
Uricosurics		
Sulfinpyrazone	↑ verapamil oral clearance (~3-fold) ↓ bioavailability (~60%)	Blood pressure lowering effect may be reduced.
	No change in PK with intravenous verapamil administration	
Anticoagulants		
Dabigatran	<u>*Verapamil immediate release*</u> ↑ dabigatran (C_{max} up to 180%) and AUC (up to 150%) <u>*Verapamil sustained release*</u> ↑ dabigatran (C_{max} up to 90%) and AUC (up to 70%)	The risk of bleeding may increase. The dose of dabigatran with oral verapamil may need to be reduced. (See dabigatran label for dosing instructions).
Other direct oral anticoagulants (DOACs)	Increased absorption of DOACs since they are P-gp substrates and, if applicable, also reduced elimination of DOACs which are metabolized by Cyp 3A4, may increase the systemic bioavailability of DOACs.	Some data suggest a possible increase of the risk of bleeding, especially in patients with further risk factors (see DOAC label for further information).
Other Cardiac therapy		
Ivabradine	Concomitant use with ivabradine is contraindicated due to the additional heart rate lowering effect of verapamil to ivabradine	See section Contraindications

Other		
Grapefruit juice	↑ R-(~49%) and S-(~37%) verapamil AUC ↑ R-(~75%) and S-(~51%) verapamil Cmax	Elimination half-life and renal clearance not affected. Grapefruit juice should therefore not be ingested with verapamil.
St. John's Wort	↓ R-(~78%) and S-(~80%) verapamil AUC with corresponding reductions in Cmax	

Other Drug Interactions and Additional Drug Interaction Information

HIV antiviral agents:
Due to the metabolic inhibitory potential of some of the HIV antiviral agents, such as ritonavir, plasma concentrations of verapamil may increase. Caution should be used or dose of verapamil may be decreased.

Lithium:
Increased sensitivity to the effects of lithium (neurotoxicity) has been reported during concomitant verapamil hydrochloride-lithium therapy with either no change or an increase in serum lithium levels. The addition of verapamil hydrochloride, however, has also resulted in the lowering of the serum lithium levels in patients receiving chronic stable oral lithium. Patients receiving both drugs should be monitored carefully.

Neuromuscular blocking agents:
Clinical data and animal studies suggest that verapamil hydrochloride may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing). It may be necessary to decrease the dose of verapamil hydrochloride and/or the dose of the neuromuscular blocking agent when the drugs are used concomitantly.

Aspirin**:** increased tendency to bleed

Ethanol (alcohol):
Elevation of ethanol plasma levels

HMG Co-A Reductase Inhibitors ("Statins"):
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 the statin dose and retitrate against serum cholesterol concentrations.
Fluvastatin, pravastatin and rosuvastatin are not metabolized by CYP3A4 and are less likely to interact with verapamil.

Antihypertensives, diuretics, vasodilators
Potentiation of the hypotensive effect

Protein-bound drugs:
As verapamil hydrochloride is highly bound to plasma proteins, it should be administered with caution to patients receiving other highly protein-bound drugs.

Inhalation anesthetics:
When used concomitantly, inhalation anesthetics and calcium antagonists, such as verapamil hydrochloride injection, should each be titrated carefully to avoid excessive cardiovascular depression.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of verapamil in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Because animal reproduction studies are not always predictive of human response, during pregnancy (especially in the first trimester), verapamil should only be used if considered essential by the physician.

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

Lactation

Verapamil hydrochloride/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 verapamil 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, verapamil 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 Undesirable effects

The following adverse events 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,
bradycardia,
tachycardia,
palpitations,
hypotension,
flushing,
oedema peripheral,

fatigue.

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

MedDRA System Organ Class	**Common**	**Uncommon**	**Rare**	**Unknown**
Immune system disorders				Hypersensitivity
Nervous system disorders	Dizziness, Headache		Paresthesia, Tremor	Extrapyramidal disorder, paralysis (tetraparesis)[1] , Seizures, convulsion, Somnolence
Metabolism and nutrition disorders				Hyperkalaemia
Psychiatric disorders			Somnolence	Nervousness
Ear and labyrinth disorders			Tinnitus	Vertigo
Cardiac disorders	Bradycardia	Palpitations, Tachycardia		Atrioventricular block (1°, 2°, 3°), Cardiac failure, Sinus arrest, Sinus bradycardia; Bradyarrhythmia, asystole
Vascular disorders	Flushing, Hypotension			Vasodilation, Erythromelalgia
Respiratory, thoracic and mediastinal disorders				Bronchospasm, Dyspnoea
Gastrointestinal disorders	Constipation, Nausea	Abdominal pain	Vomiting	Abdominal discomfort, Gingival hyperplasia, Ileus
Hepatobiliary disorders				Hepatitis
Skin and subcutaneous tissue disorders			Hyperhidrosis	Angioedema, Stevens-Johnson syndrome, Erythema multiforme, Alopecia, Itching, Pruritus, Purpura, Rash maculopapular, Urticaria, Rash, Erythema

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, Transaminases increased, Blood alkaline phosphatase 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 *Interactions with other medicinal products and other forms of interaction* section.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal.

4.9 Overdose

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

Treatment
The usual intensive care measures should be taken. Verapamil hydrochloride cannot be removed by haemodialysis.

The specific antidote is calcium, e.g. 10-20 ml in a 10% calcium gluconate solution administered intravenously (2.25-4.5 mmol), repeated if necessary or given as a continuous drip infusion (e.g. 5 mmol/hour). The following measures may also be necessary:
In the case of 2nd or 3rd degree AV block, sinus bradycardia, asystole: Atropine, isoprenaline, orciprenaline or pacemaker therapy. Asystole should be handled by the usual measures including beta adrenergic stimulation (e.g., isoproterenol hydrochloride).

In the case of hypotension: Dopamine, dobutamine, norepinephrine.

If there are any signs of continuing myocardial failure: Dopamine, dobutamine, if necessary repeated calcium injections, and possibly other medication that increases cardiac contractility combined with isoprenaline.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

ATC Code: C08DA01
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.

The chemical name of verapamil hydrochloride is benzeneacetonitrile, α-[3-[{2-(3, 4dimethoxyphenyl) ethyl} methylaminol] propyl]-3, 4-dimethoxy-α-(1-methylethyl) hydrochloride.

It has a molecular weight of 491.07 and the molecular formula is C27H38N204 • HCl.
Mechanism of action and Pharmacodynamic effects Verapamil inhibits the transmembrane influx of calcium ions into the heart and vascular smooth muscle cell. The myocardial oxygen demand is lowered directly as a result of the effect on the energy consuming metabolic processes of the myocardial cell and indirectly due to a reduction of the afterload.

Due to its effect on coronary vascular smooth muscle, Isoptin enhances myocardial blood flow, even in post-stenotic areas, and relieves coronary spasms.

These properties contribute to the anti-ischaemic and antianginal efficacy of Isoptin in all types of coronary artery disease.

Isoptin has a marked antiarrhythmic effect, particularly in supraventricular arrhythmias. It delays impulse conduction in the AV node. Owing to this, sinus rhythm is restored and/or ventricular rate is normalised, depending on the type of arrhythmia. Normally, the rate is either not affected or only minimally lowered.

The antihypertensive effect of Isoptin stems from a decrease in peripheral vascular resistance, without an increase in heart rate as a reflex response. As early as day 1 of treatment, blood pressure falls; the effect is found to persist also in long-term therapy.

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. Half-life values between 3 and 7 hours have been measured for the elimination of unchanged substance from the plasma after single intravenous and oral administration. Bioavailability is about two times higher with repeated administration. The presence of food has no effect on the bioavailability of verapamil.

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

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

In coronary heart disease and hypertension, no correlation was found between the therapeutic effect and the plasma concentration; a definite correlation with the plasma level was determined only for the effect on the PR interval.

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

Special Populations

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.

Geriatric:

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

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

Hepatic insufficiency:
The half-life of verapamil is prolonged in patients with impaired liver function owing to lower oral clearance and a higher volume of distribution.
Verapamil hydrochloride, administered intravenously, has been shown to be rapidly metabolized.

5.3 Preclinical Safety Data

Reproduction studies have been performed in rabbits and rats at oral verapamil doses up to 180 mg/m2/day and 360 mg/m2/day (compared to a maximum recommended human oral daily dose of 300 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 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.

The cardiovascular findings and the diffuse gingival hyperplasia seen in the chronic toxicity of verapamil hydrochloride are taken into account in Section 4.8 (Undesirable Effects).

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Sodium chloride
Hydrochloric acid 10% (as pH adjuster)
Water for Injections

6.2 Incompatibilities

Isoptin solution for injection is incompatible with alkaline solutions. In the absence of compatability studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Do not store above 30°C. Keep the ampoules in the outer carton in order to protect from light.

6.5 Nature and contents of container

2 ml ampoules of Ph. Eur. type I glass.
Each pack contains: 5 x 2 ml ampoules.

6.6 Special precautions for disposal and other handling of the product

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Viatris Healthcare Limited Damastown Industrial Park, Mulhuddart, Dublin 15, DUBLIN, Ireland

8. MARKETING AUTHORISATION NUMBER

MA1507/03201

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 31st October 2023

10. DATE OF REVISION OF THE TEXT