PRODUCT NAME	:	Karvil	**COUNTRY :** Philippines		**LOCATION :** Indrad / Baddi		**Supersedes A/W No.:**
ITEM / PACK	:	Insert	**NO. OF COLORS:** 1		**REMARK :**		
DESIGN STYLE	:	Front-Back	**PANTONE SHADE NOS.:**		**SUBSTRATE :**		
CODE	:	xxxxxxxx-5343	■ Black		**Activities**	**Department**	**Name**	**Signature**	**Date**
DIMENSIONS (MM)	:	150 x 300			Prepared By	**Pkg.Dev**			
ART WORK SIZE	:	S/S			Reviewed By	**Pkg.Dev**			
DATE	:	02-01-2018			Approved By	**Quality**			

xxxxxxxx-5343

CARVEDILOL

KARVIL 6.25
KARVIL 12.5
KARVIL 25

6.25 mg, 12.5 mg and 25 mg Tablet
Combined Alpha and Beta Adrenoceptor Blocker

FORMULATION:
Each tablet contains:
Carvedilol ..... 6.25 mg, 12.5 mg and 25 mg

PRODUCT DESCRIPTION
Carvedilol (Karvil 6.25) 6.25 mg Tablet and Carvedilol (Karvil 25) 25 mg Tablet are white to off-white, round, flat, beveled-edge uncoated tablet with breakline on one side and plain on other side.
Carvedilol (Karvil 12.5) 12.5 mg Tablet is an old rose mottled, round, flat, beveled-edge uncoated tablet with breakline on one side and plain on other side.

CLINICAL PHARMACOLOGY
Carvedilol is a potent antihypertensive agent with a dual mechanism of action. It possesses both β-adrenergic receptor blocking activity and alpha-adrenergic antagonistic activity. Carvedilol is non-selective beta adrenoreceptor antagonist at clinically relevant doses. Alpha-blocking activity of carvedilol is thought to be the predominant mechanism of validation. However, there is no reflex tachycardia because of associated-blockade. At higher concentration it also exerts calcium channel antagonist property. The calcium channel blocking activity of carvedilol is responsible for increasing the blood flow in some regional vascular beds.

PHARMACOKINETICS

Absorption and Distribution
Carvedilol is rapidly absorbed after a single oral dose with maximum plasma concentration (Cmax) achieved within 1 to 2 hours (tmax) in healthy volunteers and hypertensive patients.
After oral administration, Carvedilol undergoes extensive first-pass hepatic metabolism that results in a relatively low and variable absolute bioavailability of about 25%.
Carvedilol is available as a racemic mixture of its R (+) - and S (-)-enantiomers and stereoselective differences in pharmacokinetics have been reported. In healthy volunteers, mean AUC values for the S (-)-enantiomer were lower than those for the R (+)-enantiomer after intravenous and oral administration of racemic Carvedilol. The difference was greatest after oral administration with the enantiomeric ratio (R: S) ranging from 1.6 to 4.4 (median 2.7). The mean maximum plasma concentration of R(+)-Carvedilol was 2.6-fold greater than that of S (-)-Carvedilol and absolute oral bioavailability was 31% for the R (+)-enantiomer and 15% for the S (-)-enantiomer in healthy volunteers indicating marked stereoselectivity in first-pass hepatic metabolism.
Carvedilol is a highly lipophilic compound that is extensively distributed into extravascular tissues following absorption. The volume of distribution is about 1.5 to 2L/kg in healthy volunteers. Carvedilol is highly bound to plasma proteins (> 95%). Binding appears to be lower for the S (-) -enantiomer than for the R (+)- enantiomer and is unchanged in patients with hepatic disease.

Metabolism and Excretion
Carvedilol is rapidly and extensively metabolised b the liver with less than 2% of a dose recovered as unchanged drug in urine. Clearance is almost exclusively via hepatic metabolism with the major metabolites being the glucuronide conjugate, aliphatic side-chain oxidative products and aromatic ring hydroxylated conjugates; some of these appear to be pharmacologically active although the clinical relevance of this has not been established.
The average elimination half-life of carvedilol is approximately 6 hours. Plasma clearance is approximately 500-700 mL/min. The primary route of excretion is via feces. Elimination is mainly biliary. A minor part is eliminated via the kidneys in the form of various metabolites.

INDICATIONS
Used in the management of essential hypertension and angina pectoris, and as an adjunct to standard therapy in symptomatic heart failure.

DOSAGE AND ADMINISTRATION
Hypertension - The recommended starting dose of Carvedilol is 6.25 mg twice daily. If this dose is tolerated, the dose should be maintained for 7 to 14 days, and then increased to 12.5mg twice daily. The dose may be increased further, if necessary, at intervals of at least two weeks, to 50 mg once daily or in divided doses, or as prescribed by the physician. A dose of 12.5mg once daily may be adequate for elderly patients.
Heart failure - The initial dose is 3.125 mg twice daily by mouth. If tolerated, the dose should be doubled after two weeks to 6.25 mg twice daily and then increased gradually, at intervals not less than two weeks, to the maximum dose tolerated, this should not exceed 25 mg twice daily in patients with severe heart failure or in those weighing less than 85 kg (187 lbs) or 50 mg twice daily in patients with mild to moderate heart failure weighing more than 85 kg, or as prescribed by the physician. It should be taken with food to reduce the risk of hypotension.
ANGINA PECTORIS - Initial dose of 12.5 mg twice daily by mouth, increased after two days to 25 mg twice daily or as prescribed by the physician.
LEFT VENTRICULAR DYSFUNCTION FOLLOWING MYOCARDIAL INFARCTION - The initial dose is 6.25 mg twice daily, increased after 3 to 10 days, if tolerated, to 12.5 mg twice daily and then to a target dose of 25 mg twice daily. A lower initial dose may be used in symptomatic patients. Or as prescribed by the physician.

CONTRAINDICATIONS
Carvedilol is contraindicated in patients with NYHA class IV decompensated cardiac failure requiring intravenous inotropic therapy, bronchial asthma or related bronchospastic conditions, second or third degree AV block, sick sinus syndrome (unless a permanent pacemaker is in place), cardiogenic shock or severe bradycardia.
Use of Carvedilol in patients with clinically manifested hepatic impairment is not recommended.
Carvedilol is contraindicated in patients with hypersensitivity to the drug.

WARNINGS
Hepatic injury: Mild hepatocellular injury, confirmed by rechallenge, has occurred rarely with Carvedilol therapy. If the patient has laboratory evidence of liver injury or jaundice, Carvedilol should be stopped and not restarted.
Chronic Obstructive Pulmonary Disease: Carvedilol should be used with caution in patients with chronic obstructive pulmonary disease (COPD) with a bronchospastic component who are not receiving oral or inhaled medication, and only if the potential benefit outweighs the potential risk.
In patients with a tendency to bronchospasm, respiratory distress can occur as a result of a possible in airway resistance. Patients should be closely monitored during initiation and up-titration of carvedilol and the dose of carvedilol should be reduced if any evidence of bronchospasm is observed during treatment.
Peripheral Vascular Disease: β-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease. Caution should be exercised in such individuals.
Anesthesia & Major Surgery: If Carvedilol treatment is to be continued preoperatively, particular care should be taken when anesthetic agents, which depress myocardial function such as ether, cyclopropane and trichloroethylene, are used.
Diabetes & Hypoglycemia: β-blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia. Patients subject to spontaneous hypoglycemia, or diabetic patients receiving insulin or oral hypoglycemic agents should be cautioned about these possibilities and Carvedilol should be used with caution in such patients.
Thyrotoxicosis: β-adrenergic blockade may mask clinical signs of hyperthyroidism, such as tachycardia. Abrupt withdrawal of β-blockade may be followed by an exacerbation of the symptoms of hyperthyroidism or may precipitate thyroid storm.

PRECAUTIONS
Carvedilol should not be discontinued abruptly, particularly in patients with ischemic heart disease. The withdrawal should be gradual (over a period of two weeks).
Carevedilol may induce bradycardia. If patient's pulse rate drops below 55 beats/min., the dosage of Carvedilol should be reduced, as Carvedilol is reported to cause bradycardia.
Lower starting dose of Carvedilol should be used to decrease the likelihood of syncope or hypotension.
During initiation of therapy, the patient should be cautioned to avoid situations such as driving or hazardous tasks, where injury could result, to avoid the risk of syncope.
Rarely, use of Carvedilol in patients with congestive heart failure has resulted in deterioration of renal function. Worsening of cardiac failure or fluid retention may occur during up-titration of Carvedilol. If such symptoms occur, diuretics should be increased and the Carvedilol dose should not be advanced until clinical stability resumes.
In congestive heart failure patients with diabetes, Carvedilol therapy may lead to worsening hyperglycemia, which responds to intensification of hypoglycemic therapy. It is recommended that blood glucose should be monitored when Carvedilol dosing is initiated in such patients and the dose should be adjusted or the therapy should be discontinued if required.
Care should be taken in administering carvedilol to patients with history of serious hypersensitivity reactions, and in those undergoing desentisation therapy, as β-blockers may increase both the sensitivity towards allergens and seriousness of anaphylactic reactions.
Patients with history psoriasis associated with β-blocker therapy should take carvedilol only after consideration of the risk-benefit ratio.
Careful monitoring of ECG and blood pressure is necessary in patients receiving concomitant therapy with calcium channel blockers of the verapamil or diltiazem type or other antiarrhythmic drugs.
Caution should be taken in the administration of carvedilol to patients suspected of having pheochromocytoma.
Caution should be taken in the administration of carvedilol to patients suspected of having Prinzmetal's variant angina.
Wearers of contact lenses should bear in mind the possibility of reduced lacrimation.

PREGNANCY AND LACTATION
Carvedilol should be used in pregnant women or nursing mothers only if the potential benefits outweigh the potential risk. There is no adequate clinical experience with Carvedilol in pregnant women. Carvedilol is excreted in human milk.
Beta-blockers reduce placental perfusion, which may result in intrauterine fetal death, and immature and premature deliveries. In addition, adverse effects (especially hypoglycemia and bradycardia) may occur in fetus and neonate. There may be an increased risk of cardiac and pulmonary complications in the neonate in postnatal period. There is no evidence from animal studies that carvedilol has any teratogenic effects.

DRUG INTERACTIONS
Anesthetics: Hypotensive effects of carvedilol may be potentiated by general anesthetics, and anesthetic that cause myocardial depression such as ether, cyclopropane, and trichloroethylene should preferably be avoided.
Antiarrhythmics: Use of carvedilol with antiarrhythmic drugs and other drugs affecting cardiac conduction can precipitate bradycardia and heart block. Quinidine and carvedilol have negative inotropic action on the heart; bradycardia and hypotension have occured in patients given with carvedilol.
Antibacterials: Plasma concentration of Carvedilol may be reduced by rifampicin.
Antidepressants: Bradycardia and heart block , occurring shortly after starting fluoxetine therapy have been reported. Use of fluoxetine increased the plasma concentration of Carvedilol in patients with heart failure but no clinical effects were noted.
Antihypertensive: An enhanced antihypertensive effect is seen when other antihypertensives are given with betablockers. Carvedilol can potentiate the severe orthostatic hypotension that may follow the initial dose of alpha blockers prazosin and can exacerbate rebound hypertension following withdrawal of clonidine treatment.
Calcium Channel Blockers: Use of calcium channel blockers with beta blockers (Carvedilol) has resulted in hypotension, bradycardia, conduction defect, and heart failure.
Cardiac Glycosides: Carvedilol has been reported to increase plasma concentrations of digoxin.
Cyclosporin: Cyclosporin plasma concentrations increased when Carvedilol was added to treatment regimen. It is recommended that Cyclosporin concentrations should be monitored carefully if cycloprin and Carvedilol are used together.

ADVERSE EFFECTS
Carvedilol is generally well tolerated, partly because of the combined alpha and beta blocking properties of the molecule allow clinical efficacy to be attained with lower dosages than might be required if it were a single-action drug. The most frequently reported adverse events in patients being treated with carvedilol are related to its vasodilatory (postural hypotension, dizziness and headaches) and β-blocking (dyspnea, bronchospasm, bradycardia, malaise and asthenia) properties. Adverse events are generally more common early in therapy, are dosage-related and appear to have a lower incidence than is seen with pure β-blockade.
The adverse events reported frequently with carvedilol in clinical trials in patients with congestive heart failure were hyperuricemia, hypoglycemia, hyponatremia, increased alkaline phosphatase, glycosuria, somnolence, impotence, abnormal renal function, and albuminuria.
"For suspected adverse reaction, report to FDA: www.fda.gov.ph or to Torrent: www. torrentpharma.com".
Patient must seek medical attention immediately at the first sign of any adverse drug reaction shall appear.

OVERDOSAGE & TREATMENT
Signs and Symptoms of Intoxication
In the event of overdosage, there maybe severe hypotension, bradycardia, heart failure, cardiogenic shock and cardiac arrest. There may also be respiratory problems, bronchospasm, vomiting, disturbed, consciousness and generalized seizures.
Treatment of Intoxication
In addition to general procedures, vital parameters must be monitored and corrected, if necessary, under intensive care conditions. The following supportive therapies can be used:
Patients should be placed in the supine position.
Atropine: 0.5 to 2 mg i.v. (for excessive bradycardia).
Glucagon: initially 1 to 10 mg i.v. then 2 mg to 5 mg mg/hr as a long-term infusion (to support cardiovascular function).
Sympathomimetics according to body-weight and effect: dobutamine, isoprenaline, orciprenaline or adrenaline. If positive inotropic effect is required, phosphodiesterase inhibitors (PDE) e.g. Milrinone, should be considered.
If peripheral vasodilation dominates the intoxication profile then norfenephrine or noradrenaline should be administered with continuous monitoring of circulatory conditions.
In the case of drug-resistant bradycardia, pacemaker therapy should be initiated.
Treatment of bronchospasm
For bronchospasm, β-sympathomimetics (as aerosol or i.v) or aminophylline i.v should be given
Treatment of seizures
In the event of seizures, slow i.v. injection of diazepam or clonazepam is recommended.
Important note
In cases of severe intoxication with shock, supportive treatment must be continued for sufficiently long period, as a prolongation of elimination half-life and redistribution of carvedilol from deeper compartments are to be expected. The duration of supportive / antidote therapy depends on the severity of the overdosage. The supportive treatment should therefore be continued until the patients condition has stabilized.

STORAGE CONDITION
Store at temperatures not exceeding 30°C.

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

AVAILABILITY
Carvedilol (Karvil 6.25) 6.25 mg Tablet - Alu-Alu Blister Pack x 15's (Box of 15's) - DRP - 2702
Carvedilol (Karvil 12.5) 12.5 mg Tablet - Alu-Alu Blister Pack x 15's (Box of 15's) - DRP - 2699
Carvedilol (Karvil 25) 25 mg Tablet - Alu-Alu Blister Pack x 10's (Box of 30's) - DRP - 4024

DATE OF FIRST AUTHORIZATION
Karvil 6.25 and Karvil 12.5: November 16 ,2006
Karvil 25 : September 21, 2011

DATE OF REVISION
November 2017

torrent PHARMA

Manufactured by :
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