SUMMARY OF PRODUCT CHARACTERISTICS / PACKAGE INSERT

1. NAME OF MEDICINAL PRODUCT

Trade Name: Torvedol 6.25
Generic Name: Carvedilol Tablets USP 6.25 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Torvedol 6.25
Carvedilol Tablets USP 6.25 mg
Each uncoated tablet contains:

Carvedilol Ph. Eur. …….. 6.25 mg
Excipients……. q.s.

For Excipients , See 6.1

3. PHARMACEUTICAL FORM

Uncoated tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Congestive Heart failure
Carvedilol is indicated for the treatment of mild or moderate (NYHA class II or III) heart failure of ischemic or cardiomyopathic origin, in conjuction with digitalis, diuretics, and ACE inhibitor, to reduce the progression of disease as evidencesd by cardiovascular death, cardiovascular hospitalization, or the need to adjust other heart failure medications. Carvedilol may be used concurrently in patients receiving digitalis hydralazine or nitrate therapy.

4.2 Posology and method of administration

Congestive heart failure
The recommended stating dose of carvedilol is 3.125 mg twice daily or two weeks. If this dose is tolerated, it can then be increased to 6.25 mg twice daily. Dosing should then be doubled every 2 weeks to the highest dose tolerated by the patient. At initiation of each new dose, patients should be observed for signs of dizziness or light-headedness. The maximum recommended dose is 25 mg twice daily in patients weighing less than 85 kg (187 lbs) and 50 mg twice daily in patients weighing more than 85 kg. Carvedilol should be taken with food to slow the rate of absorption and reduce the incidence of orthostatic effects.

If congestive heart failure patients experience bradycardia (pulse rate below 55 beats/min), the dose should be reduced.
Mode of Administration: Oral

4.3 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.

4.4 Special warnings and precautions

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.

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.
If 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.
Plasma levels of Carvedilol average about 50% higher in the elderly compared to young subjects.
Compared to healthy subjects, patients with cirrhotic liver disease exhibit significantly higher concentrations of Carvedilol (approximately 4- to 7-fold) following single-dose therapy.
Although Carvedilol is metabolized primarily by the liver, plasma concentrations of Carvedilol have been reported to be increased by 40% to 50% in patients with moderate to severe renal impairment. However, the ranges of AUC values were similar for both groups.

4.5 Interactions with other medicinal products and other forms of interactions

Since Carvedilol undergoes substantial oxidative metabolism, the metabolism and pharmacokinetics of Carvedilol may be affected by induction or inhibition of cytochrome P450 enzymes. Rifampicin decreased the AUC and C_{max} of Carvedilol by about 70%. Cimetidine increased the steady-state AUC of Carvedilol by 30% with no change in C_{max}.
Following concomitant administration of Carvedilol (25 mg once daily) and digoxin, steady-state AUC and trough concentrations of digoxin were increased by 14% and 16%, respectively.
Carvedilol (12.5 mg twice daily) did not have any effect on the steady-state prothrombin time ratios and the pharmacokinetics of R (+) and S (-) warfarin following concomitant administration with warfarin.

4.6 Pregnancy, lactation and children

There are no adequate and well-controlled studies on Carvedilol in pregnant women. It is not known whether Carvedilol is excreted in human milk. Carvedilol should be used in pregnant women or nursing mothers only if the potential benefits outweigh the potential risk.

Pediatric Use
Safety and efficacy of Carvedilol in patients younger than 18 years of age have not been established

4.7 Effects on ability to drive and use machines

No studies of the effects on ability to drive and use machines have been performed.

As for other drugs which produce changes in blood pressure, patients taking Carvedilol should be warned not to drive or operate machinery if they experience dizziness or related symptoms. This applies particularly when starting or changing treatment and in conjunction with alcohol.

4.8 Undesirable effects

Carvedilol is generally well tolerated, partly because the combined α- and β-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 (dyspnoea, bronchospasm, bradycardia, malaise and asthenia) properties. Adverse events 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.

4.9 Overdose

Overdosage with Carvedilol may cause severe hypotension, bradycardia, cardiac insufficiency, cardiogenic shock and cardiac arrest. Respiratory problems, bronchospasm, vomiting, lapses of consciousness and generalized seizures may also occur.
The patient should be placed in a supine position and where necessary, kept under observation and treated under intensive-care conditions. Gastric lavage or pharmacologically induced emesis may be used shortly after ingestion.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacological properties:

Pharmacodynamics:
Carvedilol reduces systolic and diastolic blood pressure acutely, primarily by decreasing total peripheral resistance. Cardiac function is generally preserved and heart rate is either unchanged or decreased slightly.
Carvedilol is a β-adrenoceptor antagonist with weak selectivity for β_1-adrenoceptors Antagonism of β_1- adrenoceptor-mediated responses with Carvedilol is similar in potency, but longer lasting (15 to 16 hours) than that of propranolol (12 hours) and much better in both potency and duration of effect than that of labetalol (1.5 hours). Carvedilol also antagonises β_2-adrenoceptors but to a lesser extent. Carvedilol exerts its vasodilating activity primarily via antagonism of peripheral α_1-adrenoceptors. At concentrations higher than those needed to antagonise β-adrenoceptor, Carvedilol may act as a calcium channel blocker. This activity may be important in regional vascular beds, such as the cutaneous circulation, where Carvedilol (unlike other vasodilators and β-adrenoceptor antagonists) has a potent vasodilator effect. Carvedilol exhibits no intrinsic sympathomimetic/partial agonist activity and only weak membrane-stabilising (local anesthetic) activity.
Carvedilol 50mg not only attenuated the vasoconstrictive effect of noradrenaline (norepinephrine) on human hand veins, but also decreased the effect of prostaglandin $F_{2\alpha}$, a noradrenergic vasoconstrictor. In addition, the relatively weak occupancy of α-adrenoceptors by Carvedilol cannot fully explain the effective inhibition of prostaglandin $F_{2\alpha}$ - induced vasoconstriction in human hand veins in vivo when compared with the α-blocker, prazosin, again indicating another mechanism of vasodilation.

The mechanisms underlying the cardioprotective effects of Carvedilol have not been fully established but it seems clear that the antioxidant and antiproliferative effects demonstrated in vitro might be contributing factors. Although further studies are needed to confirm the findings of in vitro and in vivo studies in the clinical setting, there is no doubt that the β-blockade and vasodilation, along with the reduction in oxygen consumption, play a considerable role in the cardioprotective effects demonstrated in different experimental models.

Haemodynamic Effects

Oral Carvedilol 12.5 to 200mg reduced resting systolic blood pressure (SBP) and diastolic blood pressure (DBP) by 5 to 46% with little or no reflex tachycardia in healthy volunteers.

Single oral doses of Carvedilol 12.5 to 50mg has been shown to significantly reduce resting DBP and SBP in patients with mild to moderate essential hypertension Measurable decrease in blood pressure was observed within 1 hour when Carvedilol was administered in the dose of 12.5, 25 and 50 mg in patients with mild to moderate hypertension. Peak decreases in supine DBP were found to be 9, 15.5, 14.7 & 22.5 mm Hg for placebo, 12.5, 25 & 50 mg Carvedilol respectively and occurred within 3 & 7 hours after the dose. Once daily administration was found to keep supine DBP below baseline levels for 24 hours. SBP was also reduced but there was no substantial difference among the groups administered placebo and Carvedilol 12.5 and 25 mg. There was a marked decrease in supine SBP after the 50 mg dosage. Changes in standing DBP and SBP followed a pattern similar to the changes in supine pressures. Intra-arterial ambulatory blood pressure monitoring showed significant reductions in SBP, starting 30 minutes after a single 25mg dose in 12 patients with mild to moderate essential hypertension. A maximum SBP/DBP reduction of 30/18mm Hg was reported after 90 minutes and was maintained for 2 hours.

Carvedilol also attenuates exercise-induced increases in SBP and heart rate in healthy volunteers and patients with essential hypertension. Relative to baseline, SBP was reduced by 8.9% at rest and by 9% during exercise, and heart rate was reduced by 10.8% at rest and by 11.1% during exercise.

Carvedilol due to its α and β-blocking properties, balances between peripheral vasodilatation (α-blocking) and peripheral vasoconstriction (β-blocking) with the result of no change in after load unlike other β-blockers which by increasing peripheral vascular resistance increases after load.

Stroke index and cardiac index were preserved after single oral doses of Carvedilol (20 to 60mg) in healthy volunteers. Long-term administration of Carvedilol 25 mg/day for 6 to 9 months in patients with hypertension significantly reduced cardiac index by 12% (supine), 17% (sitting) and 12% (after exercise). After 1 year, cardiac index was reduced overall by 5% (not significant). Under resting conditions, acute administrations of Carvedilol neither affects pulmonary capillary wedge pressure nor mean pulmonary artery pressure, which are the indicators of cardiac preload. However, Carvedilol tends to reduce pulmonary capillary wedge pressure during exercise, unlike propranolol, which increases it. This effect may be related to the vasodilatory activity of Carvedilol.

Effect on Heart rate

The effect of chronic administration of Carvedilol on heart rate in patients with essential hypertension shows reduction of heart rate by a mean of 22 beats/min. and 7 beats/min. during daytime and at night, respectively in essential hypertensives with a tachycardic heart rate under control conditions. This confirms that under clinical conditions Carvedilol is devoid of intrinsic sympathomimetic activity.

Peripheral Vascular Circulation
The antihypertensive action of Carvedilol is accompanied by a pronounced fall in total peripheral resistance in healthy volunteers; a decrease of about 34% was reported after a single 50mg dose which remained evident 1 week later with continued dosing . Digital plethysmography revealed Carvedilol-induced peripheral vasodilation following a threshold oral dose of 15mg with a linear increase in response (r = 0.78) up to 75mg. Vasodilation was observed 30 minutes after administration and persisted for up to 3 hours. A significant increase in arterial blood flow (maximum 156% of baseline) and a decrease in peripheral (forearm) resistance (maximum 34%), which peaked after 4.5 hours and persisted for the entire 6-hour testing period, were observed in healthy volunteers after a single oral 75mg dose. Neither metipranolol 7mg nor Carvedilol 50mg affected venous capacity or tone. Other studies have confirmed a decrease in forearm arterial resistance following administration of Carvedilol 50mg in patients with essential hypertension.
Auto regulation of cerebral blood flow appears to be unchanged in hypertensive patients treated with Carvedilol 25mg despite a marked reduction in mean arterial blood pressure.
In spite of a marked reduction in renal perfusion pressure, renal blood flow was unchanged after single or multiple doses of Carvedilol 50mg. Renal vascular resistance was decreased and auto regulation of renal blood flow was preserved. A small but statistically significant decrease in glomerular filtration rate (8%) and filtration fraction (10%) occurred in hypertensive patients after a single 50mg dose; glomerular filtration rate was, however, preserved during 4 weeks of treatment with Carvedilol.

Myocardial function
Carvedilol significantly improved myocardial function in patients with chronic heart failure caused by left ventricular dysfunction.
In particular, reductions in after load (improvement in left ventricular ejection fraction) with no deleterious effect on left ventricular end diastolic volume have been noted. In fact, in a study involving 81 eligible patients with heart failure associated with ischemic heart disease or idiopathic dilated myopathy, echocardiography after 12 months of Carvedilol (mean 43 mg/day) or placebo therapy revealed decreased left ventricular volumes and prevention of progressive left ventricular dilation in Carvedilol recipient.

Left ventricular hypertrophy
Regression of left ventricular hypertrophy (reduced wall thickness and left ventricular mass index) has been reported after treatment with Carvedilol in patients with mild to moderate essential hypertension. Septal wall thickness was reduced from 17.7 to 16.3mm ($P<0.05$) after 6 months' treatment with Carvedilol 25 mg/day in 17 patients.

Antiproliferative effect
The antiproliferative effect of Carvedilol was examined in human vascular smooth muscle cells (VSMC). Carvedilol was found to inhibit the increase in cell number induced by foetal calf serum in 86% of human VSMC grown both from saphenous vein (17.6 ± 3.5% inhibition) and restenotic lesions (31.4 ± 5.5%) Carvedilol was found to have greater antiproliferative effect than other β adrenoceptor antagonists and comparable effect to that of Ca^{2+} channel blockers. However, the antiproliferative effect of Carvedilol on human VSMC in vitro was found to occur at concentrations higher then those in plasma. Carvedilol was also shown to inhibit proliferation (induced by PDGF, angiotensin II etc.) of smooth muscle cells and mitogenesis in in-vitro studies. In contrast to celiprolol, sotalol and labetalol. Further more, the inhibition of neointima proliferation resulted in 84% reduction in restenosis following PTCA in an experimental study in animals.

Cardioprotective and Neuroprotective effects

Two weeks' pretreatment with Carvedilol 25 mg/day significantly ($p<0.05$ vs placebo) reduced the increase in rate-pressure product and abolished the increase in QT_c duration seen after infusion of epinephrine 0.5 μg/kg in healthy volunteers.

It has been suggested that damage caused by oxidizing free radicals (molecules that carry one or more unpaired electrons) may be a factor in the pathophysiology of disease states related to congestive heart failure (arrhythmias, atherosclerosis, ischaemia and myocardial infarction). The reaction of free radicals with major constituent molecules of cells can lead to disruption of biological systems and even cell death. Lipoproteins and polyunsaturated fatty acids within cell membranes are especially vulnerable to attack from free radicals and the oxidation of lipoproteins by free radicals may be a cause of atherosclerosis.

Carvedilol has been shown to confer protection against free radical damage in a number of in vitro human and animal models of lipoprotein oxidation and injury to endothelial cells. Dose-dependent inhibition of oxygen radical-induced lipid peroxidation [50% inhibition (IC_{50}) at 2.6 μmol/L (1.1 mg/L)] and glutathione depletion [IC_{50} 1.8 μmol/L (0.7 mg/L)] was seen when bovine endothelial cells were incubated with Carvedilol. Under the same experimental conditions, celiprolol, atenolol, pindolol or propranolol showed little or no cytoprotective effect. Similarly, in an in-vivo study after administration of Carvedilol 25 mg/day to hypertensive patients for 4 months, resistance to oxidation of low-density lipoprotein (LDL) was markedly increased versus that in non-hypertensive controls. LDL oxidation parameters were not ameliorated in a control group of matched hypertensive patients who received calcium channel blockers or ACE inhibitors at conventional dosages.

Scavenging cells such as macrophages and neutrophils may be a natural source of free radicals. Carvedilol reduced the number of free radicals produced by human neutrophils. The protective effect of Carvedilol against free radicals described in the animal models occurs at higher concentrations than peak plasma concentrations of Carvedilol observed in human pharmacokinetic studies. Interestingly, a metabolite of Carvedilol, SB209995 (which has a hydroxyl group at position 1 of the carbazole moiety of Carvedilol), was found to have 10 to 64 times greater antioxidant potency than its parent compound. However, the peak plasma concentration of this metabolite in humans has not been determined. It is possible that Carvedilol provides cardio- and neuroprotection through is antioxidant activity, but these effects remain to be confirmed.

5.2. Pharmacokinetic properties

Absorption and Distribution

Carvedilol is rapidly absorbed after a single oral dose with maximum plasma concentration (C_{max}) achieved within 1 to 2 hours (t_{max}) in healthy volunteers and hypertensive patients. Peak plasma concentrations of Carvedilol increased linearly with dose and absorption was not altered after repeated doses. Furthermore, there was no accumulation of Carvedilol during multiple dose administration, as indicated by similar mean area under the plasma concentration-time curve (AUC) values compared with single dose administration.

Although the rate of absorption was decreased slightly when Carvedilol was taken with food (t_{max} increased from 0.97 to 1.3h), the extent of absorption was unaffected, as shown by unchanged AUC and C_{max} values.

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 [Fujimaki et al. 1990a] 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. About 60% of the metabolites excreted into bile are eliminated in faeces with urinary recovery accounting for 16% of metabolites.
In hypertensive patients, the terminal phase elimination half-life of Carvedilol after oral administration ranges from about 2 to 8 hours and was about 2 to 5 hours in elderly (aged > 65 years) hypertensive patients. Three-compartmental analysis revealed a prolonged apparent terminal elimination half-life of up to 14.5 hours after intravenous administration.

Pharmacokinetic Profile in Patients with Hepatic disease
Since Carvedilol undergoes extensive first-pass hepatic metabolism, it is reasonable to expect that its pharmacokinetic profile wound be altered in patients with hepatic impairment. Compared with healthy volunteers, patients with cirrhosis showed a 36% decrease (36.5 vs 23.3 L/h) in plasma clearance and a 280% increase in steady-state volume of distribution (125 vs 321 L/h). In these patients, a significant increase in C_{max} (104.3 vs 23.7 L/h) and bioavailability (82.6 vs. 18.6%) was observed compared with healthy volunteers but elimination half-life was unaltered.

Pharmacokinetic Profile in Patients with renal impairment
As Carvedilol is eliminated primarily in faeces, renal impairment would not be expected to necessitate dosage adjustment. Indeed, in hypertensive patients with chronic renal failure, peak plasma concentrations and elimination half-life of Carvedilol were not significantly altered compared with values obtained in healthy volunteers. In addition, the pharmacokinetics of Carvedilol was not altered in hypertensive patients with severe chronic renal failure who were undergoing dialysis.

Pharmacokinetic Profile in elderly Patients
The pharmacokinetics of single dose of Carvedilol was not significantly changed in elderly hypertensive patients (aged 64 to 79 years) compared with their younger counterparts, with a tendency towards increased peak plasma concentrations and AUC values in elderly patients.

5.3 Preclinical safety data

Acute Toxicity

LD_{50} of Carvedilol was found to be greater than 8000 mg/kg when given orally in both male and female mice and rats. When given intravenously LD_{50} was found to be 36 mg/kg and 27 mg/kg in female and male mice respectively and 25 mg/kg and 27 mg/kg in female and male rats respectively. Intraperitoneal administration of Carvedilol gave LD_{50} value of 364 mg/kg and 568 mg/kg in female and male mice and 769 mg/kg and 1244 mg/kg in female and male rats respectively.

Chronic toxicity

No evidence for substance-related toxic effects was observed in chronic toxicity studies carried out in rats and dogs.

Reproduction toxicity

In studies investigating the toxicity of Carvedilol for embryos in rats, 60 mg/kg/day were slightly and 300 mg/kg/day were severely toxic for the adult animal. At this high dose (300 mg/kg/day), embryotoxic and foetotoxic effects were observed (increased numbers of resorptions, reduced number of successful matings, decrease in foetal weight). In rabbits at 75 mg/kg/day, a slight increase in intra-uterine resorption was observed. In studies, investigating the peri- and postnatal toxicity in rats at 60 mg/kg/day reduced foetal weight and delayed physical development of the F_1-generation was observed. At the toxic dose of 300 mg/kg/day for the adult rat the fertility showed the following changes: prolonged mating time, reduced number of successful matings, significantly fewer corpora lutea, implants per dam and decrease in foetal weight.
In rats it was shown, that Carvedilol is excreted through the mother's milk.
No experience has been gained for the use of Carvedilol during pregnancy and the lactation period.

Teratogenicity

In studies investigating the toxicity of Carvedilol for embryos in rats, 60 mg/kg/day were slightly and 300 mg/kg/day were severely toxic for the adult animal. At this high dose (300 mg/kg/day), embryotoxic and foetotoxic effects were observed (increased numbers of resorptions, reduced number of successful matings, decrease in foetal weight). In rabbits at 75 mg/kg/day, a slight increase in intra-uterine resorption was observed. In studies, investigating the peri- and postnatal toxicity in rats at 60 mg/kg/day reduced foetal weight and delayed physical development of the F_1-generation was observed. At the toxic dose of 300 mg/kg/day for the adult rat the fertility showed the following changes: prolonged mating time, reduced number of successful matings, significantly fewer corpora lutea, implants per dam and decrease in foetal weight.
In rats it was shown, that Carvedilol is excreted through the mother's milk.
No experience has been gained for the use of Carvedilol during pregnancy and the lactation period.

Mutagenicity

No mutagenic effects of Carvedilol were seen in vitro and in vivo.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Lactose monohydrate USP-NF
Sucrose (Pharma grade) USP-NF
Polyvinyl pyrrolidone (K-30) USP
Crospovidone XL-10 USP-NF
Magnesium Stearate USP-NF
Colloidal Silicon dioxide USP-NF

6.2 Incompatibilities

None

6.3 Shelf – life

3 years

6.4 Special precautions for storage

Store below 30° C.

6.5 Nature and contents of container

Carvedilol tablets are packed in Alu -Alu blister packs of 15 tablets.

6.6 Instruction for use and handling <and disposal>

No special requirements

7.1. NAME AND ADDRESS OF MANUFACTURER

Torrent Pharmaceuticals Ltd.,
"Torrent House",
Off Ashram Road,
Ahmedabad – 380 009
INDIA.
Tel. No. : 91-79-6583060 / 6585090
Fax. No. : 91-79-6582100

7.2 NAME AND ADDRESS OF PRINCIPAL

NOT APPLICABLE

8. REGISTRATION NUMBER

NOT APPLICABLE

9. CATEGORY FOR DISTRIBUTION

PRESCRIPTION ONLY MEDICINES

10. DATE OF PUBLICATION OF THIS PACKAGE INSERT

NOT APPLICABLE