SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Isoptin SR 240 mg Prolonged-Release Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Isoptin SR Prolonged-Release Tablet contains 240 mg Verapamil Hydrochloride.

Excipients with known effect: Each prolonged release tablet contains 37.1 mg sodium.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release film-coated tablet.

The oblong tablets are film-coated and light green colour, with a breakline on both sides and the Knoll logo 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

Mild to moderate hypertension and coronary heart disease, i.e. prophylaxis of myocardial ischaemia, angina pectoris.

4.2 Posology and method of administration

The dose of verapamil hydrochloride should be adjusted individually in accordance with the severity of disease. Long-standing clinical experience shows that the average daily dose in all indications is between 240 mg and 360 mg. The daily dose should not exceed 480 mg on a long-term basis, although a higher dose may be used for a short period. There is no limitation on the duration of use. Verapamil hydrochloride should not be discontinued abruptly after long-term use. It is recommended to taper the dosage.

Verapamil hydrochloride 40mg mg tablets should be used for patients likely to display a satisfactory response to low doses (e.g. patients with hepatic dysfunction or elderly patients). For patients requiring higher dosages (e.g., 240 mg to 480 mg verapamil hydrochloride per day), formulations with a more suitable active drug content should be used.

Adults *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.

Special Populations
Renal impairment
Currently available data are described in Special Warnings and Precautions for Use Section. Verapamil hydrochloride should be used cautiously and with close monitoring in patients with impaired renal function.

Liver impairment
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 (see Special Warnings and Precautions for Use Section).

Method of administration
For oral use only.
Tablets should be taken without sucking or chewing, with sufficient liquid, preferably with or shortly after meals.
Verapamil should not be taken with grapefruit juice (see Section 4.5, Interactions).

4.3 Contraindications

- Hypersensitivity to verapamil hydrochloride or to any of the inactive ingredients;
- Cardiogenic shock:
- Second-or third-degree AV block (except in patients with a functioning artificial pacemaker);
- Sick sinus syndrome (except in patients with a functioning artificial pacemaker);
- Heart failure with reduced ejection fraction of less than 35%, and/or pulmonary wedge pressure above 20 mm Hg (unless secondary to a supraventricular tachycardia amenable to verapamil therapy);
- Atrial fibrillation/flutter, in the presence of an accessory bypass tract (e.g., Wolff-Parkinson-White syndrome, Lown-Ganong-Levine syndromes). These patients are at risk to develop ventricular tachyarrhythmia including ventricular fibrillation if verapamil hydrochloride is administered.
- Marked hypotension;
- Left ventricular failure;
- **within 7 days** of an acute MI;
- Combination with ivabradine (see section Interactions with other medicinal products and other forms of interaction)

4.4 Special warnings and precautions for use

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

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

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

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

When treating hypertension, the patient's blood pressure should be monitored at regular intervals.

Care should be taken in patients with: Broad complex ventricular tachycardia, 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). Intravenous beta-blockers should not be co-administered to patients on sustained release verapamil (except in ICU settings).

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

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

Colchicine:
There has been a single postmarketing report of paralysis (tetraparesis) associated with the combined use of verapamil and colchicine. This may have been caused by colchicine crossing the blood-brain barrier due to CYP3A4 and P-gp inhibition by verapamil. Combined use of verapamil and colchicine is not recommended. (see Section 4.5, Drug Interactions).

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

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

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

Neuromuscular transmission disorders
Verapamil hydrochloride should be used with caution in the presence of diseases in which neuromuscular transmission is affected (myasthenia gravis, Lambert-Eaton syndrome, advanced Duchenne muscular dystrophy).
Respiratory standstill has been reported for one patient with progressive muscular dystrophy following administration of Isoptin.

Other Special Populations
Renal impairment
Although impaired renal function has been shown in robust comparator studies to have no effect on verapamil pharmacokinetics in patients with 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.

Liver impairment

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

Sodium
This medicine contains 37.1 mg sodium per tablet, equivalent to 1.9 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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

Antidepressants		
Imipramine	↑ imipramine AUC (~15%)	No effect on level of active metabolite, desipramine
Antidiabetics		
Glyburide	↑ glyburide Cmax (~28%), AUC (~26%)	
Metformin	Co-administration of verapamil with metformin may reduce the efficacy of metformin.	
Anti-gout		
Colchicine	↑ colchicine AUC (~ 2.0-fold) and Cmax (~1.3-fold)	Reduce colchicine dose (see colchicine label)
Anti-infectives		
Clarithromycin	Possible ↑ in verapamil levels	
Erythromycin	Possible ↑ in verapamil levels	
Rifampicin	↓ verapamil AUC (~97%), Cmax (~94%), oral bioavailability (~92%) with oral verapamil administration	Blood pressure lowering effect may be reduced.
Telithromycin	Possible ↑ in verapamil levels	
Antineoplastics		
Doxorubicin	↑ doxorubicin AUC (104%) and Cmax (61%) with oral verapamil administration	In patients with small cell lung cancer
	No significant change in doxorubicin PK with intravenous verapamil administration	In patients with advanced neoplasms
Barbiturates		
Phenobarbital	↑ oral verapamil clearance (~5-fold)	
Benzodiazepines and other anxiolytics		
Buspirone	↑ buspirone AUC, Cmax by ~3.4-fold	
Midazolam	↑ midazolam AUC (~3-fold) and Cmax (~2-fold)	
Beta blockers		
Metoprolol	↑ metoprolol AUC (~32.5%) and Cmax (~41%) in angina patients	See Special warnings and precautions for use section
Propranolol	↑ propranolol AUC (~65%) and Cmax (~94%) in angina patients	
Cardiac glycosides		
Digitoxin	↓digitoxin total body clearance (~27%) and extrarenal clearance (~29%)	
Digoxin	Healthy subjects: ↑ Cmax (~44%) ↑ digoxin C12h (~53%), ↑ Css (~44%) and ↑ AUC (~50%)	Reduce digoxin dosage. Also see Special Warnings and Precautions for Use Section
H2 Receptor antagonists		
Cimetidine	↑ AUC of R- (~25%) and S- (~40%) verapamil with	Cimetidine reduces verapamil clearance following

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

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

Other Drug Interactions and Additional Drug Interaction Information

Antihypertensives, diuretics, vasodilators:
Potentiation of the 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.

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

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

Aspirin:
Increased tendency to bleed

Ethanol (alcohol):
Elevation of ethanol plasma levels

HMG Co-A Reductase Inhibitors ("Statins"):
Treatment with HMG CoA reductase inhibitors (e.g. simvastatin, atorvastatin or lovastatin) in a patient taking verapamil should be started at the lowest possible dose and titrated upwards. If verapamil treatment is to be added to patients already taking an HMG CoA reductase inhibitor (e.g. simvastatin, atorvastatin or lovastatin), consider a reduction in the statin dose and retitrate against serum cholesterol concentrations.
Fluvastatin, pravastatin and rosuvastatin are not metabolized by CYP3A4 and are less likely to interact with verapamil.

Dabigatran:
When oral verapamil was co-administered with dabigatran etexilate (150 mg), a P- gp substrate, the Cmax and AUC of dabigatran were increased but magnitude of this change differs depending on time between administration and the formulation of verapamil. Co- administration of verapamil 240 mg extended-release at the same time as dabigatran etexilate resulted in increased dabigatran exposure (increase of Cmax by about 90 % and AUC by about 70 %).
Close clinical surveillance is recommended when verapamil is combined with dabigatran etexilate and particularly in the occurrence of bleeding, notably in patients having a mild to moderate renal

impairment.

4.6 Fertility, pregnancy and lactation

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

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

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

Lactation
Verapamil hydrochloride/metabolites are excreted in human 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.

A risk to the newborns/infants cannot be excluded. Due to the potential for serious adverse reactions in nursing infants, verapamil should only be used during lactation if it is essential for the welfare of the mother.

4.7 Effects on ability to drive and use machines

Due to its antihypertensive effect, depending on the individual response, verapamil hydrochloride may affect the ability to react to the point of impairing the ability to drive a vehicle, operate machinery or work under hazardous conditions. This applies all the more at the start of treatment, when the dose is raised, when switching from another drug and in conjunction with alcohol. Verapamil may increase the blood levels of alcohol and slow its elimination. Therefore, the effects of alcohol may be exaggerated.

4.8 Undesirable effects

The following adverse events reactions have been reported with verapamil from clinical studies, postmarketing surveillance or Phase IV clinical trials and are listed below by system organ class.

Frequencies are defined as:
very common (≥1/10);
common (≥1/100 to <1/10);
uncommon (≥1/1,000 to <1/100);
rare (≥1/10,000 to <1/1,000);
very rare (<1/10,000);
not known (cannot be estimated from the available data).

The most commonly reported ADRs were:
headache,
dizziness,
gastrointestinal disorders: nausea, constipation and abdominal pain,
bradycardia,
tachycardia,
palpitations,
hypotension,
flushing,
oedema peripheral,
fatigue.

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

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

				Erythema, Rash
Musculoskeletal and connective tissue disorders				Arthralgia, Muscular weakness, Myalgia
Renal and urinary disorders				Renal failure
Reproductive system and breast disorders				Erectile dysfunction, Galactorrhea, Gynecomastia
General disorders and administration site conditions	Oedema peripheral	Fatigue		
Investigations				Blood prolactin increased, Hepatic enzymes increased
Injury, poisoning and procedural complications				Elevated pacing threshold *

[1] There has been a single postmarketing report of paralysis (tetraparesis) associated with the combined use of verapamil and colchicine. This may have been caused by colchicine crossing the blood-brain barrier due to CYP3A4 and P-gp inhibition by verapamil. *See Interactions with other medicinal products and other forms of interaction section.*

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Symptoms
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, hyperglycaemia, metabolic acidosis and acute respiratory distress syndrome. Fatalities have occurred as a result of overdose.

Treatment
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. Asystole should be handled by the usual measures including beta adrenergic stimulation (e.g., isoproterenol hydrochloride).

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

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

ATC Code: C08DA01

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

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

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

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

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

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

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

5.2 Pharmacokinetic properties

Verapamil hydrochloride is a racemic mixture consisting of equal portions of the R-enantiomer and the S-enantiomer. Verapamil is extensively metabolized. Norverapamil is one of 12 metabolites identified in urine, has 10 to 20% of the pharmacologic activity of verapamil and accounts for 6% of

excreted drug. The steady-state plasma concentrations of norverapamil and verapamil are similar. Steady state after multiple once daily dosing is reached after three to four days.

Absorption
Greater than 90% of verapamil is rapidly absorbed from the small intestine after oral administration. Mean systemic availability of the unchanged compound after a single dose of IR verapamil is 22% and that of SR verapamil approximately 33%, owing to an extensive hepatic first-pass metabolism. Bioavailability is about two times higher with repeated administration. Peak verapamil plasma levels are reached one to two hours after IR administration, and four to five hours after SR administration. The peak plasma concentration of norverapamil is attained approximately one and five hours after IR or SR administration, respectively. The presence of food has no effect on the bioavailability of verapamil.

Distribution
Verapamil is widely distributed throughout the body tissues, the volume of distribution ranging from 1.8–6.8 L/kg in healthy subjects. Plasma protein binding of verapamil is approximately 90%.
Metabolism Verapamil is extensively metabolized. In vitro metabolic studies indicate that verapamil is metabolized by cytochrome P450 CYP3A4, CYP1A2, CYP2C8, CYP2C9 and CYP2C18. In healthy men, orally administered verapamil hydrochloride undergoes extensive metabolism in the liver, with 12 metabolites having been identified, most in only trace amounts. The major metabolites have been identified as various N and O-dealkylated products of verapamil. Of these metabolites, only norverapamil has any appreciable pharmacological effect (approximately 20% that of the parent compound), which was observed in a study with dogs.

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

Populations
Paediatric:
Limited information on the pharmacokinetics in the paediatric population is available. After intravenous dosing, the mean half-life of verapamil was 9.17 hours and the mean clearance was 30 L/h, whereas it is around 70 L/h for a 70-kg adult. Steady-state plasma concentrations appear to be somewhat lower in the paediatric population after oral dosing compared to those observed in adults.

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

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

Hepatic insufficiency:
The half-life of verapamil is prolonged in patients with impaired liver function owing to lower oral clearance and a higher volume of distribution.

Verapamil hydrochloride, administered intravenously, has been shown to be rapidly metabolized.

5.3 Preclinical Safety Data

Reproduction studies have been performed in rabbits and rats at oral verapamil doses up to 180 mg/m2/day and 360 mg/m2/day (compared to a maximum recommended human oral daily dose of 300 mg/m2) and have revealed no evidence of teratogenicity. In the rat, however, a dose similar to the clinical dose (360 mg/m2) was embryocidal and retarded foetal growth and development. These effects occurred in the presence of maternal toxicity (reflected by reduced food consumption and weight gain of dams). This oral dose has also been shown to cause hypotension in rats.
There are, however, no adequate and well-controlled studies in pregnant women.

The cardiovascular findings and the diffuse gingival hyperplasia seen in the chronic toxicity of verapamil hydrochloride are taken into account in section 4.8 (undesirable effects).

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Microcrystalline cellulose
Sodium alginate
Povidone
Magnesium stearate
Hypromellose
Macrogol 400
Macrogol 6000
Talc
Titanium dioxide (E171)
Quinoline yellow and indigotine aluminium lacquer
(quinoline yellow E104, indigo carmine E132)
Montan glycol wax.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

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 28 tablets.

6.6 Special precautions for disposal and other handling of the product

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

7. MARKETING AUTHORISATION HOLDER

Mylan IRE Healthcare Limited
Unit 35/36
Grange Parade
Baldoyle Industrial Estate
Dublin 13
Ireland

8. MARKETING AUTHORISATION NUMBER

PA 2010/3/5

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

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10. DATE OF REVISION OF THE TEXT

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