Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Isoptin SR 240mg Prolonged-Release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Isoptin SR 240mg Prolonged-Release Tablet contains 240 mg verapamil hydrochloride.

Excipients: Each prolonged release tablet contains up to 32mg (1.39 mmol) sodium.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet.

Product imported from Poland.
Isoptin SR tablets are light green, oblong in shape and marked with two triangles on one side.
The tablets can be divided into equal halves but must not be crushed or chewed.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Isoptin SR 240 mg Prolonged Release Tablets are indicated in the treatment of mild to moderate hypertension and coronary heart disease, i.e. prophylaxis of myocardial ischaemia, angina pectoris.

4.2 Posology and method of administration

For oral administration.

Hypertension: The adult dose is one tablet (240 mg) in the morning, increasing if necessary after one week to 240 mg in the morning and 240 mg in the evening, with an interval of 12 hours. In elderly patients, the initial dose is half a tablet (120 mg) in the morning, increasing by 120 mg increments at weekly intervals according to patient response.

Angina pectoris: The usual dose is 120-240 mg twice daily according to patient response. It is recommended that low initial doses with upward titration are used in new patients.

Verapamil should not be taken with grapefruit juice (see interactions).

In patients with impaired liver function, metabolism of the drug 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.

4.3 Contraindications

Isoptin SR 240 mg Prolonged Release Tablets are contra-indicated in patients with known hypersensitivity to verapamil and any of its excipients.

Isoptin SR 240 mg Prolonged Release Tablets are also contra-indicated in patients with cardiovascular shock, acute myocardial infarction complicated by bradycardia, marked hypotension or left ventricular failure, severe conduction disorders (2nd or 3rd degree AV block, sinoatrial block), atrial fibrillation/flutter, concomitant Wolff-Parkinson-White syndrome, untreated decompensated heart failure and sick sinus syndrome.

Isoptin SR 240mg Prolonged-Release Tablets are contra-indicated for use in patients **within 7 days** of an acute MI.

4.4 Special warnings and precautions for use

When treating hypertension, the patient's blood pressure should be monitored at regular intervals. Care should be taken in patients with:
1st degree AV block
Broad complex ventricular tachycardia
Progressive muscular dystrophy
Bradycardia less than 50 beats/minute
Systolic blood pressure less than 90 mmHg
Atrial fibrillation/flutter
Simultaneous pre-excitation syndrome, e.g. Wolff-Parkinson-White syndrome (risk of inducing ventricular tachycardia)
Uncompensated heart failure (to be treated by the physician before initiating treatment).
Severe hepatic impairment (See Section 4.2)
Intravenous beta-blockers should not be co-administered to patients on sustained release verapamil (except in ICU settings).
Diseases in which neuromuscular transmission is affected (myasthenia gravis, Lambert-Eaton syndrome, advanced Duchenne muscular dystrophy)

Although impaired renal function has been shown in robust comparator studies to have no effect on verapamil pharmacokinetics in patients with end-stage 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.

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).

Each prolonged release tablet contains up to 32mg (1.39 mmol) sodium. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

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.

The following table provides a list of potential drug 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	Additional information follows
Terazosin	↑ terazosin AUC (~24%) and Cmax (~25%)	
Antiarrhythmics		
Flecainide	Minimal affect on flecainide plasma clearance (<~10%); no effect on verapamil plasma clearance	Additional information follows
Quinidine	↓oral quinidine clearance (~35%)	
Antiasthmatics		
Theophylline	↓oral and systemic CL by ~20%	Reduction of CL was lessened in smokers (~11%)
Anticonvulsants		
Carbamazepine	↑ carbamazepine AUC (~46%) in refractory partial epilepsy patients	Additional information follows
Antidepressants		
Imipramine	↑ imipramine AUC (~15%)	No effect on level of active metabolite, desipramine
Antidiabetics		
Glyburide	↑ glyburide Cmax (~28%), AUC (~26%)	
Anti-gout agents		
Colchicine	Possible ↑ colchicine levels	Additional information follows
Anti-infectives		
Clarithromycin	Possible ↑ in verapamil levels	
Erythromycin	Possible ↑ in verapamil levels	
Rifampin	↓ verapamil AUC (~97%), Cmax (~94%), oral bioavailability (~92%)	Additional information follows
Telithromycin	Possible ↑in verapamil levels	
Antineoplastics		
Doxorubicin	doxorubicin AUC (89%) and C_{max} (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 (~3-fold) and Cmax (~2-fold)	
Beta blockers		

Metoprolol	↑ metoprolol AUC (~32.5%) and Cmax (~41%) in angina patients	Additional information follows
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 by ~45-53% ↑ Css by ~42% and ↑ AUC by ~52%	
H2 Receptor antagonists		
Cimetidine	↑ AUC of R- (~25%) and S- (~40%) verapamil with corresponding ↓ in R-and S-verapamil clearance	
Immunologics		
Ciclosporin	↑ ciclosporin AUC, Css, Cmax by ~45%	
Everolimus	Possible ↑ everolimus levels	
Sirolimus	Possible ↑ sirolimus levels	
Tacrolimus	Possible ↑ tacrolimus levels	
Lipid lowering agents		
Atorvastatin	Possible ↑ atorvastatin levels Increase verapamil AUC (~42.8%)	Additional information follows
Lovastatin	Possible ↑ lovastatin levels	
Simvastatin	↑ simvastatin AUC (~2.6-fold), C_{max}(~4.6-fold)	
Serotonin receptor antagonists		
Almotriptan	↑ almotriptan AUC (~20%) ↑ C_{max} (~24%)	
Uricosurics		
Sulfinpyrazone	↑ verapamil oral clearance (~3-fold) ↓ bioavailability (~60%)	Additional information follows
Other		
Grapefruit juice	↑ R- (~49%) and S- (~37%) verapamil AUC ↑ R- (~75%) and S- (~51%) verapamil C_{max}	Elimination half life and renal clearance not affected
St. John's Wort	↓ R- (~78%) and S- (~80%) verapamil AUC with corresponding reductions in C_{max}	

Other Drug Interactions and Additional Drug Interaction Information

Colchicine: Colchicine is a substrate for both CYP3A and the efflux transporter, P-gp. Verapamil is known to inhibit CYP3A and P-gp.

When verapamil and colchicine are administered together, the potential inhibition of P-gp and/or CYP3A by verapamil may lead to increased exposure to colchicine. (See Section 4.4, Special Warnings and Special Precautions for Use).

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).

Antihypertensives, diuretics, vasodilators: Potentiation of the hypotensive effect.

Prazosin, terazosin: Additive hypotensive effect.

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

Quinidine: Hypotension. Pulmonary edema may occur in patients with hypertrophic obstructive cardiomyopathy.

Carbamazepine: Increased carbamazepine levels. This may produce carbamazepine side effects such as diplopia, headache, ataxia or dizziness.

Lithium: Increased lithium neurotoxicity.

Rifampin: Blood pressure lowering effect may be reduced.

Sulfinpyrazone: Blood pressure lowering effect may be reduced.

Neuromuscular blockers: The effect of neuromuscular blocking agents may be potentiated.

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.

4.6 Fertility, pregnancy and lactation

Isoptin SR 240mg Prolonged-Release Tablets should not be given during pregnancy (especially in the first trimester) unless, in the physician's judgement, it is essential for the patient's well-being.

There are no adequate data from the use of verapamil hydrochloride in pregnant women.

Verapamil crosses the placenta and has been measured in umbilical cord blood.

Verapamil is excreted in human breast 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.
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

Depending on individual susceptibility, the patient's ability to drive or operate machinery may be impaired.

This is particularly true in the initial stages of treatment, when changing over from another drug, and also with respect to the consumption of alcohol.

4.8 Undesirable effects

Adverse reactions have been spontaneously reported during the post-approval use of oral verapamil. These events are reported voluntarily from a population of an unknown rate of exposure. Therefore, it is not possible to estimate the true incidence of adverse events or establish a causal relationship to verapamil exposure.

Significant adverse events reported with verapamil are listed below by system organ class:

System Organ Class	**Adverse Event**
Immune system disorders	Hypersensitivity
Metabolism and nutrition disorders	Glucose tolerance impaired
Psychiatric disorders	Nervousness
Nervous system disorders	Headache Dizziness Paraesthesia Tremor Hypoesthesia Somnolence Neuropathy peripheral Extrapyramidal disorder
Ear and labyrinth disorders	Vertigo Tinnitus
Cardiac disorders	Atrioventricular block (1°, 2°, 3°) Sinus bradycardia Sinus arrest Cardiac arrest Bradyarrhythmia Palpitations Tachycardia Cardiac failure
Vascular disorders	Hypotension Flushing Erythromelalgia
Respiratory, thoracic and mediastinal disorders	Bronchospasm
Gastrointestinal disorders	Nausea Vomiting Constipation Ileus Gingival hyperplasia Abdominal pain Abdominal discomfort Abdominal distension
Skin and subcutaneous tissue disorders	Angioedema Stevens-Johnson syndrome Erythema multiforme Rash maculopapular Alopecia Urticaria Purpura

	Pruritus Photosensitivity reaction Erythema Rash
Musculoskeletal and connective tissue disorders	Muscular weakness Myalgia Arthralgia
Reproductive system and breast disorders	Erectile dysfunction Gynaecomastia Galactorrhoea
General disorders and administration site conditions	Oedema peripheral Fatigue
Investigations	Hepatic enzyme increased Blood prolactin increased
Injury, poisoning and procedural complications	Elevated pacing threshold *

* This has been reported in patients with pacemakers while on verapamil hydrochloride treatment.

4.9 Overdose

The symptoms of overdosage include hypotension, shock, loss of consciousness, 1st and 2nd degree AV block (frequently as Wenckebach's phenomenon with or without escape rhythms), total AV block with total AV dissociation, escape rhythm, asystole, sinus bradycardia, sinus arrest.

Treatment of overdose depends upon the type and severity of symptoms. Verapamil hydrochloride cannot be removed by haemodialysis. The specific antidote is calcium, e.g. 10-20 ml of 10% calcium gluconate solution i.v. (2.25-4.5 mmol), if necessary by repeated injection or continuous infusion (e.g. 5 mmol/hr). Gastric lavage, taking the usual precautionary measures, may be appropriate. The usual emergency measures for acute cardiovascular collapse should be applied, and followed by intensive care.

Similarly, in the case of 2nd and 3rd degree AV block, atropine, isoprenaline, orciprenaline and, if required, pacemaker therapy should be considered.

If there are signs of myocardial insufficiency, dopamine, dobutamine, cardiac glycosides or calcium gluconate (10-20 ml of a 10% solution) should be administered.

In the case of hypotension, after appropriately positioning the patient, dopamine, dobutamine or noradrenaline may be given.

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

Fatalities have occurred as a result of overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: C08DA01

The calcium antagonist verapamil inhibits the transmembrane influx of calcium ions into the heart and vascular smooth muscle cells.

The antihypertensive effect of Isoptin SR 240 mg Prolonged Release Tablets results from a decrease in peripheral vascular resistance, without an increase in heart rate as a reflex response. As early as day one of treatment, blood pressure falls and the effect persists in long-term therapy.

Isoptin is suitable for the treatment of all types of hypertension: for monotherapy in mild to moderate hypertension and combined with other antihypertensives (in particular with diuretics and according to more recent findings, with ACE inhibitors) in more severe types of hypertension.

Due to its calcium antagonistic effect in the smooth muscle of the coronaries, Isoptin enhances myocardial blood flow, even in post-stenotic areas, and relieves coronary spasm.

Isoptin has an additional anti-arrhythmic 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.

5.2 Pharmacokinetic properties

About 92% of verapamil is absorbed rapidly from the small intestine. Mean systemic availability of the unchanged compound after a single dose is 22% owing to an extensive hepatic first pass metabolism. Bioavailability is about 2 times higher with the repeated administration.

Peak verapamil hydrochloride plasma levels are reached one to two hours after IR administration. The elimination half-life is 3 to 7 hours. Verapamil hydrochloride in plasma is approximately 90% protein bound. The drug is extensively metabolized. A number of metabolites are generated in humans (twelve have been identified). Of these metabolites, only norverapamil has any appreciable pharmcological effect (approximately 20% that of the parent compound), which was observed in a study with dogs.

Verapamil hydrochloride and its metabolites are primarily eliminated by the renal route. Only 3 to 4% of the renally excreted drug is eliminated as the unchanged drug. About 50% of the dose is eliminated renally within 24 hours, 70% within five days. Up to 16% of a dose is excreted in faeces. Impaired renal function has no effect on verapamil hydrochloride pharmacokinetics, as shown by comparative studies in patients with end-stage renal failure and subjects with healthy kidneys. The half-life of verapamil is prolonged in patients with impaired liver function owing to lower oral clearance and a higher volume of distribution.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Sodium alginate
Povidone
Magnesium stearate
Purified water
Hypromellose
Macrogol 400
Macrogol 6000
Talc
Titanium dioxide (E171)
Quinoline yellow (E104)
Indigo carmine (E132)
Glycol wax

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf life expiry date for this product shall be the date shown on the blister and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Aluminium and PVC/PVDC blister packs containing 30 tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

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8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA1562/092/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17th May 2013

10 DATE OF REVISION OF THE TEXT