PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

ISOPTIN SR 240 mg sustained release (SR) tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sustained release tablet contains 240 mg of the active substance verapamil hydrochloride.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

Light green, oblong film-coated tablet with single score-line.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Angina pectoris, mild to moderate hypertension, supraventricular tachydysrhythmia. Prophylaxis of supraventricular relapses after electro-cardioversion.

4.2 Posology and method of administration

Posology

The dose of **ISOPTIN SR 240 mg** should adjusted individually in accordance with the severity of disease. Long-standing clinical experience shows that the average dose in all indications is between 240 mg and 360 mg. The daily dose should not exceed 480 mg on a long-term basis.

There is no limitation on the duration of use. **ISOPTIN SR 240 mg** should not be discontinued abruptly after long-term use. It is recommended to taper the dosage. In patients with impaired liver function, metabolism of the medicine is delayed to a greater or lesser extent depending on the severity of hepatic dysfunction, thus potentiating and prolonging the effects of verapamil hydrochloride.

Therefore, the dosage needs to be adjusted with special caution in patients with impaired liver function and low doses should be given initially. Tablets should be taken whole without sucking or chewing, with sufficient liquid, preferably with or shortly after meals.

Angina pectoris and supraventricular dysrhythmia: Half to one tablet every 12 hours.

Hypertension: One tablet per day (preferably in the morning).

If the desired response is not obtained in 7 days, the dose may be increased to one tablet in the morning, and half a tablet at night. The maximum recommended dose is one tablet every 12 hours.

4.3 Contraindications

ISOPTIN SR 240 mg is contraindicated in patients with:

- Hypersensitivity to the verapamil hydrochloride or to any of the inactive ingredients listed in section 6.1.
- Cardiogenic shock.
- Acute myocardial infarction with complications.
- Second- and third-degree atrioventricular (AV) block except in patients with a functioning artificial pacemaker.
- Second- and third-degree sinoatrial (SA) block, except for patients fitted with a pacemaker.
- Sick sinus syndrome, except in patients with a functioning artificial pacemaker.
- Congestive heart failure.
- Atrial fibrillation/flutter and concomitant presence of accessory pathways (e.g. Wolff-Parkinson-White or Lown-Ganong-Levine syndrome). In these patients, **ISOPTIN SR 240 mg** therapy poses an increased risk of ventricular tachycardia, including ventricular fibrillation.

- Concomitant administration of ivabradine (see section 4.5).

Beta receptor blockers should not be administered intravenously in conjunction with **ISOPTIN SR 240 mg** (except in intensive care medicine, see section 4.5).

4.4 Special warnings and precautions for use

Conduction disorder/first degree AV block/bradycardia/asystole:

ISOPTIN SR 240 mg affects AV and sinus nodes and delays AV conduction. **ISOPTIN SR 240 mg** should be used with caution, since second- or third-degree AV block (see section 4.3) or unifascicular, bifascicular or trifascicular bundle branch block warrants discontinuation of treatment and the initiation of appropriate therapy, if required. **ISOPTIN SR 240 mg** affects AV and sinus nodes and may lead to asymptomatic first-, second- or third-degree AV block and transient bradycardia, sometimes accompanied by nodal escape rhythms or asystole. This is more likely to occur in patients with sick sinus syndrome, which is more common in older patients. PR interval prolongation is correlated with verapamil plasma concentrations, especially during the early titration phases of therapy. In patients not suffering from sick sinus syndrome, asystole is normally of short duration (a few seconds or less), with a spontaneous return to AV node or normal sinus rhythm. If this does not occur immediately, appropriate treatment should be initiated without delay (see section 4.8). Marked first-degree block or progressive development to second- or third-degree AV block requires a reduction in dosage or, in rare instances, discontinuation of the medicine.

Anti-dysrhythmics, beta blockers and inhalation anaesthetics:

Anti-dysrhythmics (e.g. flecainide, disopyramide), beta receptor blockers (e.g. metoprolol, propranolol) and inhalation anaesthetics may mutually potentiate cardiovascular effects (severe AV block, severe drop in heart rate, onset of heart failure, marked hypotension) if administered concomitantly with **ISOPTIN SR 240 mg** (see section 4.5).

Asymptomatic bradycardia (36 beats per minute) with a migrating atrial pacemaker was observed in one patient using eye drops containing timolol (a beta blocker) and taking verapamil hydrochloride, as contained in **ISOPTIN SR 240 mg**, concomitantly.

Digoxin:

The digoxin dose should be reduced if taken concomitantly with verapamil hydrochloride, as contained in **ISOPTIN SR 240 mg** (see section 4.5).

Heart failure:

ISOPTIN SR 240 mg 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. Heart failure patients with an ejection fraction of over 35 % should be compensated before treatment begins. Adequate therapy should also be administered during treatment. **ISOPTIN SR 240 mg** should be avoided in patients with severe left ventricular dysfunction (e.g. ejection fraction less than 30 %, pulmonary wedge pressure above 20 mm Hg, or severe symptoms of heart failure) and in patients with any degree of ventricular dysfunction if they are receiving a beta-adrenergic blocker (see section 4.3). Patients with milder ventricular dysfunction should, if possible, be controlled with optimal doses of digitalis and/or diuretics before **ISOPTIN SR 240 mg** treatment.

HMG-CoA reductase inhibitors ("statins"):

See section 4.5.

Hypotension:

ISOPTIN SR 240 mg may occasionally produce symptomatic hypotension in normotensive patients. Particularly strict monitoring is required in the case of hypotension (less than 90 mm Hg systolic). In hypertensive patients, decreases in blood pressure below normal values are unusual.

Elevated liver enzymes:

Elevation of transaminases with and without concomitant elevations in alkaline phosphatase and bilirubin has been reported. Such elevations are normally transient and may disappear even in the

face of continued **ISOPTIN SR 240 mg** treatment.

Special populations

Use in patients with impaired renal function:

About 70 % of an administered dose of **ISOPTIN SR 240 mg** is excreted as metabolites in the urine. Although comparative studies have reliably shown that impaired renal function in patients presenting end-stage renal failure has no effect on the pharmacokinetic profile of **ISOPTIN SR 240 mg**, individual case reports suggest that caution should be exercised and strict monitoring implemented (abnormal prolongation of the PR interval, ECG, blood pressure, and other signs of overdosage) when administering **ISOPTIN SR 240 mg** to patients with renal impairment. **ISOPTIN SR 240 mg** is not removed by haemodialysis.

Use in patients with impaired hepatic function:

Since verapamil hydrochloride 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 **ISOPTIN SR 240 mg** to about 15 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 pharmacological effects should be carried out.

Accessory bypass tract (Wolff-Parkinson-White or Low-Ganong-Levine):

Some patients with paroxysmal and/or chronic atrial fibrillation or atrial flutter and a coexisting accessory AV pathway have developed an increased anterograde 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 hydrochloride, as contained in **ISOPTIN SR 240 mg** has not been established, such patients receiving oral **ISOPTIN SR 240 mg** may be at risk (see section 4.3).

Patients with hypertrophic cardiomyopathy (IHSS):

A variety of serious adverse effects can occur in patients with hypertrophic cardiomyopathy - pulmonary oedema and/or severe hypotension, sinus bradycardia, AV block and sinus arrest. Most adverse effects respond well to dose reduction.

Use in patients with attenuated neuromuscular transmission:

Caution should be exercised when prescribing **ISOPTIN SR 240 mg** for patients previously diagnosed with impaired neuromuscular transmission (Myasthenia gravis, Lambert-Eaton syndrome, progressive Duchenne muscular dystrophy). It has been reported that **ISOPTIN SR 240 mg** decreases neuromuscular transmission in patients with Duchenne's muscular dystrophy, and that **ISOPTIN SR 240 mg** prolongs recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease the dosage of **ISOPTIN SR 240 mg** when it is administered to patients with attenuated neuromuscular transmission.

Excipient warning

ISOPTIN SR 240 mg contains 34 mg sodium per sustained release tablet, equivalent to 1,70 % of the WHO recommended maximum daily intake of 2 g sodium, for an adult.

4.5 Interaction with other medicines and other forms of interaction

In vitro metabolic studies indicate that verapamil is metabolized by cytochrome P450 CYP3A4, CYP1A2, CYP2C8, CYP2C9 and CYP2C18. 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 medicine interactions.

Verapamil has been shown to be an inhibitor of CYP3A4 enzymes and P-glycoprotein (P-gp). Concomitant administration of verapamil and another medicine, mainly metabolised via CYP3A4 or representing a P-gp substrate, can increase the active substance concentration of the concomitant medicine, thus potentiating or prolonging the therapeutic effect and increasing the adverse events

associated with the concomitant medicine.

Potential pharmacokinetic interactions are highlighted in the following table:

Potential interactions		
Concomitant medicine	**Potential effect on ISOPTIN SR 240 mg or concomitant medicine**	**Comment**
Alpha blockers		
Prazosin	↑ prazosin C_{max} (~40 %) with no effect on half-life	Additive antihypertensive effect.
Terazosin	↑ terazosin AUC (~24 %) and C_{max} (25 %)	
Anti-dysrhythmics		
Flecainide	Minimal effect on flecainide plasma clearance (<~10 %); no effect on verapamil plasma clearance	Further information (see section 4.4 - Antidysrhythmics, beta receptor blockers and inhalation anaesthetics).
Quinidine	↓ oral quinidine clearance (~35 %)	Hypotension. Pulmonary oedema may occur in patients with hypertrophic obstructive cardiomyopathy.
Amiodarone	Increase in amiodarone plasma levels	
Antiasthmatics		
Theophylline	↓ oral and systemic CL by ~20 %	Reduction of CL was lessened in smokers (~11 %).

Potential interactions		
Concomitant medicine	**Potential effect on ISOPTIN SR 240 mg or concomitant medicine**	**Comment**
Anticonvulsants/Antiepileptics		
Carbamazepine	↑ carbamazepine AUC (~46 %) in refractory partial epilepsy patients	Increased carbamazepine levels. This may trigger adverse events such as diplopia, headaches, ataxia or dizziness/vertigo.
	Reduction in verapamil hydrochloride plasma levels	
Phenytoin	Verapamil plasma concentrations ↓	
Antidepressants		
Imipramine	↑ imipramine AUC (~15 %)	No effect on level of active metabolite, desipramine.
	Increased verapamil hydrochloride plasma levels	
Antidiabetics		
Glibenclamide	↑ glibenclamide C_{max} (~28 %), AUC (~26 %)	
	Increased verapamil hydrochloride plasma levels	
Gout treatments		
Colchicine	↑ of AUC (~ 2,0-fold) and C_{max}	Reduction in the dose of

Potential interactions		
Concomitant medicine	**Potential effect on ISOPTIN SR 240 mg or concomitant medicine**	**Comment**
	(~ 1,3-fold) of colchicine	colchicine (concomitant use of colchicine with verapamil hydrochloride is not recommended).
Anti-infectives		
Clarithromycin	Possible ↑ in verapamil levels	
Erythromycin	Possible ↑ in verapamil levels	
Rifampicin	With oral administration of verapamil ↓ in AUC (~97 %), C_{max} (~94 %) and oral bioavailability (~92 %) of verapamil	Potential reduction in anti-hypertensive effect.
	No change in the PK with intravenous administration of verapamil	
Telithromycin	Possible ↑ in verapamil levels	
Antineoplastics		
Doxorubicin	With oral administration of verapamil ↑ in AUC (104 %) and C_{max} (61 %) of doxorubicin	In patients with small-cell lung cancer.
	No significant changes in doxorubicin PK with intravenous verapamil administration	In patients with advanced tumours.

Potential interactions		
Concomitant medicine	**Potential effect on ISOPTIN SR 240 mg or concomitant medicine**	**Comment**
Azole fungistatics		
Clotrimazole	Increased verapamil hydrochloride plasma levels	
Ketoconazole	Increased verapamil hydrochloride plasma levels	
Itraconazole	Increased verapamil hydrochloride plasma levels	
Barbiturates		
Phenobarbital	↑ oral verapamil clearance (~5-fold)	
Benzodiazepines and other anxiolytics		
Buspirone	↑ buspirone AUC, C_{max} by ~3,4-fold	
	Increased verapamil hydrochloride plasma levels	
Midazolam	↑ midazolam AUC (~3-fold) and C_{max} (~2-fold)	
	Increased verapamil hydrochloride plasma levels	
Beta blockers		
Metoprolol	↑ metoprolol AUC (~32,5 %) and C_{max} (~41 %) in patients with angina pectoris	See section 4.4.
	Increased verapamil	

Potential interactions		
Concomitant medicine	**Potential effect on ISOPTIN SR 240 mg or concomitant medicine**	**Comment**
	hydrochloride plasma levels	
Propranolol	↑ propranolol AUC (~65 %) and C_{max} (~94 %) in patients with angina pectoris	See section 4.4.
	Increased verapamil hydrochloride plasma levels	
Cardiac glycosides		
Digitoxin	↓ digitoxin total clearance (~27 %) and extrarenal clearance (~29 %)	
Digoxin	In healthy subjects: C_{max} of digoxin ↑ (~44 %), C_{12h} of digoxin ↑ (~53 %), C_{ss} of digoxin ↑ (~44 %) and AUC of digoxin ↑ (~50 %)	Reduction in digoxin dose (see section 4.4.).
H_2 Receptor antagonists		
Cimetidine	↑ AUC of R- (~25 %) and S- (~40 %) verapamil with corresponding ↓ in R- and S-verapamil clearance	Cimetidine reduces verapamil clearance after intravenous administration of verapamil.
Immunological medicines/Immunosuppressants		
Cyclosporine	↑ cyclosporine AUC, C_{ss}, C_{max}	

Potential interactions		
Concomitant medicine	**Potential effect on ISOPTIN SR 240 mg or concomitant medicine**	**Comment**
	by ~45 %	
Everolimus	Everolimus-AUC ↑ (~3,5-fold), C_{max} ↑ (~2,3-fold), verapamil: C_{trough} ↑ (~2,3-fold)	Potential determination of concentration and dose adjustment of everolimus required.
Sirolimus	Sirolimus-AUC ↑ (~2,2-fold); S-verapamil-AUC ↑ (~1,5-fold)	Potential determination of concentration and dose adjustment of sirolimus necessary.
Tacrolimus	Possible ↑ tacrolimus levels	
Lipid-lowering medicines/HMG-CoA reductase inhibitors		
Atorvastatin	Possible ↑ atorvastatin levels AUC of verapamil ↑ (~43 %)	See below for additional information
Lovastatin	Possible ↑ in lovastatin levels AUC (~63 %) and C_{max} (~32 %) of verapamil ↑	
Simvastatin	AUC (~2,6-fold) and C_{max} (~4,6-fold) of simvastatin ↑	
Serotonin receptor agonists		
Almotriptan	AUC (~20 %) and C_{max} (~24 %) of almotriptan ↑	
	Increased verapamil hydrochloride levels	
Uricosuric medicine		

Potential interactions		
Concomitant medicine	**Potential effect on ISOPTIN SR 240 mg or concomitant medicine**	**Comment**
Sulfinpyrazone	Oral clearance of verapamil ↑ (~3-fold), bioavailability ↓ (~60 %)	Potential reduction in antihypertensive effect
	No change in the PK with intravenous use of verapamil	
Other cardiac treatments		
Ivabradine	Concomitant use with ivabradine is contraindicated due to the additional heart rate-reducing effect of verapamil on ivabradine.	See section 4.3
Other		
Grapefruit juice	↑ in AUC of R- (~49 %) or S-verapamil (~37 %) ↑ in the C_{max} of R- (~75 %) or S-verapamil (~51 %)	Elimination half-life and renal clearance not affected. Food and drink containing grapefruit should be avoided whilst taking **ISOPTIN SR 240 mg**.
	Increased verapamil hydrochloride plasma levels	
St. John's wort	↓ in the R- (~78 %) or S-verapamil (~80 %) with corresponding reductions in C_{max}	

Other medicine interactions and additional medicine interaction information

HIV antiviral medicines

Verapamil plasma concentrations may increase due to the inhibiting potential of some HIV antiviral medicines, such as ritonavir. They should therefore be used with caution and the dose of verapamil should be reduced if necessary.

Similarly, verapamil may increase the plasma levels of these medicinal products by influencing degradation.

Lithium

Increased sensitivity to the effects of lithium (neurotoxicity) have been reported following concomitant administration with lithium. Lithium levels were unchanged or increased during treatment.

Pharmacokinetic and pharmacodynamic interactions between oral **ISOPTIN SR 240 mg** and lithium have been reported. **ISOPTIN SR 240 mg** may result in lowering of serum lithium levels in patients receiving chronic stable oral lithium therapy. An increased sensitivity to the effects of lithium may occur. Patients receiving both medicines must be monitored carefully.

Muscle relaxants

Both clinical and experimental animal data show that verapamil may potentiate the effects of muscle relaxants (both curare and depolarising). It may therefore be necessary to reduce the verapamil dose and/or the dose of the muscle relaxant, if both are administered concomitantly.

Acetylsalicylic acid

Increased tendency to bleed.

Dabigatran

Elevated dabigatran C_{max} and AUC levels were recorded following concomitant administration of oral verapamil and dabigatran etexilate (150 mg), a substrate of P-gp. The extent of these changes depends on the time of administration and the verapamil formulation used.

Concomitant administration of **ISOPTIN SR 240 mg** and dabigatran etexilate led to increased dabigatran exposure (increase of C_{max} and AUC by approximately 90 % and 70 %, respectively).

Close clinical monitoring is recommended if verapamil is combined with dabigatran etexilate, especially in the event of bleeding and particularly in patients with mild to moderate renal impairment.

Other direct oral anticoagulants (DOACs)

Both CYP3A4 and P-gp inhibitors such as verapamil can increase DOAC plasma concentrations to a clinically relevant extent. Some data suggest a potential increase in the risk of bleeding, particularly in patients presenting risk factors. The DOAC dose should be reduced during concomitant administration of verapamil, if required.

Ethanol (alcohol)

Delayed ethanol degradation and elevated ethanol plasma levels, thus potentiating the effect of alcohol.

HMG Co-A reductase inhibitors ("statins")

In patients receiving verapamil, HMG-CoA reductase inhibitor treatment (e.g. simvastatin, atorvastatin or lovastatin) should be started at the lowest possible dose and up-titrated. If **ISOPTIN SR 240 mg** is added to existing HMG-CoA reductase inhibitor therapy (e.g. simvastatin, atorvastatin or lovastatin), a statin dose reduction should be considered, with back-titration against the serum cholesterol concentration.

The risk of myopathy/rhabdomyolysis is increased following concomitant administration of higher doses of verapamil and simvastatin. The simvastatin dose should be adjusted accordingly (see section 4.4).

Fluvastatin, pravastatin and rosuvastatin are not metabolised via cytochrome P450 isoenzyme 3A4. An interaction with verapamil is less likely.

Antihypertensives, diuretics, vasodilators

Potentiation of the hypotensive effect with the risk of excessive hypotension.

Anti-dysrhythmics (e.g. flecainide, disopyramide), beta receptor blockers (e.g. metoprolol, propranolol), inhalation anaesthetics

Mutual potentiation of cardiovascular effects (severe AV block, severe drop in heart rate, onset of heart failure and exacerbated hypotension).

A study in healthy volunteers showed that the concomitant administration of flecainide and **ISOPTIN SR 240 mg** may have additive effects on myocardial contractility, AV conduction, and repolarisation.

Concomitant therapy with flecainide and verapamil may result in additive negative inotropic effect and prolongation of AV conduction.

When used concomitantly, inhalation anaesthetics and calcium antagonists should be titrated carefully to avoid excessive cardiovascular depression.

Quinidine

Until further data are obtained, combined therapy of **ISOPTIN SR 240 mg** and quinidine in patients with hypertrophic cardiomyopathy should probably be avoided.

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 **ISOPTIN SR 240 mg** 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.

Digitalis

Whenever overdigitalisation is suspected, the daily dose of digitalis (e.g. digoxin) should be reduced or temporarily discontinued.

Disopyramide

Until data on possible interactions between **ISOPTIN SR 240 mg** and disopyramide are obtained, disopyramide should not be administered within 48 hours before or 24 hours after verapamil administration.

4.6 Fertility, pregnancy and lactation

Pregnancy

Verapamil hydrochloride, as contained in **ISOPTIN SR 240 mg**, crosses the placental barrier and can be detected in umbilical vein blood at delivery. The plasma concentration in umbilical vein blood amounts to 20 – 92 % of the plasma concentration in the maternal blood. Safety in pregnancy has not been established. There are no adequate data from the use of **ISOPTIN SR 240 mg** in pregnant women.

Breastfeeding

ISOPTIN SR 240 mg is excreted in human breast milk (milk concentration approximately 23 % of maternal plasma concentration). Breastfeeding should be discontinued during **ISOPTIN SR 240 mg** therapy.

4.7 Effects on ability to drive and use machines

Patients must be monitored regularly during **ISOPTIN SR 240 mg** therapy. Given the variation in individual reactions, the ability to react may be changed to such an extent that the ability to drive, use machines or work without secure footing is adversely affected. This applies in particular at the start of treatment, if the dosage is increased or the preparation changed, and in combination with alcohol. Blood alcohol levels may be increased and the elimination of alcohol slowed down, thus potentially enhancing the effects of alcohol.

4.8 Undesirable effects

As **ISOPTIN SR 240 mg** inhibits AV conduction, it may cause AV block. **ISOPTIN SR 240 mg** may also lead to a transient decrease in blood pressure, even in normotensive patients.

Summary of the safety profile

The most commonly reported undesirable effects were headaches, dizziness or giddiness, gastrointestinal disorders (nausea, constipation, abdominal discomfort), as well as bradycardia,

tachycardia, palpitations, hypotension, flushes, peripheral oedema and fatigue.

Tabulated list of adverse effects:

The following undesirable effects have been reported in clinical trials, post-marketing studies or phase IV clinical trials; they are ranked according to system organ class.

The frequency data are defined as follows:

Very common: may affect more than 1 in 10 patients treated

Common: may affect up to 1 in 10 patients treated

Uncommon: may affect up to 1 in 100 patients treated

Rare: may affect up to 1 in 1,000 patients treated

Very rare: may affect up to 1 in 10,000 patients treated

Unknown: frequency cannot be estimated from the available data

MedDRA system organ class	***Adverse reaction***	***Frequency***
Immune system disorders	Hypersensitivity	Unknown
Nervous system disorders	Dizziness or giddiness Headaches Neuropathy	Common
	Paraesthesia Shakiness (tremor)	Rare
	Extrapyramidal disorder Paralysis (tetraparesis)[1] Cramps	Unknown
Metabolism and nutrition disorders	Reduced glucose tolerance	Uncommon
	Hyperkalaemia	Unknown
Psychiatric disorders	Anxiety	Common

MedDRA system organ class	***Adverse reaction***	***Frequency***
	Drowsiness	Rare
Ear and labyrinth disorders	Tinnitus	Rare
	Vertigo	Unknown
Cardiac disorders	Bradycardia Heart failure may develop or existing heart failure may be exacerbated Excessive blood pressure reduction and/or orthostatic regulation disorders	Common
	Palpitations Tachycardia	Uncommon
	Atrioventricular block (1st, 2nd or 3rd degree) Heart failure Sinus arrest Sinus bradycardia Asystole	Unknown
Vascular disorders	Flushing Hypotension	Common
Respiratory, thoracic and mediastinal disorders	Bronchospasm Dyspnoea	Unknown
Gastrointestinal disorders	Constipation Nausea	Common

MedDRA system organ class	***Adverse reaction***	***Frequency***
	Abdominal pain	Uncommon
	Vomiting	Rare
	Abdominal discomfort Gingival hyperplasia Ileus	Unknown
Hepato-biliary disorders	Probably allergy-induced hepatitis with reversible increase in liver-specific enzymes	Uncommon
Skin and subcutaneous tissue disorders	Erythromelalgia	Common
	Hyperhidrosis	Rare
	Photodermatitis	Very rare
	Angioedema Stevens Johnson syndrome Erythema multiforme Alopecia Itching Pruritus Purpura Maculopapular exanthema Urticaria	Unknown
Musculoskeletal and connective tissue disorders	Aggravation of Myasthenia gravis, Lambert-Eaton syndrome and progressive Duchenne muscular dystrophy	Very rare
	Arthralgia Muscular weakness or myalgia	Unknown

MedDRA system organ class	*Adverse reaction*	*Frequency*
	(muscle and joint pain)	
Renal and urinary disorders	Renal insufficiency	Unknown
Reproductive system and breast disorders	Galactorrhoea Gynaecomastia Impotence (erectile dysfunction)	Unknown
General disorders and administration site conditions	Peripheral oedema	Common
	Fatigue	Uncommon
Investigations	Elevated blood prolactin levels Elevation of liver enzymes	Unknown

[1] There was a single post-marketing report on paralysis (tetraparesis) related to the concomitant administration of verapamil hydrochloride as contained in **ISOPTIN SR 240 mg** and colchicine. This could have been caused by the passage of colchicine through the blood-brain barrier following inhibition of CYP3A4 and P-gp by verapamil (see section 4.5).

Note

In patients fitted with pacemakers, an increase in the pacing and sensing threshold cannot be ruled out during verapamil hydrochloride therapy.

In patients with a history of cardiovascular disease, e.g. severe cardiomyopathy, congestive heart failure or recent myocardial infarction, concomitant administration of intravenous beta blockers or disopyramide with intravenous verapamil hydrochloride increased the risk of severe side effects as since both substance classes have a cardiodepressive effect (see section 4.5).

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions after authorisation of **ISOPTIN SR 240 mg** is important. It allows continued monitoring of the benefit/risk balance of **ISOPTIN SR 240 mg**. Health care

providers are asked to report any suspected adverse reactions to SAHPRA via the **6.04 Adverse Drug Reactions Reporting Form**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Symptoms:

Symptoms of **ISOPTIN SR 240 mg** overdose progress depending on the amount ingested, the time at which detoxification measures are applied and the contractile functionality of the myocardium (age-dependent).

The following symptoms have been observed with overdose:

Serious hypotension, heart failure, bradycardia up to high degree AV block and sinus arrest or tachycardia dysrhythmia, potentially culminating in cardiovascular shock and cardiac arrest.

Clouding of consciousness progressing to coma, hyperglycaemia, stupor, hypokalaemia, metabolic acidosis, hypoxia, cardiogenic shock with pulmonary oedema, impaired renal function and convulsions. Fatalities have occurred as a result of overdose.

Treatment

Detoxification and restoration of stable cardiovascular conditions are pre-requisite.

Treatment of **ISOPTIN SR 240 mg** overdose depend on the time and method of ingestion, as well as the nature and severity of the overdose symptoms.

If larger quantities of sustained-release preparations have been ingested, it should be noted that the active substance may be released and absorbed by the intestines even longer than 48 hours after intake. Therefore, patients may require observation and hospitalisation for up to 48 hours.

If overdose with sustained-release preparations is suspected, extensive elimination measures are indicated, such as induced vomiting, aspiration of the contents of the stomach and small intestine under endoscopic guidance, intestinal lavage, evacuation, high enema.

As **ISOPTIN SR 240 mg** cannot be dialysed, haemodialysis is not advisable, but haemofiltration and possibly plasmapheresis (high plasma protein binding of calcium channel blockers) are recommended.

Standard intensive care resuscitation measures, such as extrathoracic cardiac massage, ventilation, defibrillation and/or pacemaker therapy.

Specific measures:

Elimination of cardiodepressive effects, hypotension and bradycardia.

Bradycardia dysrhythmia is treated symptomatically with atropine and/or beta sympathomimetic medicines (isoprenaline, orciprenaline); in the case of life-threatening bradycardia dysrhythmia, temporary pacemaker therapy is required. Asystole should be treated by standard methods, including beta adrenergic stimulation (isoprenaline).

Calcium is a specific antidote, repeated if necessary, or administered as a continuous drip infusion.

Hypotension, as a result of cardiogenic shock and arterial vasodilation, is treated with dopamine, dobutamine, epinephrine or norepinephrine. Serum calcium should be maintained at high-normal to slightly elevated levels. Additional fluid replacement therapy is administered in the early stages due to arterial vasodilation (Ringer's or sodium chloride solution).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A.7.1 Vasodilators, hypotensive medicines.

Pharmacotherapeutic group: Selective calcium channel blockers with predominantly cardiac effects, phenyl alkylamine derivatives.

ATC code: C08DA01.

Mechanism of action

Verapamil hydrochloride belongs to the group of calcium channel blockers. Verapamil hydrochloride inhibits the transmembrane influx of calcium ions through muscle cells. It lowers the myocardial oxygen requirement *in vitro* directly by intervening in energy-consuming metabolic processes in the cardiac muscle cell and indirectly by reducing the

afterload. Verapamil hydrochloride also acts as a calcium channel blocker on smooth muscle, particularly in the region of the vessels and gastrointestinal tract. The calcium-blocking effect on

the smooth vascular muscle tissue of the coronary arteries increases myocardial perfusion, and relaxes coronary spasms. Verapamil hydrochloride's antihypertensive action is based on lowering of peripheral vascular resistance-with no rebound increase in heart rate. There is no reflex increase in cardiac output. Consequently, blood pressure drops.

Verapamil hydrochloride possesses well-developed anti-dysrhythmic effects, particularly in the presence of supraventricular dysrhythmia. It delays conduction in the atrioventricular node. The result, depending on the type of rhythm disorder, is the restoration of sinus rhythm and/or normalization of ventricular frequency. Normal heart rates are unaffected or lowered slightly.

5.2 Pharmacokinetic properties

Verapamil is a racemic mixture consisting of equal portions of the R and S enantiomers. Verapamil is extensively metabolised. Norverapamil is one of 12 metabolites that can be detected in the urine; it possesses 10 to 20 % of the pharmacological activity of verapamil and accounts for 6 % of the excreted active substance.

The steady-state plasma concentrations of norverapamil and verapamil are comparable. Steady-state is reached after three to four days with repeated daily dosing.

Absorption

Greater than 90 % of verapamil is rapidly absorbed from the small intestine following oral administration. Mean systemic availability of the unchanged substance after a single dose of non-sustained-release verapamil is 22 % compared to approximately 32 % with sustained-release verapamil, owing to an extensive hepatic first-pass metabolism. Bioavailability increases approximately two-fold with repeated dosing. Following the administration of non-sustained-release verapamil, peak plasma concentrations are reached after one to two hours compared to four to five hours after administration of sustained-release verapamil. Norverapamil peak plasma concentrations are reached after one hour (non-sustained-release) or after five hours (sustained-release).

The bioavailability of verapamil is unaffected if the medicinal product is taken with food.

Distribution

Verapamil is widely distributed in the body tissues; the volume of distribution is 1,8 to 6,8 L/kg in healthy subjects. Verapamil hydrochloride in plasma is approximately 90 % proteinbound.

Biotransformation

Verapamil is extensively metabolized. *In vitro* studies show that verapamil is metabolised by the cytochrome P450 isoenzymes CYP3A4, CYP1A2, CYP2C8, CYP2C9 and CYP2C18. Oral verapamil is extensively metabolised in the liver in healthy men.

A number of metabolites are generated in humans (twelve have been identified, but mostly only in traces). The majority of metabolites consist of various N- and O-dealkylated degradation products of verapamil. Of these metabolites, only norverapamil has any appreciable pharmacological effect (approximately 20 % that of the parent substance), which was observed in a study with dogs.

Elimination

Following intravenous infusion, verapamil is rapidly eliminated bi-exponentially, with a faster early distribution phase (half-life about four minutes) and a slower terminal elimination phase (half-life two to five hours).

The elimination half-life of oral verapamil is three to seven hours post-dose.

Verapamil hydrochloride and its metabolites are primarily eliminated by the renal route. About 50 % of the dose administered is eliminated via the kidneys within 24 hours, and 70 % within five days. Up to 16 % are excreted with the faeces. About 3 to 4 % of the active substance is excreted unchanged via the kidneys. Total clearance is approximately on par with hepatic blood flow, about 1 L/h/kg (range: 0,7 to 1,3 L/h/kg).

Considerable inter-individual differences are apparent in terms of clearance.

Special populations

Paediatric population

Only limited pharmacokinetic data are available regarding use in the paediatric population. Following intravenous administration, the mean half-life was 9,17 hours and the average clearance

30 L/h compared to 70 L/h in an adult weighing 70 kg. Steady-state plasma concentrations after oral administration appear to be lower in children than in adults.

Elderly patients

Age may influence the pharmacokinetic effects in patients with high blood pressure. The elimination half-life may be prolonged in elderly patients. The anti-hypertensive effect of verapamil is not age-dependent.

Impaired renal function

Impaired renal function does not impact the pharmacokinetic profile, as shown by comparative studies in patients with end-stage renal failure and subjects with healthy kidneys.

Verapamil and norverapamil cannot be removed through haemodialysis.

Impaired hepatic function

The half-life is prolonged in patients with impaired hepatic function. This is due to the reduced clearance of the orally administered substance and the increased distribution volume.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Magnesium stearate

Microcrystalline cellulose

Povidone

Purified water

Sodium alginate

Tablet coating

Hypromellose

Indigo carmine aluminium compound

Macrogol 400

Macrogol 600

Montan glycol wax

Quinoline yellow

Talc

Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Packs of 30 and 100 sustained release tablets in amber glass bottles.

Packs of 30 film-coated tablets in PVC/PVDC/Aluminium blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Not applicable.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Abbott Laboratories S.A. (Pty) Ltd

Abbott Place

219 Golf Club Terrace

Constantia Kloof 1709

South Africa

8. REGISTRATION NUMBER

South Africa: V/7.1/280

Country	Registration number	Distribution Category
Botswana	B9305405	S2
Ghana	FDA/SD.183-2096	Prescription Only Medicine
Kenya	4477	Prescription Only Medicine
Mauritius	R4120/02/14	Prescription Only Medicine
Namibia	90/7.1.4/0068	NS2
Zimbabwe	97/12.6/3277	Prescription Preparations (P.P.)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 October 2012

10. DATE OF REVISION OF THE TEXT

5 August 2022

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