

## **PRESENTATION**

**Duroil<sup>®</sup> 6.25** Tablet: Each film coated tablet contains Carvedilol INN 6.25 mg.

**Duroil<sup>®</sup> 12.5** Tablet: Each film coated tablet contains Carvedilol INN 12.5 mg.

**Duroil<sup>®</sup> 25** Tablet: Each film coated tablet contains Carvedilol INN 25 mg.

## **PHARMACOLOGY**

Carvedilol is a racemic mixture in which nonselective  $\beta$ -adrenoreceptor blocking activity is present in the S(-) enantiomer and  $\alpha$ -adrenergic blocking activity is present in both R(+) and S(-) enantiomers at equal potency. Carvedilol has no intrinsic sympathomimetic activity.

## **PHARMACOKINETIC**

Carvedilol is rapidly and extensively absorbed following oral administration, with absolute bioavailability of approximately 25% to 35% due to a significant degree of first-pass metabolism. Following oral administration, the apparent mean terminal elimination half-life of carvedilol generally ranges from 7 to 10 hours. Plasma concentrations achieved are proportional to the oral dose administered. When administered with food, the rate of absorption is slowed, as evidenced by a delay in the time to reach peak plasma levels, with no significant difference in extent of bioavailability. Taking carvedilol with food should minimize the risk of orthostatic hypotension.

Carvedilol is extensively metabolized. Following oral administration less than 2% of the dose was excreted unchanged in the urine. Carvedilol is metabolized primarily by aromatic ring oxidation and glucuronidation. The oxidative metabolites are further metabolized by conjugation via glucuronidation and sulfation. The metabolites of carvedilol are excreted primarily via the bile into the faeces. Demethylation and hydroxylation at the phenol ring produce three active metabolites with  $\beta$ -receptor blocking activity. Based on preclinical studies, the 4-hydroxyphenyl metabolite is approximately 13 times more potent than carvedilol for  $\beta$ -blockade.

Compared to carvedilol, the three active metabolites exhibit weak vasodilating activity. Plasma concentrations of the active metabolites are about one-tenth of those observed for carvedilol and have pharmacokinetics similar to the parent compound.

Carvedilol undergoes stereoselective first-pass metabolism with plasma levels of R(+)-carvedilol approximately 2 to 3 times higher than S(-)-carvedilol following oral administration in healthy subjects. The mean apparent terminal elimination half-lives for R(+)-carvedilol range from 5 to 9 hours compared with 7 to 11 hours for the S(-)-enantiomer. Carvedilol is more than 96% bound to plasma proteins, primarily with albumin. The plasma-protein binding is independent of concentration over the therapeutic range. Carvedilol is a basic, lipophilic compound with a steady state volume of distribution of approximately 115 L, indicating substantial distribution into extravascular tissues. Plasma clearance ranges from 500 to 700 mL/min.

## **INDICATIONS AND USES**

*Congestive Heart Failure:* Carvedilol is indicated for the treatment of mild or moderate heart failure of ischemic or cardiomyopathic origin, in conjunction with digitalis, diuretics and ACE inhibitors, to reduce the progression of disease as evidenced by cardiovascular death, cardiovascular hospitalization, or the need to adjust other heart failure medications.

Carvedilol may be used in patients unable to tolerate an ACE inhibitor. Carvedilol may be used in patients who are or are not receiving digitalis, hydralazine or nitrate therapy.

*Hypertension:* Carvedilol is also indicated for the management of essential hypertension. It can be used alone or in combination with other antihypertensive agents especially with thiazide type diuretics.

### **DOSAGE AND ADMINISTRATION**

*Hypertension:* Initially 12.5 mg once daily, increased after 2 days to usual dose of 25 mg once daily; if necessary may be further increased at intervals of at least 2 weeks to max.50 mg daily in single or divided doses; *Elderly:* Initial dose of 12.5 mg daily may provide satisfactory control.

*Angina:* Initially 12.5 mg twice daily, increased after 2 days to 25 mg twice daily.

*Heart failure (under special supervision):* Initially 3.125 mg twice daily (with food), dose increased at intervals of at least 2 weeks to 6.25 mg twice daily, then to 12.5 mg twice daily, then to 25 mg twice daily, increase to highest dose tolerated, max. 25 mg twice daily in patients with severe heart failure or body-weight less than 85 kg and 50 mg twice daily in patients over 85 kg.

### **CONTRAINDICATION**

Carvedilol is contraindicated in patients with severe chronic 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.

### **SIDE EFFECT**

In general carvedilol is well tolerated at doses up to 50 mg daily. Most adverse events reported were of mild to moderate. These are postural hypotension, dizziness, headache, fatigue, gastro-intestinal disturbances, bradycardia, occasionally diminished peripheral circulation, peripheral oedema and painful extremities, dry mouth, dry eyes, eye irritation or disturbed vision, impotence, disturbances of micturition, influenza like symptoms, rarely angina. AV block exacerbation of intermittent claudication or Raynaud's phenomenon; allergic skin reactions, exacerbation of psoriasis, nasal stuffiness, wheezing, depressed mood, sleep disturbances, paraesthesia, heart failure, changes in liver enzymes, thrombocytopenia, leucopenia also reported.

### **WARNING**

Monitoring: At the first symptoms/sign of liver dysfunction (e.g., pruritus, dark urine, persistent anorexia, jaundice, right upper quadrant tenderness, unexplained "flu-like" symptoms) laboratory testing should be performed. If the patient has laboratory evidence of liver injury or jaundice, therapy should be stopped and should not be restarted.

Cardiovascular effects: Because carvedilol has  $\beta$ -blocking activity, it should not be discontinued abruptly, particularly in patients with ischemic heart disease. Instead of, Carvedilol should be discontinued over 1 or 2 weeks.

In clinical trials, carvedilol caused bradycardia in 2% of hypertensive patients and 9% of CHF patients. If pulse rate drops < 55 beats/min, dose should be reduced.

To decrease the likelihood of excessive hypotension, treatment should be initiated with 3.125 mg twice/day for CHF patients and a 6.25 mg twice/day for hypertensive patients. Dosage should be increased slowly, and the drug should always be taken with food. During initiation of therapy, caution the patient to avoid situations such as driving or hazardous tasks where injury could result.

Bronchospasm, nonallergic (e.g., chronic bronchitis, emphysema): Patients with bronchospastic disease should, in general, not receive  $\beta$ -blockers. Carvedilol may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if carvedilol is used, to use the smallest effective dose so that inhibition of endogenous or exogenous  $\beta$ -agonists minimised.

### **DRUG INTERACTION**

Drug interactions have been seen with co-administration of carvedilol and digoxin, resulting in an increased bioavailability of digoxin. This increase is not clinically significant and does not correlate with pharmacologic response. Pharmacokinetics studies demonstrated a lack of drug interaction between carvedilol and hydrochlorothiazide, cimetidine, torsemide and warfarin.

### **USE IN PREGNANCY AND LACTATION**

There is no evidence from animal studies that carvedilol has any teratogenic effects. Embryotoxicity was observed only after large doses in rabbits. The relevance of these findings for humans is uncertain. Animal studies have showed that carvedilol crosses the placental barrier and is excreted in breast milk and therefore the possible consequences of alpha and beta blockade in the human foetus and neonate should be borne in mind. With other alpha and beta blocking agents effects have included perinatal and neonatal distress (bradycardia, hypotension, respiratory depression, hypoglycaemia, hypothermia). Carvedilol is therefore not recommended for use in pregnancy or in breast-feeding mothers.

### **USE IN PAEDIATRIC PATIENT**

The safety and efficacy of carvedilol in paediatric patients have not been established.

### **STORAGE CONDITION**

Store in a cool and dry place. Protect from light and moisture.

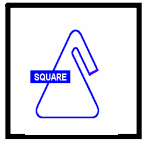
## **HOW SUPPLIED**

**Duroi<sup>®</sup> 6.25** tablet: Each box contains 3x10 tablets in blister pack.

**Duroi<sup>®</sup> 12.5** tablet: Each box contains 3x10 tablets in blister pack.

**Duroi<sup>®</sup> 25** tablet: Each box contains 3x10 tablets in blister pack.

® Registered Trade Mark



***SQUARE  
PHARMACEUTICALS LTD.  
BANGLADESH***