ISOPTIN® 80
Verapamil hydrochloride

NAME OF THE MEDICINAL PRODUCT
Isoptin® 80 mg, immediate release (IR) tablets, contain verapamil hydrochloride 80mg

PRODUCT DESCRIPTION
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.

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 C27H38N2O4 • HCl.

The immediate release (IR) tablets 80 mg verapamil hydrochloride.

INDICATION
For the treatment of angina pectoris and prophylaxis of arrhythmia.

DOSAGE AND ADMINISTRATION
Adults: 240 – 480 mg/day divided in 3 - 4 doses of administration
Patients with severe impaired liver function should take 30% of the dosage.

CONTRAINDICATIONS
Verapamil hydrochloride is contraindicated in:
- Hypersensitivity to the active substance or to any of the inactive ingredients
- Cardiogenic shock
- Acute myocardial infarction with complications
- Second or third degree atrioventricular block (except in patients with a functioning artificial pacemaker)
- Sick sinus syndrome (except in patients with a functioning artificial pacemaker)
- Congestive heart failure
- Atrial fibrillation/flutter and an accessory bypass tract (e.g., Wolff-Parkinson-White, Lown-Ganong-Levine syndromes)
- Combination with Ivabradine (see section “Drug Interactions”)

WARNING AND PRECAUTIONS
Use with caution in the presence of:
- First degree AV block
- Hypotension
- Bradycardia
- Severely impaired liver function
- Diseases in which neuromuscular transmission is affected (myasthenia gravis, Lambert-Eaton syndrome, advanced Duchenne muscular dystrophy

DRUG 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 due to pharmacokinetic reasons:

Concomitant drug	Potential effect on verapamil or concomitant drug
Alpha blockers	
Prazosin	↑prazosin Cmax (~40%) with no effect on half-life
Terazosin	↑terazosin AUC (~24%) and Cmax (~25%)
Antiarrhythmics	
Flecainide	Minimal affect on flecainide plasma clearance (<~10%); no effect on verapamil plasma clearance
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
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-infectives	
Clarithromycin	Possible ↑ in verapamil levels
Erythromycin	Possible ↑ in verapamil levels
Rifampin	↓ verapamil AUC (~97%), Cmax (~94%), oral bioavailability (~92%)
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
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 by ~45-53% ↑ digoxin Css by ~42% and ↑ digoxin AUC by ~52%
H2 Receptor antagonists	
Cimetidine	↑AUC of R- (~25%) and S- (~40%) verapamil with corresponding ↓ in R- and S-verapamil clearance
Immunologics	

Cyclosporine	↑ cyclosporine AUC, Css, Cmax by ~45%
Everolimus	Possible ↑ everolimus levels
Sirolimus	Possible ↑ sirolimus levels
Tacrolimus	Possible ↑ tacrolimus levels
Lipid lowering agents	
Atorvastatin	Possible ↑ atorvastatin levels
Lovastatin	Possible ↑ lovastatin levels
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%)
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 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
St. John's Wort	↓ R- (~78%) and S- (~80%) verapamil AUC with corresponding reductions in Cmax

Other Drug Interactions and Additional Drug Interaction Information

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.

Colchicine
Colchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (P-gp).
Verapamil is known to inhibit CYP3A and P-gp. When verapamil and colchicine are administered together, inhibition of P-gp and/or CYP3A by verapamil may lead to increased exposure to colchicine. Combined use is not recommended.

Sulfinpyrazone
Blood pressure lowering effect may be reduced.

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

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.

PREGNANCY AND LACTATION
There are no adequate data from the use of verapamil hydrochloride in pregnant women.
Verapamil hydrochloride should be used during pregnancy only if clearly needed.
Verapamil crosses the placenta and has been measured in umbilical cord blood.

Nursing Mothers
Verapamil hydrochloride 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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
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.

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
Psychiatric disorders			Somnolence	
Metabolism and Nutrion disorder				Hyperkalemia
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.

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 although administration of parenteral calcium, beta adrenergic stimulation and gastrointestinal irrigation have been used in the treatment of verapamil hydrochloride overdose.

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.

PHARMACOLOGIC PROPERTIES

Pharmacodynamic Properties

Verapamil hydrochloride blocks the transmembrane influx of calcium ions into cardiac and vascular muscle cells. It lowers the myocardial oxygen requirement directly by intervening in energy-consuming metabolic processes in the cardiac muscle cell and indirectly by reducing the afterload.

The calcium-blocking effect on the smooth vascular muscle tissue of the coronary arteries increases myocardial perfusion, even in poststenotic tissue, and relaxes coronary spasms.

Verapamil hydrochloride's antihypertensive action is based on lowering of peripheral vascular resistance – with no rebound increase in heart rate. Normal blood pressures are not appreciably affected.

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

Pharmacokinetic Properties

Greater than 90% of verapamil is rapidly absorbed 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 two times higher with repeated administration.

Peak verapamil hydrochloride plasma levels are reached one to two hours after IR administration. The elimination half-life is three to seven 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 pharmacological 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 renally excreted drug is eliminated as unchanged drug. About 50% of a dose is eliminated renally within 24 hours, 70% within five days. Up to 16% of a dose is excreted in the feces.

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.

STORAGE

Store at temperature not exceed 30^{o}C

Packaging

Box, 5 strips @10 film-coated tablets

Reg. No. DKL 0200202717A1

ON MEDICAL PRESCRIPTION ONLY

HARUS DENGAN RESEP DOKTER

Manufactured by:

PT. Abbott Indonesia

Jl. Raya Jakarta Bogor Km. 37

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