AUSTRALIAN PRODUCT INFORMATION – DILATREND® (CARVEDILOL) TABLETS

1 NAME OF THE MEDICINE

Carvedilol.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

DILATREND tablets contain 6.25 mg, 12.5 mg or 25 mg of carvedilol.

Excipients of known effect: lactose, and sugars.

DILATREND tablets contain lactose monohydrate, povidone, sucrose, crospovidone, colloidal anhydrous silica, magnesium stearate, iron oxide yellow (6.25 mg and 12.5 mg tablets only), iron oxide red (12.5 mg tablets only).

3 PHARMACEUTICAL FORM

DILATREND 6.25 mg: Yellow, round, biconvex tablet, with bilateral scoreline, engraved with BM on one side and F1 on the other.

DILATREND 12.5 mg: Light brown, round, biconvex tablet, with bilateral scoreline, engraved with BM on one side and H3 on the other.

DILATREND 25 mg: White to pale yellowish beige, round, biconvex tablet, with bilateral scoreline, engraved with BM on one side and D5 on the other.

The tablet(s) can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

DILATREND is indicated for the treatment of hypertension. Data have not been provided to support the use of this drug in renovascular disease.

DILATREND is indicated for the treatment of patients with symptomatic mild to severe (NYHA Class II - IV) congestive heart failure (CHF) as an adjunct to conventional treatments (e.g. diuretics, digoxin, ACE inhibitors and vasodilators).

4.2 DOSE AND METHOD OF ADMINISTRATION

Hypertension: Once daily dosing is recommended.

Adults: The recommended dose for initiation of therapy is 12.5 mg once a day for the first 2 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 up to the recommended maximum daily dose of 50 mg given once or twice daily.

Elderly: The recommended dose for initiation of therapy is 12.5 mg once daily, which has provided satisfactory control in some patients. If the response is inadequate, the dose may be titrated at intervals of at least two weeks up to the recommended maximum daily dose.

Carvedilol can be combined with other anti-hypertensive agents, thiazide diuretics in particular.

Symptomatic congestive heart failure (CHF):

Dosage must be individualised and closely monitored by a physician during up-titration.

For patients receiving digitalis, diuretics and ACE inhibitors, dosing of these agents should be stabilised prior to initiation of DILATREND treatment.

It is recommended that DILATREND be taken with food to slow the rate of absorption and to reduce the risk of orthostatic effects. The tablets should be swallowed with sufficient fluid.

The recommended starting dose is 3.125 mg (half a 6.25 mg tablet) twice daily for 2 weeks. If this dose is tolerated, the dosage may subsequently be increased, at intervals of not less than two weeks, to 6.25 mg twice daily, followed by 12.5 mg twice daily, then 25 mg twice daily. Dosing should be increased to the highest level tolerated by the patient.

The recommended maximum daily dose is 25 mg twice daily in patients with mild or moderate CHF weighing less than 85 kg. In patients with mild or moderate CHF weighing more than 85 kg, the recommended maximum daily dose is 50 mg twice daily. For all patients with severe CHF the recommended maximum daily dose is 25 mg twice daily.

For severe CHF, before commencement of therapy, patients should be fully clinically evaluated to ensure that they have sitting systolic blood pressure ≥ 85 mmHg, no more than trace edema of the peripheral limbs, no new pulmonary rales or ascites, optimisation of diuretic therapy and other established therapy such as ACE inhibitors and angiotensin-II antagonists, no recent unstable angina, cardiac surgery or ventricular arrhythmias and no recent use of intravenous positive inotropic or vasodilator agents (other than digitalis).

Before each dose increase, the patient should be evaluated by the physician for symptoms of worsening heart failure, vasodilation or bradycardia. If either heart failure or vasodilation occurs the dose of DILATREND should not be increased until symptoms of heart failure or vasodilation have been stabilised.

If bradycardia (pulse rate < 55 beats/minute) occurs the dose of DILATREND should be reduced.

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 DILATREND or temporarily discontinue DILATREND. If carvedilol 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 DILATREND is discontinued for more than two weeks, therapy should be recommenced at 3.125 mg twice daily and up titrated in line with the above dosing recommendations. Such episodes do not preclude subsequent successful up-titration of carvedilol. Symptoms of

vasodilatation 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 DILATREND if necessary.

Hepatic dysfunction: Since plasma levels have been shown to be increased in patients with cirrhosis, DILATREND is contraindicated in patients with significant liver disease.

Renal dysfunction: Dosage adjustments are not required for mild to moderate impairment, however, in patients with underlying renal insufficiency, renal function should be monitored during up-titration of DILATREND and the drug discontinued or dosage reduced if worsening of renal function occurs.

4.3 CONTRAINDICATIONS

DILATREND must not be used in patients with:

- New York Heart Association (NYHA) Class IV decompensated heart failure requiring intravenous inotropic support.
- Bronchial asthma (two cases of death from status asthmaticus have been reported in patients receiving single doses of carvedilol) or related bronchospastic conditions *including chronic obstructive pulmonary disease (COPD) with a bronchospastic component*.
- Allergic disorders (including Asthma and allergic rhinitis) which may suggest a predisposition to bronchospasm.
- Severe sinus bradycardia (less than 45 to 50 beats per minute) or sick sinus syndrome (unless a permanent pacemaker is in place).
- Shock (including cardiogenic and hypovolaemic shock).
- Second and third degree atrioventricular block.
- Known hypersensitivity to DILATREND.
- Hepatic impairment; DILATREND is contraindicated in patients with clinically manifest liver dysfunction.
- Severe hypotension (systolic blood pressure < 85 mmHg).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

BETA-BLOCKERS CAN CAUSE WORSENING HEART FAILURE. SINCE DILATREND HAS BETA-BLOCKING PROPERTIES, CARE MUST BE TAKEN DURING INITIATION AND UP-TITRATION OF THE DRUG IN HEART FAILURE PATIENTS, SINCE WORSENING HEART FAILURE HAS BEEN OBSERVED IN THIS PHASE OF TREATMENT. IN ORDER TO MINIMISE THE RISK OF THESE EVENTS, IT IS CRITICAL TO CAREFULLY FOLLOW THE RECOMMENDED DOSING FOR DILATREND IN PATIENTS WITH CONGESTIVE HEART FAILURE (see Section 4.2 Dose and method of administration).

There are a number of important pharmacokinetic and pharmacodynamic interactions with other drugs, e.g. digoxin, ciclosporin, rifampicin, anaesthetic drugs, or antiarrhythmic drugs (see Section 4.5 Interactions with other medicines and other forms of interactions).

Abrupt withdrawal
In patients with heart failure, ischaemic heart disease or angina pectoris, abrupt cessation of therapy may lead to deterioration. There have been reports of severe exacerbation of angina, and of

myocardial infarction or ventricular arrhythmias occurring in patients with angina pectoris, following abrupt discontinuation of beta-blocker therapy. Therefore, when discontinuing DILATREND in patients with angina pectoris the dosage should be gradually reduced over a period of about 2 weeks and the patient should be carefully observed. The same frequency of administration should be maintained. If angina markedly worsens or acute coronary insufficiency develops, re-institute DILATREND therapy promptly, at least temporarily.

Prinzmetal's variant angina
Agents with non-selective beta-blocking activity may provoke chest pain in patients with Prinzmetal's variant angina. There has been no clinical experience with carvedilol in these patients, although the alpha-blocking activity of carvedilol may prevent such symptoms. Caution should be taken in the administration of carvedilol to patients suspected of having Prinzmetal's variant angina.

Bradycardia
In clinical trials, DILATREND caused bradycardia in about 2% of hypertensive patients and 9% of congestive heart failure patients. If pulse rate drops below 55 beats/minute, the dosage should be reduced.

Hypotension
Hypotension and postural hypotension occurred in 9.7% and syncope in 3.4% of congestive heart failure patients receiving DILATREND compared to 3.6% and 2.5% of placebo patients, respectively. The risk for these events was highest during the first 30 days of dosing, corresponding to the up-titration period and was a cause for discontinuation of therapy in 0.7% of DILATREND patients, compared to 0.4% of placebo patients.

To decrease the likelihood of syncope or excessive hypotension, treatment should be initiated with 3.125 mg b.i.d. for congestive heart failure patients. Dosage should then be increased slowly, according to recommendations in the 4.2 Dose and method of administration section, and the drug should be taken with food. During initiation of therapy, the patient should be cautioned to avoid situations such as driving or hazardous tasks, where injury could result should syncope occur.

Labile hypertension
DILATREND should be used with caution in patients with labile or secondary hypertension until further clinical experience is available.

Peripheral vascular disease and Raynaud's phenomenon
DILATREND should be used with caution in patients with peripheral vascular disease (e.g. Raynaud's phenomenon) as beta-blockers can precipitate or aggravate symptoms of arterial insufficiency.

Hypertensive patients with left ventricular failure
In hypertensive patients who have congestive heart failure controlled with digitalis, diuretics and/or an angiotensin-converting enzyme inhibitor, DILATREND may be used. However, since it is likely that such patients are dependent, in part, on sympathetic stimulation for circulatory support, it is recommended that dosing follow the instructions for patients with congestive heart failure.

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

Ocular effects
Animal studies have shown that carvedilol binds to the melanin of the uveal tract. The significance of this in humans is not known but periodic ophthalmic examinations are advisable while the patient is taking carvedilol.

Oculomucocutaneous syndrome whose signs include conjunctivitis sicca, psoriasiform rashes and sclerosing serositis has occurred with the chronic use of one beta-adrenergic blocking agent (practolol). This syndrome has not been observed in association with carvedilol or any other such agent. However, physicians should be alerted to the possibility of such reactions and discontinue treatment in the event that they occur.

Wearers of contact lenses should bear in mind the possibility of reduced lacrimation.

Diabetes and hypoglycaemia
Care should be taken in the administration of carvedilol to patients with diabetes as it may be associated with worsening control of blood glucose, or the early signs and symptoms of acute hypoglycaemia may be masked or attenuated. Non-selective beta-blockers may potentiate insulin-induced hypoglycaemia and delay recovery of serum glucose levels. Patients subject to spontaneous hypoglycaemia, or diabetic patients receiving insulin or oral hypoglycaemic agents, should be cautioned about these possibilities and carvedilol should be used with caution. It is recommended that blood glucose be monitored when carvedilol dosing is initiated, adjusted or discontinued (see Section 4.5 Interactions with other medicines and other forms of interactions: Pharmacodynamic interactions).

Thyrotoxicosis
Beta-adrenergic blockade may mask the clinical signs of hyperthyroidism such as tachycardia. Abrupt withdrawal of beta-blockade may be followed by an exacerbation of the symptoms of hyperthyroidism or may precipitate thyroid storm.

Hypersensitivity reactions
Care should be taken in administering carvedilol to patients with a history of serious hypersensitivity reactions, and in those patients undergoing desensitisation therapy, as beta-blockers may increase both the sensitivity towards allergens and the severity of hypersensitivity reactions. Such patients may be unresponsive to the usual doses of adrenaline used to treat allergic reaction.

Risk of anaphylactic reaction
While taking beta-blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of adrenaline used to treat allergic reaction.

Severe cutaneous adverse reactions (SCARs)
Very rare cases of severe cutaneous adverse reactions such as toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) have been reported during treatment of carvedilol (see Section 4.8 Adverse effects (Undesirable effects), Post-Marketing Experience). Carvedilol should be permanently discontinued in patients who experience severe cutaneous adverse reactions possibly attributable to carvedilol.

Non-allergic bronchospasm (e.g., chronic bronchitis and emphysema)
Patients with bronchospastic disease should, in general not receive beta-blockers. DILATREND may be used with caution.

In clinical trials of patients with congestive heart failure, patients with bronchospastic disease were enrolled if they did not require oral or inhaled medication to treat their bronchospastic disease. In such patients, it is recommended that carvedilol be used with caution. The dosing recommendations should be followed closely and the dose should be lowered if any evidence of bronchospasm is observed during up-titration. (see Section 4.5 Interactions with other medicines and other forms of interactions: Pharmacodynamic interactions).

Phaeochromocytoma
In patients with this condition an alpha-blocking drug (e.g. phentolamine or phenoxybenzamine) should be administered before the beta-blocker to avoid exacerbation of hypertension. Although carvedilol has alpha- and beta-blocking pharmacological activities, there is no experience with its use in this condition. Therefore, caution should be taken in the administration of carvedilol to patients suspected of having phaeochromocytoma.

Hepatic injury
Mild hepatocellular injury, confirmed by rechallenge, has occurred rarely with DILATREND therapy.

In controlled studies of congestive heart failure, the incidence of liver function abnormalities reported as adverse experiences was 5.0% (38 of 765 patients) in patients receiving DILATREND and 4.6% (20 of 437 patients) in those receiving placebo. Three patients receiving carvedilol (0.4%) and two patients receiving placebo (0.5%) in placebo-controlled trials withdrew for abnormal hepatic function.

Hepatic injury has been reversible and has occurred after short-and/or long-term therapy with minimal clinical symptomatology. No deaths due to liver function abnormalities have been reported.

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

Renal function
Rarely, use of carvedilol in patients with congestive heart failure has resulted in deterioration of renal function. Patients at risk appear to be those with low blood pressure (systolic blood pressure < 100 mmHg), ischaemic heart disease and diffuse vascular disease, and/or underlying renal insufficiency. Renal function has returned to baseline when carvedilol was stopped. In patients with these risk factors it is recommended that renal function should be monitored during up-titration of DILATREND and the drug discontinued or dosage reduced if worsening of renal function occurs.

Use in the elderly
In congestive heart failure trials of carvedilol worldwide, there were no notable differences in efficacy or the incidence of adverse events between older (≥ 65 years) and younger patients. With the exception of dizziness (incidence 8.8% in the elderly vs 6% in younger patients) there were no events in the world-wide hypertensive trial population for which the incidence in the elderly exceeded that in the younger population by greater than 2%.

Paediatric use
Safety and efficacy of DILATREND in patients younger than 18 years of age has not been established. Use of DILATREND in paediatric patients is not recommended as substantial information regarding benefits and risks is missing. (see section 5.1 Pharmacodynamic properties; Clinical trials).

Effects on laboratory tests
Carvedilol does not affect laboratory tests.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Pharmacokinetic interactions
Effects of carvedilol on the pharmacokinetics of other drugs

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.

Digoxin: An increased exposure of digoxin of up to 56% has been shown in some studies in healthy subjects and patients with heart failure, when given carvedilol. A significantly larger effect has been seen in male patients compared to female patients. Therefore, monitoring of digoxin levels and signs and symptoms of digoxin toxicity is recommended when initiating, adjusting or discontinuing carvedilol (see Section 4.4 Special warnings and precautions for use, 4.5 Interactions with other medicines and other forms of interactions: Pharmacodynamic interactions). Carvedilol had no effect on digoxin administered intravenously.

Ciclosporin and tacrolimus: Two studies in renal and cardiac transplant patients receiving oral ciclosporin have shown an increase in ciclosporin plasma concentration following the initiation of carvedilol. It appears that carvedilol increases the absorption of ciclosporin (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 ciclosporin dose was necessary. Therefore, due to wide interindividual variability of ciclosporin levels, it is recommended that ciclosporin concentrations are monitored closely after initiation of carvedilol therapy and that the dose of ciclosporin be adjusted as appropriate. In case of IV administration of ciclosporin, no interaction with carvedilol is anticipated. Furthermore, there is evidence that CYP3A4 is involved in the metabolism of carvedilol. As tacrolimus is a substrate of P-glycoprotein and CYP3A4, its pharmacokinetics may also be affected by carvedilol through these interaction mechanisms.

Effects of other drugs and other substances on the pharmacokinetics of carvedilol

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. Retrospective analysis of side effects in clinical trials showed that CYP2D6 poor metabolisers had a higher rate of dizziness during up-titration, presumably resulting from vasodilating effects of the higher concentrations of the alpha-blocking R-enantiomer. Some examples observed in patients or in healthy subjects are listed below but the list is not exhaustive.

Grapefruit juice: Consumption of a single dose of 300 ml grapefruit juice (an inhibitor of CYP3A4 and CYP1A2) was shown to result in a 16% increase of the AUC of carvedilol in comparison to water. While the clinical relevance of this observation is unclear, it is advisable that patients should avoid concomitant intake of grapefruit juice at least until a stable dose-response relationship is established.

Rifampicin: In a study in 12 healthy subjects, exposure to carvedilol decreased by around 60% during concomitant administration with rifampicin and a decrease effect of carvedilol on the systolic blood pressure during exercise was observed. The mechanism for the interaction is not known but it may be due to the induction of the intestinal P-glycoprotein by rifampicin. A close monitoring of the beta-blockade activity in patients receiving concomitant administration of carvedilol and rifampicin is appropriate.

Cimetidine: The AUC of carvedilol was increased by 30% without associated increase in C_{max} in healthy male subjects receiving concomitant cimetidine which is not a potent CYP2D6 inhibitor.

Amiodarone: An *in vitro* study with human liver microsomes has shown that amiodarone and desethylamiodarone inhibited the oxidation of R- and S-carvedilol. The trough concentration of S-carvedilol was significantly increased by 2.2-fold in heart failure patients receiving carvedilol and amiodarone concomitantly as compared to patients receiving carvedilol monotheraphy. The effect on S-carvedilol was attributed to desethylamiodarone, a metabolite of amiodarone, which is a strong inhibitor of CYP2C9. Monitoring of the beta-blockade activity in patients treated with the combination carvedilol and amiodarone is advised.

Fluoxetine and paroxetine: In a randomised, cross-over study in 10 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's AUC, and a non-statistically 35% increase of the S-enantiomer's AUC as compared to the placebo group. However, no differences in adverse events and no statistically significant differences in blood pressure and heart rate were noted between treatment groups. The effect of paroxetine, a strong CYP2D6 inhibitor, on carvedilol pharmacokinetics was investigated in 12 healthy subjects following single oral carvedilol administration. In the study, the AUC of R-carvedilol and S-carvedilol were increased by approximately 2.5-fold and 1.9-fold, respectively. Despite significant increase in R- and S-carvedilol exposure, no clinical effects were observed in these healthy subjects. Care should be taken when carvedilol is combined with fluoxetine or paroxetine in clinically unstable patients.

Alcohol: Concomitant consumption of alcohol can potentiate the antihypertensive action of carvedilol and cause different adverse reactions, such as syncope and hypotension. Alcohol intake was shown to have acute hypotensive effects which possibly augment the blood pressure reduction caused by carvedilol. As carvedilol is only sparingly soluble in water but soluble in ethanol, the presence of alcohol could affect the rate and/or extent of intestinal absorption of carvedilol by increasing its solubility. Furthermore, carvedilol was shown to be partly metabolized by CYP2E1, an enzyme known to be both induced and inhibited by alcohol.

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). Therefore, in patients taking insulin or oral hypoglycaemics, regular monitoring of blood glucose is recommended (see Section 4.4 Special warnings and precautions for use: Diabetes and).

Catecholamine depleting agents: Patients treated with both carvedilol 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.

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.

Non-dihydropyridines calcium channel blockers, amiodarone or other antiarrhythmic drugs: Care should be taken when prescribing beta-blockers with non-dihydropyridines calcium blockers, amiodarone or other antiarrhythmics because their combination with carvedilol can increase the risk of AV conduction disturbances. Isolated cases of conduction disturbance (rarely with haemodynamic compromise) have been observed when carvedilol is co-administered with diltiazem. As with other agents with beta-blocking properties, if carvedilol is to be administered orally with non-dihydropyridines calcium channel blockers of the verapamil or diltiazem type, amiodarone or other antiarrhythmics it is recommended that ECG and blood pressure be monitored.. Interactions have been reported during concomitant beta-blocker therapy with the Class IA agents disopyramide, and less frequently quinidine; Class IB agents, tocainide, mexiletine and lignocaine; the Class IC agent, flecainide; the Class III agent, amiodarone; and the Class IV antiarrhythmic agents.

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 hypotensive effects of carvedilol and anaesthetic drugs.

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

Beta-agonist bronchodilators: Non-cardioselective beta-blockers oppose the bronchodilator effects of beta-agonist bronchodilators. Careful monitoring of patients is recommended.

Digoxin: The combined use of beta-blockers and digoxin may result in additive prolongation of atrioventricular (AV) conduction time (see Section 4.5 Interactions with other medicines and other forms of interactions: Pharmacokinetic interactions - Effects of carvedilol on the pharmacokinetics of other drugs above).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
When mated with similarly treated male rats, oral administration of carvedilol to adult female rats at a toxic dose (300 mg/kg/day, 55 times the MRHD on a body surface area basis) resulted in impairment of fertility (poor mating, fewer corpora lutea and fewer implants). No adverse effects on fertility were seen at 60 mg/kg/day (11 times the MRHD on a body surface area basis).

Use in pregnancy – Pregnancy Category C
There is no adequate clinical experience with carvedilol in pregnant women.Carvedilol should not be used during pregnancy unless the potential benefit outweighs the potential risk.

Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown.

Beta-blockers reduce placental perfusion, which may result in intrauterine fetal death, and immature and premature deliveries. In addition, adverse effects (especially hypoglycaemia and bradycardia) may occur in the fetus and neonate. There may be an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period. There is no evidence from animal studies that carvedilol has any teratogenic effects.

Studies in rats have shown that carvedilol and/or its metabolites cross the placental barrier. Carvedilol was embryotoxic and fetotoxic at doses greater than 60 mg/kg/day in rats and 15 mg/kg/day in rabbits (11 and 5 times, respectively, the MRHD based on body surface area). Maternal toxicity was noted in rats and rabbits at doses greater than 60 and 75 mg/kg/day, respectively.

Use in lactation
Carvedilol is excreted in breast milk, although the risk of affecting the child appears unlikely at therapeutic doses, the possibility of the consequences of alpha- and beta-blockage should be borne in mind. DILATREND must not be used during lactation unless the anticipated benefits outweigh the possible risks.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Individually varying reactions can impair alertness (e.g. patients' capacity for driving or operating machinery). This applies particularly when starting or changing treatment and in conjunction with alcohol.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

DILATREND is well tolerated by most patients. Most of the adverse reactions are transient and occur at the beginning of treatment. Adverse reactions are related to the pharmacological effects and to the dose.

DILATREND has been evaluated for safety in mild to moderate congestive heart failure in more than 1900 patients worldwide of whom 1300 participated in U.S. clinical trials. Approximately 54% of the total treated population received DILATREND for at least 6 months and 20% received DILATREND for at least 12 months. The adverse experience profile of DILATREND in congestive heart failure patients was consistent with the pharmacology of the drug and the health status of the patients. In U.S. clinical trials comparing DILATREND in daily doses up to 100 mg (n=765) to placebo (n=437), 5.4% of DILATREND patients discontinued for adverse experiences vs. 8.0% of placebo patients. Generally, the overall incidence of adverse experiences in U.S. placebo-controlled trials was not related to dose. However, there was an increased incidence of dizziness, abnormal vision (primary blurry vision), and bradycardia, with increasing dose.

More Common Events (occurring with a frequency of >1%)
Events occurring with a frequency of ≥2%

Table 1 shows adverse events in U.S. placebo-controlled clinical trials of congestive heart failure patients that occurred with an incidence of 2% or more regardless of causality and were more frequent in drug-treated patients than placebo-treated patients. Median study medication exposure was 6.33 months for DILATREND and placebo patients.

In addition to the events in Table 1, asthenia, cardiac failure, flatulence, anorexia, dyspepsia, palpitation, extrasystoles, hyperkalaemia, arthritis, angina pectoris, insomnia, depression, anaemia, viral infection, dyspnoea, coughing, respiratory disorder, rhinitis, rash and leg cramps were also reported, but rates were equal to, or more common in placebo-treated patients.

Table 1 Adverse Events in U.S. Placebo-Controlled Congestive Heart Failure Trials Frequency ≥ 2% in DILATREND Treated Patients, Regardless of Causality

	Adverse Reactions	
	DILATREND (n=765) % occurrence	**Placebo (n=437)** % occurrence
Autonomic Nervous System		
Sweating increased	2.9	2.1
Body as a Whole		
Fatigue	23.9	22.4
Chest Pain	14.4	14.2
Pain	8.6	7.6
Injury	5.9	5.5
Drug level increased	5.1	3.7
Oedema generalised	5.1	2.5
Oedema dependent	3.7	1.8
Fever	3.1	2.3
Oedema legs	2.2	0.2
Cardiovascular		
Bradycardia	8.8	0.9
Hypotension	8.5	3.4
Syncope	3.4	2.5
Hypertension	2.9	2.5
AV block	2.9	0.5
Angina pectoris aggravated	2.0	1.1
Central Nervous System		
Dizziness	32.4	19.2
Headache	8.1	7.1
Paraesthesia	2.0	1.8
Gastrointestinal		
Diarrhoea	11.8	5.9
Nausea	8.5	4.8
Abdominal pain	7.2	7.1
Vomiting	6.3	4.3
Haematology		
Thrombocytopenia	2.0	0.5
Metabolic		
Hyperglycaemia	12.2	7.8
Weight increase	9.7	6.9
Gout	6.3	6.2
BUN increased	6.0	4.6
NPN increased	5.8	4.6
Hypercholesterolaemia	4.1	2.5
Dehydration	2.1	1.6
Hypervolaemia	2.0	0.9
Musculoskeletal		
Back Pain	6.9	6.6
Arthralgia	6.4	4.8
Myalgia	3.4	2.7
Resistance Mechanism		
Upper respiratory tract infection	18.3	17.6
Infection	2.2	0.9
Respiratory		
Sinusitis	5.4	4.3
Bronchitis	5.4	3.4
Pharyngitis	3.1	2.7

	Adverse Reactions	
	DILATREND (n=765) % occurrence	**Placebo (n=437)** % occurrence
Urinary/Renal		
Urinary tract infection	3.1	2.7
Haematuria	2.9	2.1
Vision		
Vision abnormal	5.0	1.8

The following adverse events were reported more frequently with DILATREND in placebo-controlled trials in patients with congestive heart failure.

Events occurring with frequency of > 1% to < 2%
Body as a Whole: Peripheral oedema, allergy, sudden death, malaise, hypovolaemia.

Cardiovascular System: Fluid overload, and postural hypotension.

Central and Peripheral Nervous System: Hyperaesthesia and vertigo.

Gastrointestinal: Melaena and periodontitis.

Liver and Biliary System: AST and ALT increased.

Haematology: Purpura, prothrombin decreased.

Metabolic and Nutritional: Hyperuricaemia, hypoglycaemia, hyponatraemia, increased alkaline phosphatase, glycosuria.

Psychiatric: Somnolence.

Reproductive, male: Impotence.

Urinary System: Abnormal renal function, albuminuria.

Less Common > 0.1% to ≤ 1%
The following adverse events were reported as possibly or probably related in worldwide open or controlled trials with DILATREND in patients with hypertension or congestive heart failure.

Cardiovascular: Peripheral ischaemia, tachycardia.

Central and Peripheral Nervous System: Hypokinesia.

Gastrointestinal: Hyperbilirubinaemia, increased hepatic enzymes (0.2% of hypertension patients and 0.4% of congestive heart failure patients were discontinued from therapy because of increases in hepatic enzymes; see Section 4.4 Special warnings and precautions for use: Use in hepatic impairment).

General: Substernal chest pain, oedema.

Psychiatric: Sleep disorder, aggravated depression, impaired concentration, abnormal thinking, paranoia, emotional lability.

Respiratory System: Asthma (see Section 4.3 Contraindications).

Reproductive, male: Decreased libido.

Skin and Appendages: Pruritus, rash erythematous, rash maculopapular, rash psoriaform, photosensitivity reaction.

Special Senses: Tinnitus.

Urinary System: Micturition frequency.

Autonomic Nervous System: Dry mouth, sweating increased.

Metabolic and Nutritional: Hypokalaemia, diabetes mellitus, hypertriglyceridaemia.

Haematology: Anaemia, leucopenia.

The following events were reported in ≤ 0.1% of patients (all clinical trials) and are potentially important: complete AV block, bundle branch block, myocardial ischaemia, cerebrovascular disorder, convulsions, migraine, neuralgia, paresis, anaphylactoid reaction, alopecia, exfoliative dermatitis, amnesia, GI haemorrhage, bronchospasm, pulmonary oedema, decreased hearing, respiratory alkalosis, increased BUN, decreased HDL, pancytopenia, and atypical lymphocytes.

Adverse events in severe congestive heart failure
The overall safety and tolerability of DILATREND in the COPERNICUS study in patients with severe CHF was found to be in good agreement with the established safety profile for patients with mild and moderate CHF.

The incidence of serious adverse events was lower in the carvedilol (39.0%) than in the placebo (45.5%) group, and the rate of withdrawal from treatment due to adverse events was also lower in the carvedilol (9.5%) than in the placebo (11.3%) group.

The most frequently occurring serious adverse events were cardiovascular disorders, the incidences of which were lower in the carvedilol (26.3%) than in the placebo group (34.2%). Among cardiovascular disorders, worsening heart failure was the most commonly reported serious adverse event. During initiation of treatment the risk of worsening heart failure was similar in the two groups, but with continued treatment the risk of worsening heart failure decreased in the carvedilol group resulting in a slightly lower overall incidence in the carvedilol group (26%) compared with the placebo group (31.5%). The risk of experiencing vasodilatory events such as dizziness, hypotension and syncope was highest during initiation of carvedilol treatment and the risk decreased with continued treatment. Within the body system “body as a whole” the most frequently reported serious adverse event was sudden death and the incidence was lower in the carvedilol group.

Table 2 Adverse events in the COPERNICUS trial occurring with a frequency ≥2%

	Adverse Events	
	DILATREND (n=1156) % occurrence	**Placebo (n= 1133)** % occurrence
Body as a Whole		
Asthenia	10.9	9.4
Sudden death	3.9	6.1
Abdominal pain	2.2	3.0
Infection	2.5	2.4
Pain in extremity	2.1	2.5
Back pain	2.9	1.4
Accidental injury	1.7	2.0
Cardiovascular System		
Heart failure	26.0	31.5
Hypotension	13.9	8.2
Chest Pain	6.8	7.6
Bradycardia	10.3	2.7
Syncope (including presyncope)	7.6	5.0
Angina pectoris	5.5	4.1
Atrial fibrillation	2.2	4.3
Ventricular tachycardia	1.6	3.9
Hypertension	2.6	2.2
Unstable angina pectoris	2.0	2.7
AV block first degree	2.3	1.6
Peripheral vascular disorder	1.6	2.4
Myocardial infarct	1.6	2.2
Ventricular fibrillation	1.0	2.1
Nervous System		
Dizziness	24.1	16.8
Headache	4.8	3.0
Gastrointestinal		
Diarrhoea	4.8	3.1
Nausea	3.8	3.3
Haematology		
Anaemia	2.4	2.0
Metabolic		
Weight gain	11.7	10.7
Peripheral oedema	7.0	6.4
Generalised oedema	6.0	4.9
Hyperglycaemia	4.5	3.3
Gout	3.5	2.7
Hypokalaemia	2.5	3.4
Hyperkalaemia	3.3	1.9
Creatinine increased	2.9	1.4
Diabetes mellitus	2.0	1.7
Musculoskeletal System		
Muscle cramps	2.0	1.2
Respiratory System		
Upper respiratory infection	13.6	12.6
Dyspnea	11.2	11.0
Bronchitis	5.2	4.5
Cough increased	4.5	4.2
Lung oedema	3.5	4.1
Lung disorder	4.0	3.2
Pneumonia	3.2	3.9
Urinogenital System		
Kidney function abnormal	2.1	2.3
Urinary tract infection	1.6	2.4
Vision		
Blurred vision	2.8	2.2
Skin and appendages	7.1	6.9

Post-Marketing Experience
The following adverse events have been identified during post-marketing use of carvedilol. As these events are reported from a population of uncertain size, it is not possible to reliably estimate their frequency and/or establish a causal relationship to drug exposure.

Cardiac disorders: Sinus arrest in predisposed patients (e.g. elderly patients or patients with pre-existing bradycardia, sinus node dysfunction or atrioventricular block).

Metabolism and Nutrition Disorders: Due to the beta-blocking properties, it is also possible for latent diabetes mellitus to become manifest, manifest diabetes to be aggravated, and blood glucose counter-regulation to be inhibited.

Renal and Urinary Disorders: Isolated cases of urinary incontinence in women, which resolved upon discontinuation of the medication, have been reported.

Skin and Subcutaneous Tissue Disorders: Alopecia. Severe cutaneous adverse reactions (toxic epidermal necrolysis, Stevens-Johnson syndrome) (see Section 4.4 Special warnings and precautions for use). Hyperhidrosis.

Psychiatric disorders: Hallucination

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Cases of overdosage with DILATREND alone or in combination with other drugs have been reported. Quantities ingested in some cases exceeded 1000 mg. Symptoms experienced included low blood pressure and heart rate. Standard supportive treatment was provided and individuals recovered.

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

Treatment
Treatment of overdose should consist of general supportive measures.

The patient should be monitored for the above mentioned signs and symptoms and managed according to the best judgement of the treating physicians and according to standard practice for patients with beta-blocker overdose (e.g. atropine, transvenous pacing, glucagon, phosphodiesterase inhibitors such as milrinone, beta-sympathomimetics).

NOTE: In the event of severe intoxication with symptoms of shock, supportive treatment with antidotes must be continued for a sufficiently long period of time since prolonged elimination half-life and redistribution of carvedilol from deeper compartments can be expected. Duration of antidote therapy is dependent upon severity of overdose. Supportive measures should therefore be continued until the patient is stabilised.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Alpha (α) and Beta (β) adrenergic receptor blocking agents,

ATC code: C07AG02

Mechanism of action
Carvedilol is a dual action cardiovascular agent; a vasodilating, non-selective beta-blocking agent with antioxidant properties. Vasodilation has been shown to be mediated primarily by selective blockade of $alpha_1$-adrenoreceptors.

Carvedilol is a racemic mixture. In animal models, both enantiomers have alpha-adrenergic receptor blocking properties. The beta-adrenergic receptor blocking properties are non-selective for $beta_1$-and $beta_2$-adrenoreceptors and are associated with the S-enantiomer of carvedilol. Carvedilol has no intrinsic sympathomimetic activity and like propranolol, it has membrane-stabilising properties. Carvedilol suppresses the renin-angiotensin-aldosterone system through beta-blockade.

The mechanism for the beneficial effects of carvedilol in congestive heart failure has not been established. Possible mechanisms include neurohormonal inhibition, beta-blockade, balanced vasodilation (reduced preload and afterload), antioxidant activity, potent anti-ischaemic activity, and inhibition of neutrophil adhesion. Antioxidant activity and inhibition of neutrophil adhesion have been demonstrated in *in vitro* and *in vivo* animal models and in *in vitro* human models.

Carvedilol reduces the peripheral vascular resistance by vasodilation predominantly mediated through selective $alpha_1$-antagonism and beta-blockade prevents reflex tachycardia with the net result that heart rate is slightly decreased.

In hypertensive patients, a reduction in blood pressure is not associated with a concomitant increase in total peripheral resistance, as observed with pure beta-blocking agents. Renal blood flow and renal function are maintained. Peripheral blood flow is maintained; therefore, cold extremities (often observed with drugs possessing beta-blocking activity) are rarely seen. Fluid retention does not occur.

In studies that compared the acute haemodynamic effects of carvedilol to baseline measurements in patients with congestive heart failure, there were significant reductions in systemic blood pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, and heart rate. Initial effects on cardiac output, stroke volume index and systemic vascular resistance were small and variable.

In terms of chronic haemodynamic effects (12 to 14 weeks) carvedilol significantly reduced systemic blood pressure, pulmonary artery pressure, right atrial pressure, systemic vascular resistance and heart rate while stroke volume index was increased.

In patients with ischaemic cardiomyopathy, long-term treatment (6 months) with carvedilol (6.25, 12.5 and 25 mg) reduced left ventricular dimensions measured echocardiographically.

In patients with renal impairment, the autoregulatory blood supply is preserved and the glomerular filtration is unchanged during chronic treatment with carvedilol.

A normal ratio of high density lipoproteins to low density lipoproteins (HDL:LDL) is maintained. Serum electrolytes are also unaffected.

During one small randomised trial in patients with hypertension and non-insulin dependent diabetes carvedilol exerted no significant effect on fasting glucose, post-prandial glucose concentration and glycosylated haemoglobin A_1. In another trial of non-insulin dependent diabetics, carvedilol did not significantly affect glucose tolerance test result. A third trial in hypertensive non-diabetic subjects with metabolic syndrome and baseline insulin resistance carvedilol demonstrated a modest but non-significant increase in insulin sensitivity. A fourth trial demonstrated a decrease in plasma glucose and insulin responses to a glucose load in hypertensive non-insulin dependent diabetics.

Clinical trials
The use of this agent in congestive heart failure (CHF) patients has been shown to reduce cardiovascular hospitalisation, improve patient well-being, slow the progression of the disease and reduce the risk of death.

Four U.S. multicentre, double-blind, placebo-controlled studies enrolled 1,094 patients (696 randomised to carvedilol) with New York Heart Association (NYHA) class II - III heart failure and ejection fraction < 0.35. The vast majority was on digitalis, diuretics and an ACE-inhibitor at study entry. Patients were assigned to the studies based upon exercise ability. An Australia-New Zealand double-blind, placebo-controlled study randomised 415 patients (half to carvedilol) with less severe heart failure. All protocols excluded patients expected to undergo cardiac surgery during the 6 to 12 months of double-blind follow-up. All randomised patients had tolerated a 2-week course on carvedilol 6.25 mg b.i.d.

In each study, there was a primary end-point, either progression of heart failure (one U.S. study) or exercise tolerance (2 U.S. studies meeting enrolment goals and the Australia-New Zealand study). There were many secondary end-points specified in these studies, including NYHA classification, patient and physician global assessments, and cardiovascular hospitalisation. Death was not a specified end-point in any study, but it was analysed in all studies. Other analyses not prospectively planned included the sum of deaths and total or cardiovascular hospitalisations. In situations where the primary end-points of a trial do not show a significant benefit of treatment, assignment of significance values to the other results is complex, and such values need to be interpreted cautiously.

The results of the U.S. and Australia-New Zealand trials were as follows:
Slowing Progression of Heart Failure: One U.S. multicentre study (366 subjects) had as its primary end-point the sum of cardiovascular mortality, cardiovascular hospitalisation and sustained increase in heart failure medications. Heart failure progression was reduced, during an average follow-up of 7 months, by 48% (p=0.008).

In the Australia-New Zealand study, death and total hospitalisations were reduced by about 25% over 18-24 months. In the three largest U.S. studies, death and total hospitalisations were reduced by 19%, 39% and 49%, these results being nominally statistically significant in the last two studies. The Australia-New Zealand results were statistically borderline.

Functional Measures: None of the multicentre studies had NYHA classification as a primary end-point, but all such studies had it as a secondary end-point. There was at least a trend toward

improvement in NYHA class in all studies. Exercise tolerance was the primary end-point in 3 studies; in none was a statistically significant effect found.

Subjective Measures: Quality of life, as measured with a standard questionnaire (a primary end-point in one study), was unaffected by carvedilol. However, patients' and investigators' global assessments showed significant improvement in most studies.

Mortality: Mortality was not a planned endpoint in any study. Overall, the results from four US studies are consistent with a beneficial effect of carvedilol on mortality due to the consistency of the results seen across different trials. However, the actual effect, size and statistical difference of this observation are difficult to define.

Severe Congestive Heart Failure (COPERNICUS) Trial

In a large, multi-centre, double-blind, placebo-controlled mortality trial (COPERNICUS), 2,289 patients with stable, severe, CHF of ischaemic, or non-ischaemic origin, on standard therapy, were randomised to either carvedilol (1,156 patients) or placebo (1,133 patients). Patients had left ventricular systolic dysfunction with a mean ejection fraction of < 20%, sitting systolic blood pressure ≥ 85 mmHg, no more than trace edema of the peripheral limbs, no new pulmonary rales or ascites, optimisation of diuretic therapy and other established therapy such as ACE inhibitors and angiotensin-II antagonists, no recent unstable angina, cardiac surgery or ventricular arrhythmias and no recent use of intravenous positive inotropic or vasodilator agents (other than digitalis). The primary efficacy parameter was all-cause mortality and the secondary efficacy parameters were defined as combined mortality or hospitalisations for heart failure, mortality or cardiovascular hospitalisations and mortality or all-cause hospitalisations. Interim analyses were conducted to determine whether the Data Safety Monitoring Board (DSMB) could recommend the study to be terminated early due to convincing evidence of benefit or harm. Deaths were classified as either cardiovascular or non-cardiovascular, and within the group of cardiovascular deaths as being due to left ventricular dysfunction or other cardiovascular causes.

Efficacy results

At the fourth interim analysis, the upper interim monitoring boundary was exceeded, indicating a statistically significant survival benefit for patients on carvedilol. As a result, the DSMB recommended early termination of the trial.

Primary Efficacy Parameter

The rate of survival was significantly higher in the patients receiving carvedilol than the placebo group. The benefit of carvedilol became apparent after about 100 days of treatment. All-cause mortality was reduced by 35% from 19.7% in the placebo group to 12.8% in the carvedilol group (Cox proportional hazards, p=0.00013). The mortality benefit of carvedilol was consistent across all sub-populations investigated. The most frequent cause of death, sudden death, was reduced by 41% in the carvedilol group (5.3% vs 8.9%).

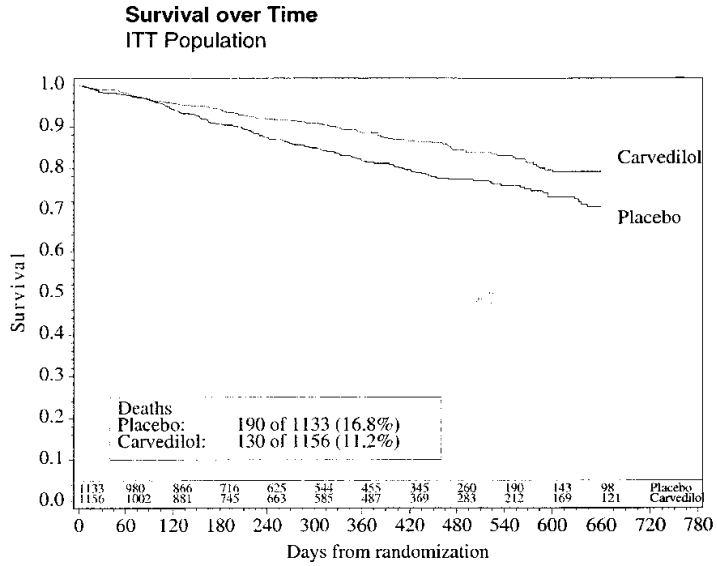


Figure 1: Rate of survival over time

Secondary Efficacy Parameters

Hospitalisations due to worsening heart failure, cardiovascular hospitalisations and all hospitalisations were significantly reduced under carvedilol therapy. Thus, the combined risk of death or hospitalisation due to worsening heart failure was reduced by 31% (p=0.000004), death or cardiovascular hospitalisation by 27% (p=0.000023) and death or all hospitalisation by 24% (p=0.00004).

Table 3 One-year Kaplan-Meier estimates of the incidences of the combined endpoints death or hospitalisations, hazard ratio estimates and log-rank p values. ITT Population

	Total Events Placebo	One-Year K-M Estimate Placebo	Total Events Carvedilol	One-Year K-M Estimate Carvedilol	Hazard Ratio (Carvedilol vs Placebo) (95% CI)	p Value (Log-Rank Test)	% Risk Reduction
Death or hospitalisations for heart failure	357	0.379	271	0.255	0.691 (0.590, 0.809)	0.000004	31
Death or cardiovascular hospitalisations	395	0.417	314	0.302	0.727 (0.627, 0.843)	0.000023	27
Death or all hospitalisations	507	0.523	425	0.416	0.764 (0.671, 0.869)	0.000040	24

The majority of patients were hospitalised for cardiovascular reasons. Treatment with carvedilol resulted in lower rates for almost all cardiac hospitalisations (worsening heart failure, atrial and ventricular and tachyarrhythmias, myocardial infarction and unstable angina pectoris). The number of patients hospitalised for symptomatic bradycardia and symptomatic heart block were slightly higher in the carvedilol treated patients than placebo, although the total number of patients hospitalised was low (1.3% and 0.8% respectively for bradycardia and 0.3% and 0.1% respectively for heart block).

The number of patients hospitalised for non-cardiovascular events was similar in both groups (placebo 11.2%, carvedilol 10.6%).

Paediatric population

Available studies regarding safety and efficacy in children and adolescents are limited in number and size, and were focused on treatment of paediatric heart failure which however differs from the disease in adults regarding characteristics and aetiology. Because of the small number of participants compared to studies in adults and a general lack of an optimal dosing scheme for children and adolescents, the available data is not sufficient to establish a paediatric safety profile for carvedilol. Use of carvedilol in paediatric patients is therefore a safety concern and not recommended as substantial information regarding benefits and risks is missing.

5.2 PHARMACOKINETIC PROPERTIES

Absorption
Carvedilol is rapidly and extensively absorbed following oral administration. Carvedilol is a substrate of the intestinal efflux transporter P-glycoprotein which plays a major role in the bioavailability of certain medicines. The absolute bioavailability of carvedilol is approximately 25%. Plasma levels peak approximately 1 hour after an oral dose. Carvedilol undergoes stereoselective first-pass metabolism with plasma levels of R-carvedilol approximately 2- to 4-fold higher than S-carvedilol following oral administration in healthy subjects. Plasma levels increase in a dose-proportional manner.

No data on the effect of food on carvedilol tablets exist. Studies carried out with the capsule formulation indicate that food does not affect the extent of bioavailability or the maximum plasma concentration, although the time to reach maximum plasma concentration is delayed.

In vitro studies have shown that carvedilol is a substrate of the efflux transporter P-glycoprotein. The role of P-glycoprotein in the disposition of carvedilol was also confirmed *in vivo* in healthy subjects.

Distribution
Greater than 98% of carvedilol is bound to plasma proteins, primarily albumin. Carvedilol is highly lipophilic; the volume of distribution is approximately 2 L/kg and is increased in patients with liver disease. When used as directed, carvedilol is unlikely to accumulate during long-term treatment.

Metabolism
In humans, carvedilol is extensively metabolised in the liver via oxidation and glucuronidation into a variety of metabolites which are mainly excreted in the bile. The first-pass effect after oral administration amounts to about 60-75%; enterohepatic circulation of carvedilol and/or its metabolites has been shown in animals.

The oxidative metabolism of carvedilol is stereoselective. The R-enantiomer is predominantly metabolised 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 maximum plasma concentration of R-carvedilol is approximately 2-fold higher than that S-carvedilol. Although results from *in vitro* studies demonstrate that carvedilol has inhibitory potential against several P450s (CYP1A2, CYP2C9/8, CYP2C19, CYP3A and CYP2D6), it is important to note that the estimated IC_{50} values (concentration of carvedilol required to produce 50% inhibition of the CYP450 isoenzymes) for the

R- and S-enantiomers are substantially higher than their circulating peak plasma levels achieved during therapy.

The R-enantiomer is predominantly metabolised through hydroxylation.

Poor metabolisers of debrisoquine (a marker for CYP2D6) exhibited 2- to 3-fold higher plasma concentrations of R-carvedilol, compared to extensive metabolisers. In contrast, plasma levels for S-carvedilol were only increased by about 20-25% in poor metabolisers. As R-carvedilol is only responsible for alpha-blocking activity, it would be anticipated that, on average, poor metabolisers of debrisoquine would have greater alpha-blockade after carvedilol administration with little change in beta-blocking activity, compared to extensive metabolisers (see Section 4.5 Interactions with other medicines and other forms of interactions).

The pharmacokinetics of carvedilol do not appear to be different in poor metabolisers of S-mephenytoin (patients deficient in CYP2C19).

Demethylation and hydroxylation at the phenol ring produces three active metabolites with beta-receptor blocking activity. Based on preclinical studies, the 4'-hydroxyphenol metabolite is approximately 13 times more potent than carvedilol for beta-blockade. Compared to carvedilol, the three active metabolites exhibit weak vasodilating activity. In humans, the concentrations of the three active metabolites are about 10 times lower than that of the parent substance. According to an *in vitro* study using rat brain homogenate, two of the hydroxy-carbazole metabolites of carvedilol are extremely potent antioxidants, demonstrating a 30- to 80-fold greater potency than carvedilol. Clinical significance remains to be established.

Excretion
After oral administration, the elimination half-life of carvedilol is approximately 6 to 10 hours. Plasma clearance ranges from 500 to 700 mL/min. Elimination is mainly biliary, with the primary route of excretion being via the faeces. A minor portion is eliminated via the kidneys.

The pharmacokinetics of carvedilol are affected by age. AUC and T_{max} values are increased in the elderly. Plasma levels of carvedilol are approximately 50% higher in the elderly compared to young subjects.

Steady-state plasma concentrations of both carvedilol enantiomers increased proportionally over the 6.25 to 50 mg dose range in patients with congestive heart failure. Compared to healthy subjects, congestive heart failure patients had increased mean AUC and C_{max} values for both carvedilol enantiomers with up to 50% to 100% higher values observed in Class IV patients. The mean apparent terminal elimination half-life for carvedilol was similar to that observed in healthy subjects.

Pharmacokinetics in Special Populations

Patients with renal impairment
In patients with hypertension and renal insufficiency, the area under plasma level-time curve, elimination half-life and maximum plasma concentration do not change significantly. Following a single dose (12.5 mg) the mean ± SD of AUCs on day 1 were 220 ± 120 in patients with renal impairment and 165 ± 83.5 ng·h/mL in controls. Following multiple doses (25 mg daily) and on day 9, the corresponding AUCs were 618 ± 335 in patients with renal impairment and 413 ± 247 ng·h/mL in controls. Renal excretion of the unchanged drug decreases in the patients with

renal insufficiency; however changes in pharmacokinetic parameters are modest for racemic carvedilol and R-carvedilol.

Carvedilol is not eliminated during dialysis because it does not cross the dialysis membrane, probably due to its high plasma protein binding.

Patients with hepatic impairment
Carvedilol is contraindicated in patients with clinically manifest liver dysfunction (see Section 4.3 Contraindications). A pharmacokinetic study in cirrhotic patients has shown that exposure (AUC) to carvedilol was increased by 6.8-folds in patients with liver impairment as compared to healthy subjects.

Patients with heart failure
In a study in 24 Japanese patients with heart failure, the clearance of R- and S-carvedilol was significantly lower than previously estimated in healthy volunteers. These results suggested that the pharmacokinetics of R- and S-carvedilol are significantly altered by heart failure.

Geriatric use
Age has no statistically significant effect on the pharmacokinetics of carvedilol in hypertensive patients. A study in elderly hypertensive patients showed that there was no significant difference in the adverse event profile compared to younger patients. Another study which included elderly patients with coronary heart disease showed no significant difference in the adverse events reported vs those reported by younger patients.

Paediatric use
There is limited data available on pharmacokinetics in people younger than 18 years of age.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
No data available.

Carcinogenicity
Repeat dose toxicity studies showed an increase in the incidence of bile duct hyperplasia in rats at doses greater than 34 mg/kg/day following 12 and 18 months dietary treatment with carvedilol, and in dogs receiving doses greater than 30 mg/kg/day for 12 months. Focal hepatocellular hyperplasia was noted in rats at oral doses greater than 100 mg/kg/day at 3 months and greater than 30 mg/kg/day at 12 months of treatment with carvedilol. Hepatocellular hyperplasia was not noted in dogs at doses up to 300 mg/kg/day. In addition, there was a small increase in the incidence of hepatic adenomas in rats receiving carvedilol at doses greater than 100 mg/kg/day in the 18 month dietary study. There was no increase in the incidence of hepatic adenomas in the rat 2 year dietary carcinogenicity study, in which the average dose was 75 mg/kg/day. Based on AUC, this dose showed a 9- to 15- fold higher systemic exposure when compared to a dose of 50 mg/day in humans. A carcinogenicity study in mice was negative at dietary doses up to 200 mg/kg/day. Therefore, the carcinogenic risk to humans following long-term administration of carvedilol appears to be low.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to Section 2 - Qualitative and quantitative composition.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

Under no circumstances should tablets be used later than the expiry date which is clearly printed on the carton and blister labels.

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30° C. Store in a dry place. Store in original container and protect from light as the tablets discolour when exposed to light.

6.5 NATURE AND CONTENTS OF CONTAINER

Available in PA/Al/PVC/Al blister packs of 60.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

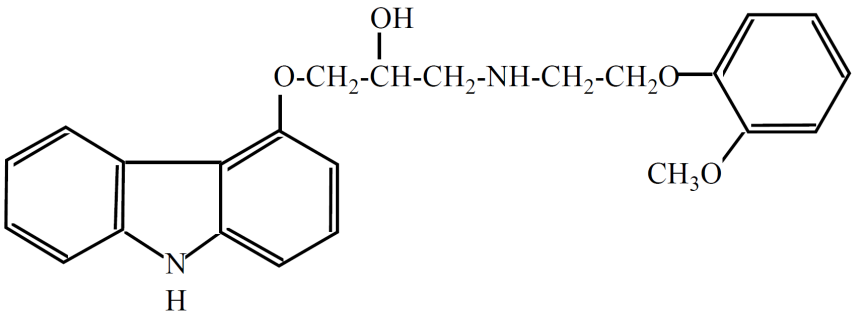
The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided.

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

The chemical name of carvedilol is (±) -1-(9 H-carbazol-4-yloxy)-3-{[2-(2-methoxyphenoxy) ethyl]amino}propan-2-ol. It has molecular formula of $C_{24}H_{26}N_2O_4$ and a molecular weight of 406.5. Carvedilol is a white, crystalline powder and has low solubility in water (0.01 mg/mL). It is soluble in ethanol (22.7 mg/mL).

Chemical structure



CAS number
CAS 72956-09-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

Pharmaco (Australia) Ltd
Level 13, 465 Victoria Avenue
Chatswood NSW 2067
Australia
Phone: 1800 201 564
Under license of CHEPLAPHARM Arzneimittel GmbH, Germany

9 DATE OF FIRST APPROVAL

21 January 1998

10 DATE OF REVISION

11 July 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Addition of Risk of Anaphylactic Reaction