Proposed professional information for ISOPTIN 40 mg

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

ISOPTIN 40 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 40 mg verapamil hydrochloride.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

White, biconvex film-coated tablets. Embossed with “40” on one side and with the “Knoll” triangle on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Angina pectoris (acute and chronic coronary insufficiency), supraventricular tachydysrhythmia.

4.2 Posology and method of administration

Posology

The average daily dose is 120 mg – 360 mg in three divided doses where possible.

Method of administration

The doses of **ISOPTIN 40 mg** as prescribed by the physician, are to be taken regularly, preferably half an hour before meals together with some liquid.

4.3 Contraindications

ISOPTIN 40 mg is contraindicated in patients with:

- Hypersensitivity to verapamil hydrochloride or any of the excipients listed in section 6.1.
- Retarded atrioventricular (AV) conduction (second- and third-degree AV block).
- Acute stage of myocardial infarction.
- Sick sinus syndrome.
- Cardiovascular shock.
- Pronounced sinoatrial (SA) conduction disorder (second- and third-degree SA block), except for patients fitted with a pacemaker.
- Heart failure with a reduced ejection fraction of less than 35 % and/or wedge pressure exceeding 20 mmHg (unless secondary to supraventricular tachycardia responding to verapamil hydrochloride).
- Atrial fibrillation/flutter and the concomitant presence of accessory pathways (e.g. Wolff-Parkinson-White (WPW) or Lown-Ganong-Levine syndrome). In these patients, **ISOPTIN 40 mg** therapy poses an increased risk of ventricular tachycardia, including ventricular fibrillation.
- Concomitantly receiving ivabradine (see section 4.5).

Beta blockers should not be administered intravenously in conjunction with **ISOPTIN 40 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 40 mg affects AV and sinus nodes and delays AV conduction. It 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.

It affects AV and sinus nodes and, in rare cases, may trigger second- or third-degree AV block, bradycardia or, in extreme cases, asystole. This is more likely to occur in patients with sick sinus syndrome, which is more common in older patients.

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 also section 4.8).

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 40 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 40 mg**, concomitantly.

Digoxin:

The digoxin dose should be reduced if taken concomitantly with verapamil hydrochloride, as contained in **ISOPTIN 40 mg** (see section 4.5).

Heart failure:

ISOPTIN 40 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. Where heart failure is present, full compensation with cardiac glycosides must be achieved before administration of **ISOPTIN 40 mg**. Adequate therapy should also be administered during treatment. **ISOPTIN 40 mg** should be avoided in

patients with severe left ventricular dysfunction (e.g. ejection fraction less than 30 %, pulmonary wedge pressure above 20 mmHg, or severe symptoms of 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 40 mg** treatment.

HMG-CoA reductase inhibitors ("statins"):

See section 4.5.

Hypotension:

ISOPTIN 40 mg may occasionally produce symptomatic hypotension in normotensive patients. Particularly strict monitoring is required in the case of hypotension (less than 90 mmHg 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 40 mg** treatment.

Special populations

Impaired renal function:

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 40 mg**, individual case reports suggest that caution should be exercised and strict monitoring implemented (ECG, blood pressure) when administering **ISOPTIN 40 mg** to patients with renal impairment.

ISOPTIN 40 mg cannot be removed through haemodialysis.

Impaired hepatic function:

In patients with diminished hepatic function (parenchymal loss/reduced blood supply) the effect of **ISOPTIN 40 mg** 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.

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 40 mg** has not been established, such patients receiving oral **ISOPTIN 40 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 and discontinuation of therapy is rarely necessary.

Use in patients with disorders with impaired neuromuscular transmission:

Caution should be exercised when prescribing **ISOPTIN 40 mg** for patients previously diagnosed with impaired neuromuscular transmission (Myasthenia gravis, Lambert-Eaton syndrome, progressive Duchenne muscular dystrophy).

Excipient warning

ISOPTIN 40 mg contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially sodium free.

4.5 Interaction with other medicines and other forms of interaction

In-vitro studies have shown that verapamil is metabolised by cytochrome P450 isoenzymes CYP3A4, CYP1A2, CYP2C8, CYP2C9 and CYP2C18.

Clinically significant interactions have been reported with CYP3A4 inhibitors responsible for increased verapamil hydrochloride plasma levels; contrastingly, inducers of CYP3A4 lower verapamil hydrochloride plasma levels. Patients should therefore be monitored for interactions.

Verapamil inhibits CYP3A4 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 40 mg or the concomitant medicine**	**Comment**
Alpha blockers		
Prazosin	C_{max} of prazosin ↑ (~ 40 %), no effect on half-life	Additive antihypertensive effect.
Terazosin	↑ in the AUC (~ 24 %) and (25 %) of terazosin	
Anti-dysrhythmics		
Flecainide	Minimal effect on plasma clearance of flecainide (<~ 10 %); no effect on verapamil plasma clearance	Further information (see section 4.4 – Anti-dysrhythmics, beta receptor blockers and inhalation anaesthetics).

Quinidine	Clearance of oral quinidine ↓ (~ 35 %)	Hypotension. Pulmonary oedema may occur in patients with hypertrophic obstructive cardiomyopathy.
Amiodarone	Increase in amiodarone plasma levels	
Antiasthmatics		
Theophylline	Oral and systemic clearance ↓ by ~ 20 %	The reduction in clearance was less pronounced in smokers (~ 11 %).
Anticonvulsants/Antiepileptics		
Carbamazepine	AUC of carbamazepine ↑ (~ 46 %) in patients with refractory partial epilepsy	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	AUC of imipramine ↑ (~ 15 %)	No effect on level of active metabolite, desipramine.

	Increased verapamil hydrochloride plasma levels	
Antidiabetics		
Glibenclamide	C_{max} (~ 28 %) and AUC of glibenclamide ↑ (~ 26 %)	
	Increased verapamil hydrochloride plasma levels	
Gout treatments		
Colchicine	↑ of AUC (~ 2,0-fold) and C_{max} (~ 1,3-fold) of colchicine	Reduction in the dose of 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 the PK of doxorubicin with intravenous use of verapamil	In patients with advanced tumours.
Azole fungistatics		
Clotrimazole	Increased verapamil hydrochloride plasma levels	
Ketoconazole	Increased verapamil hydrochloride plasma levels	
Itraconazole	Increased verapamil hydrochloride plasma levels	
Barbiturates		
Phenobarbital	Clearance of oral verapamil ↑ (~ 5-fold)	
Benzodiazepines and other anxiolytics		
Buspirone	AUC and C_{max} of buspirone ↑ (~ 3,4-fold)	
	Increased verapamil hydrochloride plasma levels	
Midazolam	AUC (~ 3-fold) and C_{max} (~ 2-fold) of midazolam ↑	
	Increased verapamil hydrochloride plasma levels	
Beta blockers		

Metoprolol	In patients with angina pectoris ↑ in the AUC (~ 32,5 %) and C_{max} (~ 41 %) of metoprolol	See section 4.4.
	Increased verapamil hydrochloride plasma levels	
Propranolol	In patients with angina pectoris ↑ in AUC (~ 65 %) and C_{max} (~ 94 %) of propranolol	
	Increased verapamil hydrochloride plasma levels	
Cardiac glycosides		
Digitoxin	↓ in total clearance of digitoxin (~ 27 %) and in extrarenal clearance (~ 29 %)	
Digoxin	In healthy subjects: C_{max} of digoxin ↑ (~ 44 %), C12h of digoxin ↑ (~ 53 %), C_{ss} of digoxin ↑ (~ 44 %) and AUC of digoxin ↑ (~ 50 %)	Reduction in digoxin dose (see section 4.4.).
H2 Receptor antagonists		
Cimetidine	AUC of R- (~ 25 %) and S-verapamil (~ 40 %) with corresponding	Cimetidine reduces verapamil clearance after intravenous administration of verapamil.

	with corresponding ↓ in R- and S-verapamil clearance	
Immunological medicines/Immunosuppressants		
Cyclosporin	AUC, C_{ss}, C_{max} of cyclosporine ↑ (~ 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	Tacrolimus levels possibly ↑	
Lipid-lowering/HMG-CoA reductase inhibitors		
Atorvastatin	Possible ↑ in 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		
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 40 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 interactions and additional 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 40 mg** and lithium have been reported. The former may result in lowering of serum lithium levels in patients receiving chronic stable oral lithium therapy. The latter may result in an increased sensitivity to the effects of lithium. Patients receiving both medicines must be monitored carefully.

***Neuromuscular blocking* medicine**

Clinical data and animal studies suggest that **ISOPTIN 40 mg** may potentiate the activity of neuromuscular blocking medicines (curare-like and depolarising). It may be necessary to decrease the dose of **ISOPTIN 40 mg** and/or the dose of the neuromuscular blocking medicine when both are used concomitantly.

Acetylsalicylic acid

Increased propensity to bleed.

Dabigatran

1.3.1.1 CURRENT APPROVED PROFESSIONAL INFORMATION

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.
Dabigatran C_{max} levels and the AUC increased by approximately 180 % and 150 %, respectively, following the administration of a rapid-release formulation of verapamil 120 mg one hour before a single dose of dabigatran etexilate. No significant interactions were observed when verapamil was administered 2 hours after dabigatran etexilate (increases of approximately 10 % and 20 % in C_{max} and AUC, 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-CoA 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 verapamil 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 the manufacturer's production information; 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 antihypertensive effect with the risk of excessive hypotension.

Antihypertensive medicines: **ISOPTIN 40 mg** may intensify the blood pressure lowering effect of concomitantly administered antihypertensives, and this often makes it possible to reduce the dose of the antihypertensives, particularly in patients on long-term treatment with **ISOPTIN 40 mg**.

Nitrates: **ISOPTIN 40 mg** has been given concomitantly with short-and long-acting nitrates without any undesirable drug interactions. The pharmacological profile of both medicines and the clinical experience suggest beneficial interactions.

Antidysrhythmics (e.g. flecainide, disopyramide), beta blockers (e.g. metoprolol, propranolol), inhalation anaesthetics

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

A study in healthy volunteers showed that the concomitant administration of flecainide and **ISOPTIN 40 mg** may have additive effects on myocardial contractility, AV conduction, and repolarisation. Concomitant therapy with flecainide and **ISOPTIN 40 mg** may result in additive negative inotropic effect and prolongation of AV conduction.

1.3.1.1 CURRENT APPROVED PROFESSIONAL INFORMATION

Intravenous beta receptor blockers should not be administered concomitantly to patients receiving intravenous verapamil therapy (except in intensive care; see section 4.3). Concomitant therapy with beta-adrenergic blockers and **ISOPTIN 40 mg** may result in additive negative effects on the heart rate, AV conduction, and/or cardiac contractility. The combination should be used only with caution and close monitoring. Concomitant administration of intravenous verapamil and anti-adrenergic medicines may lead to excessive hypotension. Simultaneous administration of intravenous beta blockers or disopyramide with intravenous verapamil increased the risk of adverse events, particularly in patients with a history of cardiovascular disease, e.g. severe cardiomyopathy, congestive heart failure or recent myocardial infarction, since both substance classes suppress myocardial contractility and AV conduction (see also section 4.8).

Animal experiments have shown that inhalation anaesthetics depress cardiovascular activity by decreasing the inward movement of calcium ions. When used concomitantly, inhalation anaesthetics and calcium antagonists should be titrated carefully to avoid excessive cardiovascular depression.

Digitalis

Chronic **ISOPTIN 40 mg** treatment can increase serum digoxin levels by 50 to 70 % during the first week of therapy, and this can result in digitalis toxicity. Whenever overdigitalisation is suspected, the daily dose of digitalis should be reduced or temporarily discontinued.

Disopyramide

Until data on possible interactions between **ISOPTIN 40 mg** and disopyramide are obtained, disopyramide should not be administered within 48 hours before or 24 hours after verapamil administration.

Quinidine

In a small number of patients with hypertrophic cardiomyopathy (IHSS), concomitant use of **ISOPTIN 40 mg** and quinidine resulted in significant hypotension. Until further data are obtained, combined therapy of **ISOPTIN 40 mg** and quinidine in patients with hypertrophic cardiomyopathy should probably be avoided. There has been a report of increased quinidine levels during verapamil therapy.

Cimetidine

The interaction between cimetidine and chronically administered **ISOPTIN 40 mg** has not been studied. Variable results on clearance have been obtained in acute studies of healthy volunteers; clearance of **ISOPTIN 40 mg** was either reduced or unchanged.

4.6 Fertility, pregnancy and lactation

Pregnancy

ISOPTIN 40 mg should be used during pregnancy only if clearly needed. Verapamil hydrochloride, as contained in **ISOPTIN 40 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.

Breastfeeding

ISOPTIN 40 mg is excreted in human milk (milk concentration approximately 23 % of maternal plasma concentration). Breastfeeding should be discontinued while **ISOPTIN 40 mg** is administered.

4.7 Effects on ability to drive and use machines

Patients must be monitored regularly during **ISOPTIN 40 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 40 mg** inhibits AV conduction, it may cause AV block. **ISOPTIN 40 mg** may also lead to a transient decrease in blood pressure, even in normotensive patients**.**

a. 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.

b. 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

Undesirable effects reported from clinical studies with verapamil and post-marketing observations

MedDRA system organ class	***Undesirable effect***	***Frequency***

Immune system disorders	Hypersensitivity	Unknown
Nervous system disorders	Dizziness or giddiness Headaches Neuropathy	Common
	Paraesthesia Shakiness (mild tremor)	Rare
	Extrapyramidal symptoms Paralysis (tetraparesis)[1] Cramps Severe facial pain	Unknown
Metabolism and nutrition disorders	Reduced glucose tolerance	Uncommon
	Hyperkaliaemia	Unknown
Psychiatric disorders	Anxiety	Common
	Drowsiness	Rare
Ear and labyrinth disorders	Tinnitus	Rare
	Vertigo	Unknown
Cardiac disorders	Bradycardia Onset of heart failure or exacerbation of pre-existing heart failure Excessive blood pressure reduction and/or orthostatic regulation disorders	Common
	Palpitations Tachycardia	Uncommon

	Atrioventricular block (1st, 2nd or 3rd degree) SA block 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
	Abdominal pain	Uncommon
	Vomiting	Rare
	Abdominal discomfort Gingival hyperplasia and burning sensations of the gums 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
	Temporary skin rash	Unknown

	Angioedema Stevens Johnson syndrome Erythema multiforme Alopecia Itching Pruritus Purpura Maculopapular exanthema Urticaria	
Musculoskeletal and connective tissue disorders	Aggravation of *Myasthenia gravis*, Lambert-Eaton syndrome and progressive Duchenne muscular dystrophy	Very rare
	Exacerbation of arthritis Arthralgia Muscular weakness or myalgia (muscle and joint pain)	Unknown
Renal and urinary disorders	Renal insufficiency Increased urination	Unknown
Reproductive system and breast disorders	Erectile dysfunction Galactorrhoea Gynaecomastia	Unknown
General disorders and administration site conditions	Peripheral oedema	Common
	Fatigue	Uncommon
Investigations	Elevated blood prolactin levels Laboratory abnormalities:	Unknown

	Reversible increase of transaminases and/or alkaline phosphatase has been observed and is most probably a response of allergic hepatitis	

[1] There was a single post-marketing report on paralysis (tetraparesis) related to the concomitant administration of verapamil hydrochloride, as contained in **ISOPTIN 40 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 under cannot be ruled out during verapamil 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 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 suspected adverse reactions after authorisation of **ISOPTIN 40 mg** is important. It allows continued monitoring of the benefit/risk balance of **ISOPTIN 40 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 of overdose:

Intoxication symptoms following **ISOPTIN 40 mg** poisoning 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 severe poisoning:

Serious hypotension, heart failure, bradycardia or tachycardia arrhythmia (e.g. junctional rhythm with AV dissociation and severe AV block), potentially culminating in cardiovascular shock and cardiac arrest.

Clouding of consciousness progressing to coma, hyperglycaemia, hypokalaemia, metabolic acidosis, hypoxia, cardiogenic shock with pulmonary oedema, impaired renal function and convulsions. Deaths have occasionally been reported.

Therapeutic measures in the event of overdose:

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

Therapeutic measures depend on the time and method of ingestion, as well as the nature and severity of the intoxication 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.

Gastric lavage is advisable after oral **ISOPTIN 40 mg** poisoning, even more than 12 hours after ingestion, if no gastrointestinal motility (bowel sounds) can be detected. If intoxication 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 40 mg** cannot be dialysed, haemodialysis is not advisable, but haemofiltration and possibly plasmapheresis (high plasma protein binding of calcium channel blockers) are recommended.

Specific counteractive measures:

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- and third-degree AV block: Atropine, isoproterenol, if necessary pacemaker therapy.

Development of myocardial insufficiency: Dopamine, dobutamine, cardiac glycosides or calcium.

Hypotension: Proper positioning, dopamine, dobutamine norepinephrine.

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 is a calcium ion influx inhibitor (slow channel blocker or calcium ion antagonist), which exerts its pharmacological effects by modulating the influx of ionic calcium across the cell membrane of the arterial smooth muscle, particularly in the region of the vessels and gastrointestinal tract as well as in conductile and contractile myocardial cells. The effect on smooth muscle manifests in vasodilatation.

As a calcium channel blocker, verapamil hydrochloride reduces myocardial oxygen consumption *in vitro* directly by intervening in the energy consuming metabolic processes of the myocardial cell, and indirectly by diminishing the peripheral resistance (afterload). It prolongs impulse conduction in the AV node. This can lead to a negative inotropic effect in the working myocardium.

1.3.1.1 CURRENT APPROVED PROFESSIONAL INFORMATION

As a result of vasodilatation, a decrease in total peripheral resistance is observed in humans. There is no reflex increase in cardiac output. Consequently, blood pressure drops.

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

Over 90 % of verapamil is quickly absorbed from the small intestine following oral administration. The mean systemic availability of the unchanged substance following a single dose of non-sustained-release verapamil is 22 % compared to approximately 32 % with sustained-release verapamil. This is due to a significant first-pass effect in the liver.
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. Up to 90 % bind to plasma proteins.

Biotransformation

1.3.1.1 CURRENT APPROVED PROFESSIONAL INFORMATION

Verapamil is extensively metabolised. *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; 12 metabolites 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, only norverapamil has any notable pharmacological effect (approximately 20 % of that of the parent substance); this was seen in a study conducted in 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.

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 patient groups

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

1.3.1.1 CURRENT APPROVED PROFESSIONAL INFORMATION

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; this was shown in comparison studies involving end-stage renal failure patients and patients 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:

Calcium hydrogen phosphate, dihydrate

Colloidal anhydrous silica

Croscarmellose sodium

Magnesium stearate

Microcrystalline cellulose

Tablet coating:

Hypromellose (type 2910, viscosity 3 mPa-s)

Macrogols, type 6000

Sodium laurilsulfate

Talc

Titanium dioxide E 171

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 30 °C, in a cool, dry place.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Hard PVC/PVDC colourless, transparent film and aluminium foil, printed or unprinted face for PVC film for 100 film-coated tablets per pack.

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: H646 (Act 101/1965)

1.3.1.1 CURRENT APPROVED PROFESSIONAL INFORMATION

Country	Registration number	Distribution Category
Botswana	B9305390	S2
Ghana	FDA/SD.183-2095	Prescription Only Medicine
Kenya	4277	Prescription Only Medicine
Namibia	14/7.1.4/0337	NS2

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

4 March 2005

10. DATE OF REVISION OF THE TEXT

27 March 2022

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