CASLOT TABLETS
(CARVEDILOL TABLETS)

COMPOSITION

CASLOT 6.25 mg

Each tablet contains
Carvedilol ……6.25 mg

CASLOT 12.5 mg

Each tablet contains
Carvedilol ……12.5 mg

CASLOT 25 mg

Each tablet contains
Carvedilol……25.0 mg

PRODUCT DESCRIPTION

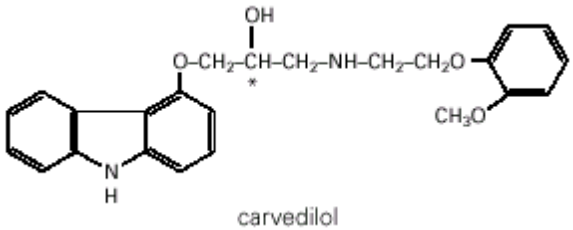
CASLOT 6.25 mg : Yellow coloured, circular, biconvex, uncoated mottled tablets with a score-line on one side and plain on the other.

CASLOT 12.5 mg : Peach coloured, circular, biconvex, uncoated mottled tablets with a score-line on one side and plain on the other.

CASLOT 25 mg : White to off-white, circular, biconvex, uncoated mottled tablets with a score-line on one side and plain on the other.

DESCRIPTION

Carvedilol is a nonselective β-adrenergic blocking agent with α_1-blocking activity. It is chemically designated as (±)-1-Carbazol-4-yloxy-3-[[2-(o-methoxyphenoxy)ethyl]amino]-propan-2-ol. The molecular formula for carvedilol is $C_{24}H_{26}N_2O_4$ and its molecular weight is 406.5.



carvedilol

CARVEDILOL

PHARMACOLOGY

Mechanism of Action

Carvedilol is a vasodilating non-selective β-blocking agent with antioxidant properties. Vasodilation is predominantly mediated through α_1-receptor antagonism. Carvedilol reduces the peripheral vascular resistance through vasodilation and suppresses the renin-angiotensin-aldosterone system through β-blockade. The activity of plasma renin is reduced and fluid retention is rare. Carvedilol has no intrinsic sympathomimetic activity and like propranolol, it has membrane stabilising properties. Carvedilol is a racemate of two stereoisomers. β-blockade is attributed to the S(-) enantiomer; in contrast, both enantiomers exhibit the same α_1-blocking activity. Carvedilol is a potent antioxidant, a scavenger of reactive oxygen radicals and an anti-proliferative agent.

Reported clinical studies have shown that the balance of vasodilation and β-blockade provided by carvedilol results in the following effects:

− In hypertensive patients, a reduction in blood pressure is not associated with a concomitant increase in total peripheral resistance, as observed with pure β-blocking agents. Heart rate is slightly decreased. Renal blood flow and renal function are maintained. Peripheral blood flow is maintained, therefore, cold extremities, often observed with drugs possessing β-blocking activity, are rarely seen.

− In patients with stable angina, carvedilol has demonstrated anti-ischaemic and anti-anginal properties. Acute haemodynamic studies demonstrated that carvedilol reduces ventricular pre- and after-load.

− In patients with left ventricular dysfunction or chronic heart failure, carvedilol has demonstrated favourable effects on haemodynamics and improvements in left ventricular ejection fraction and dimensions.

Pharmacokinetics

Carvedilol is a substrate of the intestinal efflux transporter P-glycoprotein which plays a major role in the bioavailability of certain drugs. The absolute bioavailability of carvedilol is approximately 25% in humans. Bioavailability is

stereo-selective, 30% for the R-form and 15% for the S-form. Serum levels peak at approximately 1 hour after an oral dose. There is a linear relationship between the dose and serum concentrations. Food does not affect bioavailability or the maximum serum concentration although the time to reach maximum serum concentration is delayed. Carvedilol is highly lipophilic, approximately 98% to 99% is bound to plasma proteins. The distribution volume is approximately 2 l/kg and increased in patients with liver cirrhosis. The first pass effect after oral administration is approximately 60 - 75%; enterohepatic circulation of the parent substance has been reported in animals.

The oxidative metabolism of carvedilol is stereoselective. The R-enantiomer is predominantly metabolized by CYP2D6 and CYP1A2, while the S-enantiomer is mainly metabolised by CYP2C9 and to a lesser extent by CYP2D6. Other CYP450 isoenzymes involved in the metabolism of carvedilol include CYP3A4, CYP2E1 and CYP2C19. The maximal plasma concentration of R-carvedilol is approximately 2 fold higher than that S-carvedilol. The R-enantiomer is predominantly metabolised through hydroxylation. In slow metabolisers of CYP2D6 an increase of the plasma concentration of carvedilol, mainly the R-enantiomer may occur, leading to an increase in the alpha-blocking activity. Demethylation and hydroxylation at the phenol ring produce 3 metabolites with beta-receptor blocking activity.

The average elimination half-life ranges from 6 to 10 hours. Plasma clearance is approximately 590ml/min. Elimination is mainly biliary. The primary route of excretion is via the faeces. A minor portion is eliminated via the kidneys in the form of various metabolites.

The pharmacokinetics of carvedilol are affected by age; plasma levels of carvedilol are approximately 50% higher in the elderly compared to young subjects.

In a reported study in patients with cirrhotic liver disease, the bioavailability of carvedilol was four times greater and the peak plasma level five times higher than in healthy subjects.

Since carvedilol is primarily excreted via the faeces, significant accumulation in patients with renal impairment is unlikely. In patients with impaired liver function, bioavailability is raised to as much as 80% due to a reduced first pass effect.

The pharmacokinetics of R-and S-carvedilol is significantly altered by heart failure. The clearance of R-and S-carvedilol was significantly lower in patients with heart failure than in healthy volunteers.

INDICATIONS

Hypertension
CASLOT is indicated primarily for the management of essential hypertension. It can be used alone or in combination with other antihypertensive agents (e.g. calcium channel blockers, diuretics).

Angina
CASLOT is indicated for the treatment of angina pectoris.

Chronic Heart Failure
Unless a contraindication exists carvedilol is indicated for the treatment of all patients with stable and symptomatic mild, moderate and severe chronic heart failure of ischaemic or non-ischaemic etiology in combination with standard therapies including ACE inhibitors and diuretics with or without digitalis.

DOSAGE AND ADMINISTRATION

Method of Administration
The tablets are to be swallowed with sufficient fluid. **CASLOT** should be given with food.

Duration of Treatment
Treatment with **Caslot** is a long-term therapy. Treatment should not be stopped abruptly but rather gradually reduced at weekly intervals. This is particularly important in the case of patients with concomitant coronary heart disease.

Essential hypertension
The recommended dose for initiation of therapy is 12.5 mg once a day for the first two days. Thereafter the recommended dosage is 25 mg once a day. If necessary, the dosage may subsequently be increased at intervals of at least two weeks to the recommended maximum daily dose of 50 mg, given once a day or in divided doses (twice daily).

Angina pectoris
The recommended dose for initiation of therapy is 12.5 mg twice a day for the first 2 days. Thereafter the recommended dosage is 25 mg twice a day. If necessary, the dosage may subsequently be increased at intervals of at least two weeks up to the recommended maximum daily dose of 100 mg given in divided doses (twice daily).

Symptomatic stable chronic heart failure
Dosage must be tailored to suit the individual, and closely monitored by a physician during up-titration. For those patients receiving digitalis, diuretics and

ACE inhibitors, dosing of these medicines should be stabilised prior to initiation of **CASLOT** treatment.

The recommended dose for initiation of therapy is 3.125 mg twice daily for two weeks. If this dose is tolerated, the dose may thereafter be increased, at intervals of not less than two weeks, to 6.25 mg, 12.5 mg and 25 mg twice daily. Doses should be increased to the highest level tolerated by the patient. The maximum recommended dose is 25 mg twice daily for all patients with severe CHF and for patients with mild to moderate CHF weighing less than 85 kg. In patients with mild to moderate CHF weighing more than 85 kg, the maximum recommended daily dose is 50 mg twice daily.

Before each dose increase, the patient should be evaluated by the physician for symptoms of vasodilation or worsening heart failure. Transient worsening of heart failure or fluid retention should be treated with increased doses of diuretics. Occasionally it may be necessary to lower the dose of **CASLOT** and, in rare cases, temporarily discontinue **CASLOT** treatment.

If **CASLOT** treatment is discontinued for more than one week, therapy should be recommenced at a lower dose level (twice daily) and up-titrated in line with the above dosing recommendation. If **CASLOT** treatment is discontinued for more than two weeks, therapy should be recommenced at 3.125 mg in line with the above dosing recommendation.

Symptoms of vasodilation may be managed initially by a reduction in the dose of diuretics. If symptoms persist, the dose of ACE inhibitor (if used) may be reduced, followed by a reduction in the dose of carvedilol if necessary. Under these circumstances, the dose of **CASLOT** should not be increased until symptoms of worsening heart failure or vasodilation have been stabilised.

Special dosage instructions

Renal impairment
Available pharmacokinetic data in patients with varying degrees of renal impairment (including renal failure) suggest no changes in patients with moderate to severe renal insufficiency.

Hepatic impairment
Carvedilol is contraindicated in patients with clinical manifestations of liver dysfunction (see **CONTRAINDICATIONS**).

Elderly
There is no evidence to support dose adjustment.

Children
Safety and efficacy in children (under 18 years) has not been established.

WARNINGS AND PRECAUTIONS

Chronic Congestive Heart Failure
In chronic heart failure patients, worsening cardiac failure or fluid retention may occur during up-titration of **CASLOT**. If such symptoms occur, diuretics should be increased and the **CASLOT** dose should not be advanced until clinical stability resumes. Occasionally, it may be necessary to lower the **CASLOT** dose or, in rare cases, temporarily discontinue it. Such episodes do not preclude subsequent successful titration of **CASLOT**. **CASLOT** should be used with caution in combination with digitalis glycosides, as both medicines slow AV conduction.

Renal function in Congestive Heart Failure
Reversible deterioration of renal function has been observed with **Caslot** therapy in chronic heart failure patients with low blood pressure (systolic BP <100 mmHg), ischaemic heart disease and diffuse vascular disease, and/or underlying renal insufficiency. In CHF patients with these risk factors, renal function should be monitored during up-titration of carvedilol and the drug discontinued or dosage reduced if worsening of renal failure occurs.

Bronchospastic Reactions
In patients with a tendency to bronchospastic reactions, respiratory distress can occur as a result of a possible increase in airway resistance. The following warnings will be included on the outer packaging and leaflet:

Packaging
Do not take this medicine if you have a history of wheezing due to asthma or other lung diseases.

Leaflet
Do not take carvedilol if you have ever had wheezing due to asthma or other lung diseases. If you are not sure, talk to your doctor or pharmacist before taking carvedilol.

Diabetes
Care should be taken in the administration of **CASLOT** to patients with diabetes mellitus, as the early signs and symptoms of acute hypoglycaemia may be masked or attenuated. In chronic heart failure patients with diabetes, the use of **CASLOT** may be associated with worsening control of blood glucose. Therefore, regular monitoring of blood glucose is required in diabetics when carvedilol is initiated or up-titrated and hypoglycaemic therapy adjusted accordingly.

Peripheral vascular disease
CASLOT should be used with caution in patients with peripheral vascular disease as β-blockers can precipitate or aggravate symptoms of arterial insufficiency. However as carvedilol also has alpha-blocking properties this effect is largely counterbalanced.

Raynaud's phenomenon
CASLOT should be used with caution in patients suffering from peripheral circulatory disorders (eg Raynaud's phenomenon) as there may be exacerbation of symptoms.

Thyrotoxicosis
CASLOT, like other agents with β-blocking properties, may obscure the symptoms of thyrotoxicosis.

Anaesthesia and major surgery
Caution should be exercised in patients undergoing general surgery, because of the synergistic negative inotropic effects of **CASLOT** and anaesthetic drugs.

Bradycardia
Caslot may induce bradycardia. If the patient's pulse rate decreases to less than 55 beats per minute, the dosage of **CASLOT** should be reduced.

Hypersensitivity
Care should be taken in administering **CASLOT** to patients with a history of serious hypersensitivity reactions, and in those undergoing desensitisation therapy, as β-blockers may increase both the sensitivity towards allergens and the seriousness of anaphylactic reactions.

Psoriasis
Patients with a history of psoriasis associated with β-blocker therapy should take **CASLOT** only after consideration of the risk-benefit ratio.

Concomitant use of Calcium Channel Blockers
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.

Pheochromocytoma
In patients with pheochromocytoma, an α-blocking agent should be initiated prior to the use of any β-blocking agent. Although **CASLOT** has both α- and β-blocking pharmacological activities, there is no experience with its use in this condition. Caution should therefore be taken in the administration of **CASLOT** to patients suspected of having pheochromocytoma.

Prinzmetal's Variant Angina
Agents with non-selective β-blocking activity may provoke chest pain in patients with Prinzmetal's variant angina. There is no clinical experience with **CASLOT** in these patients although the α-blocking activity of **CASLOT** may prevent such symptoms. However, caution should, be taken in the administration of **CASLOT** to patients suspected of having Prinzmetal's variant angina.

Contact Lenses
Wearers of contact lenses should be advised of the possibility of reduced lacrimation.

Withdrawal syndrome
CASLOT treatment should not be discontinued abruptly, particularly in patients suffering from ischaemic heart disease. The withdrawal of **CASLOT** should be gradual (over a period of two weeks).

Intraoperative Floppy Iris Syndrome
Intraoperative Floppy Iris Syndrome (IFIS) has been reported during cataract surgery in some patients treated with α-1 blockers (carvedilol is an alpha/beta blocker). This variant of small pupil syndrome is characterized by the combination of a flaccid iris that billows in response to intraoperative irrigation currents, progressive intraoperative miosis despite preoperative dilation with standard mydriatic drugs, and potential prolapse of the iris toward the phacoemulsification incisions. The patient’s ophthalmologist should be prepared for possible modifications to the surgical technique, such as utilization of iris hooks, iris dilator rings, or viscoelastic substances. There does not appear to be a benefit of stopping α-1 blocker therapy prior to cataract surgery.

Fitness to drive
No studies have been performed on the effects of **CASLOT** on patients' fitness to drive or to operate machinery.

Because of individually variable reactions (eg dizziness, tiredness), the ability to drive, operate machinery, or work without firm support may be impaired. This applies particularly at the start of treatment, after dose increases, on changing products, and in combination with alcohol.

Lactose: This medicinal product contains lactose, therefore patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

Sucrose: This medicinal product contains sucrose, therefore patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

CONTRAINDICATIONS

CASLOT (carvedilol) must not be used in patients with:

- Hypersensitivity to carvedilol or any component of this product.
- Unstable/decompensated heart failure.
- Marked fluid retention or overload requiring intravenous inotropic support.
- Clinically manifest liver dysfunction.

As with other beta blockers, carvedilol must not be used in patients with:

- 2^{nd} and 3^{rd} degree A-V heart block, (unless a permanent pacemaker is in place).
- Severe bradycardia (< 50 bpm).
- Sick sinus syndrome (including sino-atrial block).
- Severe hypotension (systolic blood pressure < 85mmHg).
- Cardiogenic shock.
- History of bronchospasm or asthma.

USE IN SPECIAL POPULATION

Pregnancy

There is no adequate reported clinical experience with carvedilol in pregnant women.

Animal studies are insufficient with respect to effects on pregnancy, embryonal/foetal development, parturition and postnatal development. The potential risk for humans is unknown.

Carvedilol should not be used during pregnancy unless the potential benefit outweighs the potential risk.

Beta blockers reduce placental perfusion, which may result in intrauterine foetal death, and immature and premature deliveries. In addition, adverse effects (especially hypoglycaemia and bradycardia) may occur in the foetus and neonate. There may be an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period. No substantive evidence of teratogenicity have been reported with carvedilol in animals.

Lactation

It has been reported in animal that carvedilol or its metabolites are excreted in breast milk. It is not known whether carvedilol is excreted in human milk. Breast feeding is therefore not recommended during the administration of carvedilol.

Pediatrics
Safety and efficacy in children younger than 18 years of age have not been established.

Geriatrics
There are no notable differences in efficacy or the incidence of adverse events between older (65 years of age or older) and patients above 18 years of age.

Carcinogenicity/Mutagenicity/Impairment of Fertility
In reported 2-year studies conducted in rats given carvedilol at doses up to 75 mg/kg/day (12 times the MRHD when compared on a mg/m^2 basis) or in mice given up to 200 mg/kg/day (16 times the MRHD on a mg/m^2 basis), carvedilol had no carcinogenic effect.

Carvedilol was negative when tested in a battery of genotoxicity assays, including the Ames and the CHO/HGPRT assays for mutagenicity and the *in vitro* hamster micronucleus and *in vivo* human lymphocyte cell tests for clastogenicity.

At doses ≥200 mg/kg/day (≥32 times the MRHD as mg/m^2) carvedilol was toxic to adult rats (sedation, reduced weight gain) and was associated with a reduced number of successful matings, prolonged mating time, significantly fewer corpora lutea and implants per dam and complete resorption of 18% of the litters. The no-observed-effect dose level for overt toxicity and impairment of fertility was 60 mg/kg/day (10 times the MRHD as mg/m^2).

DRUG INTERACTIONS

Pharmacokinetic interactions

Carvedilol is a substrate as well as an inhibitor of P-glycoprotein. Therefore the bioavailability of drugs transported by P-glycoprotein may be increased with concomitant administration of carvedilol. In addition, the bioavailability of carvedilol can be modified by inducers or inhibitors of P-glycoprotein.

Inhibitors as well as inducers of CYP2D6 and CYP2C9 can modify the systemic and/or presystemic metabolism of carvedilol stereoselectively, leading to increased or decreased plasma concentrations of R and S-carvedilol. Some examples observed in patients or in healthy subjects are listed below but the list is not exhaustive.

Digoxin: Digoxin concentrations are increased by about 15% when digoxin and carvedilol are administered concomitantly. Increased monitoring of digoxin levels is recommended when initiating, adjusting or discontinuing carvedilol.

Cyclosporin: Two studies in renal and cardiac transplant patients receiving oral cyclosporin have reported an increase in cyclosporin plasma concentration following the initiation of carvedilol. It appears that carvedilol increases the absorption of cyclosporin po through inhibition of P-glycoprotein activity in the intestine. In an attempt to maintain therapeutic ciclosporin levels, an average 10-20% reduction of the cyclosporin dose was necessary. Therefore, due to wide interindividual variability of cyclosporin levels, it is recommended that cyclosporin concentrations are monitored closely after initiation of carvedilol therapy and that the dose of cyclosporin be adjusted as appropriate. In case of iv administration of cyclosporin, no interaction with carvedilol is expected.

*Rifampicin: R*ifampicin administration decreased the carvedilol plasma levels most likely by induction of P-glycoprotein leading to a decrease of the intestinal absorption of carvedilol and a decrease of the antihypertensive effect.

Amiodarone: In patients with heart failure, amiodarone decreased the clearance of S-carvedilol likely by inhibition of CYP2C9. The mean R-carvedilol plasma concentration was not altered. Consequently, there is a potential risk of increased beta-blockade caused by a raised of the plasma S-carvedilol concentration.

Fluoxetine: In patients with heart failure, co-administration of fluoxetine, a strong inhibitor of CYP2D6, resulted in stereoselective inhibition of carvedilol metabolism with a 77% increase in mean R(+) enantiomer AUC. However, no difference in adverse events, blood pressure or heart rate were noted between treatment groups.

Pharmacodynamic interactions

Insulin or oral hypoglycaemics: Agents with beta-blocking properties may enhance the blood-sugar-reducing effect of insulin and oral hypoglycaemics. The signs of hypoglycaemia may be masked or attenuated (especially tachycardia). In patients taking insulin or oral hypoglycaemics, regular monitoring of blood glucose is therefore recommended.

Catecholamine-depleting agents: Patients taking both agents with beta-blocking properties and a drug that can deplete catecholamines (e.g. reserpine and monoamine oxidase inhibitors) should be observed closely for signs of hypotension and/or severe bradycardia.

Digoxin: The combined use of beta blockers and digoxin may result in additive prolongation of atrioventricular conduction time.

Verapamil, diltiazem, amiodarone or other antiarryhthmics: In combination with carvedilol can increase the risk of AV conduction disturbances.

Clonidine: Concomitant administration of clonidine with agents with beta-blocking properties may potentiate blood pressure and heart rate lowering effects. When concomitant treatment with agents with beta-blocking properties and clonidine is to be terminated, the beta-blocking agent should be discontinued first. Clonidine therapy can then be discontinued several days later by gradually decreasing the dosage.

Calcium channel blockers: Isolated cases of conduction disturbance (rarely with haemodynamic compromise) have been observed when carvedilol and diltiazem were given concomitantly. As with other agents with beta-blocking properties, if carvedilol is to be administered orally with calcium channel blockers of the verapamil or diltiazem type, it is recommended that ECG and blood pressure be monitored.

Antihypertensives: As with other agents with beta-blocking activity, carvedilol may potentiate the effect of other concomitantly administered drugs that are anti-hypertensive in action (e.g. alpha$_1$-receptor antagonists) or have hypotension as part of their adverse effect profile.

Anaesthetic agents: Careful monitoring of vital signs is recommended during anaesthesia due to the synergistic negative inotropic and hypertensive effects of carvedilol and anaesthetic drugs.

NSAIDs: The concurrent use of non-steroidal anti-inflammatory drugs (NSAIDs) and betaadrenergic blockers may result in an increase in blood pressure and lower blood pressure control.

Beta-agonist bronchodilatators: Non-cardioselective beta blockers oppose the bronchodilator effects of beta-agonist bronchodilators***.***

ADVERSE REACTIONS

a) Summary of the safety profile
The frequency of adverse reactions is not dose-dependent, with the exception of dizziness, abnormal vision and bradycardia.

(b) List of adverse reactions
The risk of most adverse reactions associated with carvedilol is similar across all indications. Exceptions are described in subsection (c).

Infections and infestations
Common: Bronchitis, pneumonia, upper respiratory tract infection, urinary tract infection

Blood and lymphatic system disorders
Common: Anaemia
Rare: Thrombocytopaenia
Very rare: Leukopenia

Immune system disorders
Very rare: Hypersensitivity (allergic reaction)

Metabolism and nutrition disorders
Common: Weight increase, hypercholesterolaemia, impaired blood glucose control (hyperglycaemia, hypoglycaemia) in patients with pre-existing diabetes

Psychiatric disorders
Common: Depression, depressed mood
Uncommon: Sleep disorders

Nervous system disorders
Very common: Dizziness, headache
Uncommon: Presyncope, syncope, paraesthesia

Eye disorders
Common: Visual impairment, lacrimation decreased (dry eye), eye irritation

Cardiac disorders
Very common: Cardiac failure
Common: Bradycardia, oedema (including generalized, peripheral, dependent and genital oedema, oedema of the legs), hypervolaemia, fluid overload
Uncommon: Atrioventricular block, angina pectoris

Vascular disorders
Very common: Hypotension
Common: Orthostatic hypotension, disturbances of peripheral circulation (cold extremities, peripheral vascular disease, exacerbation of intermittent claudication and Reynaud's phenomenon)

Respiratory, thoracic and mediastinal disorders
Common: Dyspnoea, pulmonary oedema, asthma in predisposed patients
Rare: Nasal congestion, wheezing and flu-like symptoms

Gastrointestinal disorders
Common: Nausea, diarrhoea, vomiting, dyspepsia, abdominal pain

Uncommon: Constipation
Rare: Dry mouth

Hepatobiliary disorders
Very rare: Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gammaglutamyltransferase (GGT) increased

Skin and subcutaneous tissue disorders
Uncommon: Skin reactions (e.g. allergic exanthema, dermatitis, increased sweating, urticaria, pruritus, psoriatic and lichen planus like skin lesions), alopecia

Musculoskeletal and connective tissue disorders
Common: Pain in extremities

Renal and urinary disorders
Common: Renal failure and renal function abnormalities in patients with diffuse vascular disease and/or underlying renal insufficiency, micturition disorders
Very rare: Urinary incontinence in women

Reproductive system and breast disorders
Uncommon: Erectile dysfunction

General disorders and administration site conditions
Very common: Asthenia (fatigue)
Common: Pain

(c) Description of selected adverse reactions
Dizziness, syncope, headache and asthenia are usually mild and are more likely to occur at the beginning of treatment.

In patients with congestive heart failure, worsening cardiac failure and fluid retention may occur during up-titration of carvedilol dose.

Cardiac failure is a commonly reported adverse event in both placebo and carvedilol-treated patients (14.5% and 15.4% respectively, in patients with left ventricular dysfunction following acute myocardial infarction).

Reversible deterioration of renal function has been observed with carvedilol therapy in chronic heart failure patients with low blood pressure, ischaemic heart disease and diffuse vascular disease and/or underlying renal insufficiency.

As a class, beta-adrenergic receptor blockers may cause latent diabetes to become manifest, manifest diabetes to be aggravated, and blood glucose counter-regulation to be inhibited.

Carvedilol may cause urinary incontinence in women which resolves upon discontinuation of the medication.

Other adverse events reported with carvedilol are:
BUN increased, NPN increased, arthralgia, cough increased, malaise, hypovolemia, fever, palpitation, hypertension, hypesthesia, vertigo, melena, periodontitis, hyperuricemia, hyponatremia, increased alkaline phosphatise, glycosuria, diabetes mellitus, weight loss, hyperkalaemia, creatinine increased, muscle cramps, prothrombin decreased, purpura, somnolence, albuminuria, hematuria, cerebrovascular accident, hypotonia, gastrointestinal pain, arthritis, gout, hypertriglyceridemia, peripheral ischemia, tachycardia, hypokinesia, bilirubinemia, nervousness, impaired concentration, abnormal thinking, paroniria, emotional lability, decreased libido, tinnitus, micturition frequency increased, hypokalaemia, bundle branch block, myocardial ischemia, convulsions, migraine, neuralgia, paresis, anaphylactoid reactions, amnesia, GI haemorrhage, bronchospasm, decreased hearing, respiratory alkalosis, decreased HDL, pancytopenia, atypical lymphocyte, aplastic anaemia, interstitial pneumonitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme.

OVERDOSAGE

Symptoms and signs

In the event of overdose, there may be severe hypotension, bradycardia, heart failure, cardiogenic shock and cardiac arrest. There may also be respiratory problems, bronchospasm, vomiting, disturbed consciousness and generalised seizures.

Treatment of Intoxication

Gastric lavage or induced emesis may be useful in the first few hours after ingestion.

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 mg to 2 mg i.v. (for excessive bradycardia)
Glucagon: Initially 1 to 10 mg i.v. then 2 to 5 mg/hour as 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, norepinephrine or noradrenalin should be administered with continous monitoring of the circulatory conditions.

In the case of drug-resistant bradycardia, pacemaker therapy should be initiated.

Treatment of bronchospasm
For bronchospasm, beta-sympathomimetics (as aerosol or intravenous) 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 a 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 patient's condition has stablized .

STORAGE
Store below 30°C, protected from moisture

PACKING
Blister of 10 x 10's

KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN

Date of Revision: June 2014

Manufactured by:

RANBAXY (MALAYSIA) SDN. BHD.
Lot 23, Bakar Arang Industrial Estate,
08000 Sungai Petani, Kedah
Malaysia.