ISOPTIN® SR
Verapamil hydrochloride

1. NAME OF THE MEDICINAL PRODUCT
Isoptin SR® 240 mg, sustained release (SR) tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Verapamil hydrochloride is a calcium ion influx inhibitor (slow channel blocker or calcium ion antagonist). The chemical name of verapamil hydrochloride is benzeneacetonitrile, α-[3-[{2-(3,4-dimethoxyphenyl)ethyl}methylaminol] propyl]-3,4-dimethoxy-α-(1-methylethyl) hydrochloride. It has a molecular weight of 491.07 and the molecular formula is $C_{27}H_{38}N_2O_4 \bullet HCl$.

Verapamil hydrochloride Ph Eur – 240 mg
The full list of excipients is provided in the List of Excipients section.

3. PHARMACEUTICAL FORM
Verapamil hydrochloride is a calcium ion influx inhibitor (slow channel blocker or calcium ion antagonist). Verapamil hydrochloride is an almost white, crystalline powder, practically free of odor, with a bitter taste. It is soluble in water, freely soluble in chloroform, sparingly soluble in alcohol and practically insoluble in ether.

Light green-colored sustained release (film-coated) tablets.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Hypertension

4.2 Posology and method of administration
The doses of Isoptin® SR as prescribed by the physician are to be taken regularly. The caplets are to be swallowed whole with some liquid, preferably with or shortly after meals.

Adults take 1 caplet in the morning unless otherwise prescribed by the physician. Patients requiring particularly gradual blood pressure lowering, therapy should be initiated with 120 mg of sustained released Isoptin (1/2 caplets of Isoptin SR) taken in the morning. If required, after about 2 weeks the dose may be increased up to 2 caplets daily (1 caplet morning and evening at an interval of approximately 12 hours).

Patients on long-term treatment should not take than 2 caplets transient dose increase only when directed by the physician.

For adults requiring smaller doses of Verapamil, Isoptin 80 dragee are available.

In patients with impaired hepatic function the effect of Verapamil is intensified and prolonged depending on the severity of the liver disease due to diminished drug metabolism. In these cases dosage should be adjusted with special care starting with low doses (approximately 30% of the dose given to patients with normal liver function should be administered to severe liver dysfunction patients)

Method of administration

For oral use only.

Tablets should be taken without sucking or chewing, with sufficient liquid, preferably with or shortly after meals.

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, Lown-Ganong-Levine syndromes). These patients are at risk to develop ventricular tachyarrhythmia including ventricular fibrillation if verapamil hydrochloride is administered.
- Combination with Ivabradine (See section "Interaction with other medicinal products and other forms of interaction")

4.4 Special warnings and precautions for use

Acute Myocardial infarction

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

Heart Block/ 1st Degree AV block/Bradycardia/Asystole

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

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

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

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.

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.

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

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

Neuromuscular transmission disorders
Verapamil hydrochloride should be used with caution in the presence of diseases in which neuromuscular transmission is affected (myasthenia gravis, Lambert-Eaton syndrome, advanced Duchenne muscular dystrophy).

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).

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.

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. Co-administration of verapamil and a drug primarily metabolized by CYP3A4 or being 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 due to pharmacokinetic reasons:

Potential Interactions		
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 *Special warnings and precautions for use* section.
Quinidine	↓oral quinidine clearance (~35%)	Hypotension. Pulmonary edema may occur in patients with hypertrophic obstructive cardiomyopathy.
Antiasthmatics		
Theophylline	↓oral and systemic clearance by ~20% Reduction of CL was lessened in smokers (~11%)	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 concentration	
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%), and oral bioavailability (~92%)	Blood pressure lowering effect may be reduced.
	No change in PK with intravenous verapamil administration	
Telithromycin	Possible ↑in verapamil levels	
Antineoplastics		

Doxorubicin	↑doxorubicin AUC (89%) 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: ↑ digoxin Cmax (~44%) ↑ digoxin C12h (~53%), ↑ digoxin Css (~44%) and ↑ digoxin AUC (~50%)	Reduce digoxin dosage. Also see Special Warnings and Precautions for Use Section
H2 Receptor antagonists		
Cimetidine	↑AUC of R- (~25%) and S- (~40%) verapamil with corresponding ↓in R- and S-verapamil clearance	Cimetidine reduces verapamil clearance following intravenous verapamil administration.
Immunologics/Immuno-suppressives		
Cyclosporine	↑cyclosporine 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); S-verapamil ↑ AUC (~	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 ↑verapamil AUC by ~43%	Additional information follows.
Lovastatin	Possible ↑ lovastatin levels ↑ verapamil AUC (~63%) and Cmax (~32%)	
Simvastatin	↑simvastatin AUC (~2.6-fold) and Cmax (~4.6-fold)	
Serotonin receptor agonists		
Almotriptan	↑almotriptan AUC (~20%) and ↑Cmax (~24%)	
Uricosurics		
Sulfinpyrazone	↑verapamil oral clearance (~3-fold)	Blood pressure lowering effect may be reduced.

	↓bioavailability (~60%) No change in PK with intravenous verapamil administration	
Anticoagulants		
Dabigatran	↑dabigatran Cmax (up to 180%) and AUC (up to 150%)	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 Cyp3A4, 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. The dose of DOAC with oral verapamil may need to be reduced (see DOAC label for dosing instructions).
Other Cardiac therapy		
Ivabradine	Concomitant use with ivabradine is contraindicated due to the additional heart rate lowering effect verapamil to ivabradine.	See section "Contraindication"
Other		
Grapefruit juice	↑R- (~49%) and S- (~37%) verapamil AUC ↑R- (~75%) and S- (~51%) verapamil Cmax	Elimination half-life and renal clearance not affected. Grapefruit juice should therefore not be ingested with verapamil.
St. John's Wort	↓ R- (~78%) and S- (~80%) verapamil AUC with corresponding reductions in Cmax	

Other Drug Interactions and Additional Drug Interaction Information

HIV antiviral agents

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

Lithium

Increased sensitivity to the effects of lithium (neurotoxicity) has been reported during concomitant verapamil hydrochloride-lithium therapy with either no change or an increase in serum lithium levels.

The addition of verapamil hydrochloride, however, has also resulted in the lowering of the serum lithium levels in patients receiving chronic stable oral lithium. Patients receiving both drugs should be monitored carefully.

Neuromuscular blocking agents

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

Acetylsalicylic acid

Increased tendency to bleed.

Ethanol (alcohol)
Elevation of ethanol plasma levels.

HMG-CoA Reductase Inhibitors ("Statins")
Treatment with HMG-CoA reductase inhibitors (e.g. simvastatin, atorvastatin or lovastatin) in a patient taking verapamil should be started at the lowest possible dose and titrated upwards. If verapamil treatment is to be added to patients already taking an HMG-CoA reductase inhibitor (e.g. simvastatin, atorvastatin or lovastatin), consider a reduction in the statin dose and retitrate against serum cholesterol concentrations.

Fluvastatin, pravastatin and rosuvastatin are not metabolized by CYP3A4 and are less likely to interact with verapamil.

Antihypertensives, diuretics, vasodilators
Potentiation of the hypotensive effect.

4.6 Pregnancy and lactation
Pregnancy
Teratogenic Effects
There are no adequate and well-controlled study data in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed (see *Preclinical Safety Data* Section).

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

Verapamil hydrochloride/metabolites are excreted in human milk. Limited human data from oral administration has shown that the infant relative dose of verapamil is low (0.1 – 1% of the mother's oral dose) and that verapamil use may be compatible with breastfeeding.

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

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

4.8 Undesirable effects
The following adverse 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, as well as bradycardia, tachycardia, palpitations, hypotension, flushing, edema peripheral and fatigue.

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

MedDRA System Organ Class	Common	Uncommon	Rare	Unknown
Immune system disorders				Hypersensitivity
Nervous system disorders	Dizziness, Headache		Paresthesia Tremor	Extrapyramidal disorder, paralysis (tetraparesis)[1], Seizures
Metabolism and Nutrion disorder				Hyperkalemia
Psychiatric disorders			Somnolence	
Ear and labyrinth disorders			Tinnitus	Vertigo
Cardiac disorders	Bradycardia	Palpitations, Tachycardia		Atrioventricular block (1°, 2°, 3°), Cardiac failure, Sinus arrest, Sinus bradycardia; asystole
Vascular disorders	Flushing, Hypotension			
Respiratory, thoracic and mediastinal disorders				Bronchospasm Dyspnoea
Gastrointestinal disorders	Constipation, Nausea	Abdominal pain	Vomiting	Abdominal discomfort, Gingival hyperplasia, Ileus
Skin and subcutaneous tissue disorders			Hyperhidrosis	Angioedema, Stevens-Johnson syndrome, Erythema multiforme, Alopecia, Itching, Pruritus, Purpura, Rash maculopapular, Urticaria
Musculoskeletal and connective tissue disorders				Arthralgia, Muscular weakness, Myalgia
Renal and urinary disorder				Renal failure
Reproductive system and breast disorders				Erectile dysfunction, Galactorrhea, Gynecomastia
General disorders and administration site conditions	Edema peripheral	Fatigue		

Investigations				Blood prolactin increased, Hepatic enzymes increased

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

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions is an important way to gather more information to continuously monitor the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via pv.indonesia@abbott.com and/or via:

Pusat Farmakovigilans/ MESO Nasional Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif
Badan Pengawas Obat dan Makanan
Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id;
Website: https://e-meso.pom.go.id

4.9 Overdose

Clinical manifestations

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

Treatment

Treatment of verapamil hydrochloride overdose should be mainly supportive and individualized. Beta-adrenergic stimulation and/or parenteral administration of calcium injection (calcium chloride) have been effectively used in treatment of deliberate overdosage with oral verapamil hydrochloride.

Clinically significant hypotensive reactions or high-degree AV block should be treated with vasopressor agents or cardiac pacing, respectively. Asystole should be handled by the usual measures including beta adrenergic stimulation (e.g., isoproterenol hydrochloride), other vasopressor agents or cardiopulmonary resuscitation.

Due to the potential for delayed absorption of the sustained release product, patients may require observation and hospitalization for up to 48 hours. Verapamil hydrochloride cannot be removed by hemodialysis.

5. PHARMACOLOGIC 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 odorless 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-(3,4-dimethoxyphenyl)ethyl}methylaminol]propyl]-3,4-dimethoxy-α-(1-methylethyl) hydrochloride.

It has a molecular weight of 491.07 and the molecular formula is $C_{27}H_{38}N_2O_4 \bullet HCl$.

Mechanism of action and Pharmacodynamic effects

Verapamil inhibits the calcium ion (and possibly sodium ion) influx through slow channels into conductile and contractile myocardial cells and vascular smooth muscle cells. The antiarrhythmic effect of verapamil appears to be due to its effect on the slow channel in cells of the cardiac conductile system.

Electrical activity through the sinoatrial (SA) and atrioventricular (AV) nodes depends, to a significant degree, upon calcium influx through the slow channel. By inhibiting this influx, verapamil slows AV conduction and prolongs the effective refractory period within the AV node in a rate-related manner.

This effect results in a reduction of the ventricular rate in patients with atrial flutter and/or atrial fibrillation and a rapid ventricular response. By interrupting reentry at the AV node, verapamil can restore normal sinus rhythm in patients with paroxysmal supraventricular tachycardias (PSVT), including Wolff-Parkinson-White (W-P-W) syndrome. Verapamil has no effect on conduction across accessory bypass tracts.

Clinical efficacy and safety

Verapamil does not alter the normal atrial action potential or intraventricular conduction time, but depresses amplitude, velocity of depolarization and conduction in depressed atrial fibers.

In the isolated rabbit heart, concentrations of verapamil that markedly affect SA nodal fibers or fibers in the upper and middle regions of the AV node have very little effect on fibers in the lower AV node (NH region) and no effect on atrial action potentials or His bundle fibers.

Verapamil does not induce peripheral arterial spasm nor does it alter total serum calcium levels.

Verapamil reduces afterload and myocardial contractility. In most patients, including those with organic cardiac disease, the negative inotropic action of verapamil is countered by reduction of afterload and cardiac index is usually not reduced, but in patients with moderately severe to severe cardiac dysfunction (pulmonary wedge pressure above 20 mm Hg, ejection fraction less than 30%), acute worsening of heart failure may be seen. Peak therapeutic effects occur within three to five minutes after a bolus injection of verapamil.

The commonly used intravenous doses of 5 to 10 mg verapamil hydrochloride produce transient, usually asymptomatic, reduction in normal systemic arterial pressure, systemic vascular resistance and contractility; left ventricular filling pressure is slightly increased.

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 SR verapamil is 32%, owing to an extensive hepatic first-pass metabolism.

Bioavailability is about two times higher with repeated administration.

Peak verapamil hydrochloride plasma levels are reached four to five hours after SR administration.

The peak plasma concentration of norverapamil is attained approximately five hours after SR administration. The presence of food has no effect on the bioavailability of verapamil.

Distribution

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

Metabolism

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

Elimination

Following oral administration, the elimination half-life is three to seven hours. Approximately 50% of an administration dose is eliminated renally within 24 hours, 70% within five days. Up to 16% of a dose is excreted in the feces. About 3% to 4% of renally excreted drug is excreted as unchanged drug. The total clearance of verapamil is nearly as high as the hepatic blood flow, approximately 1 L/h/kg (range: 0.7-1.3 L/h/kg).

Special Populations

Pediatric: Limited information on the pharmacokinetics in the paediatric population is available. 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.

5.3 Preclinical safety data

Reproduction studies have been performed in rabbits and rats at oral verapamil doses up to 180mg/m^2/day and 360 mg/m^2/day (compared to a maximum recommended human oral daily dose of 300 mg/m^2) and have revealed no evidence of teratogenicity. In the rat, however, a dose similar to the clinical dose (360 mg/m^2) 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose
Sodium Alginate
Povidone
Magnesium Stearate
Purified Water

Hypromellose
Macrogols Type 400
Macrogols Type 6000
Talc
Titanium Dioxide
FD&C Blue No 2 Aluminium Lake
D&C Yellow No. 10 Lake

Incompatibilities
Not applicable.

Shelf life
Expiry date is indicated on the packaging

Special precautions for storage
Store at temperature not exceed 30°C
Expiry limit after opening the packaging: 3 months

Special precautions for disposal and other handling
No special requirements.

Nature and contents of container
Glass bottle of 50 sustained release tablets
Reg. No. DKL1900207497A1

ON MEDICAL PRESCRIPTION ONLY
HARUS DENGAN RESEP DOKTER
Prescription-Only Medicine

Manufactured by:
PT. Abbott Indonesia
Jl. Raya Jakarta Bogor Km. 37
Depok, Indonesia

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