AMENDED PACKAGE INSERT

Ditran Tablets 25 mg
(Carvedilol)

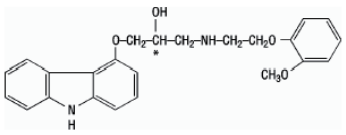
[Ingredient]

Each Tablet Contains：

Carvedilol ……25mg

[Description]

Carvedilol is a nonselective β-adrenergic blocking agent with α1-blocking activity. It is (±)-1-(Carbazol-4-yloxy)-3-[[2-(o-methoxyphenoxy)ethyl]amino]-2-propan ol. Carvedilol is a racemic mixture with the following structure:



Carvedilol is a white to off-white powder with a molecular weight of 406.5 and a molecular formula of $C_{24}H_{26}N_2O_4$. It is freely soluble in dimethylsulfoxide; soluble in methylene chloride and methanol; sparingly soluble in 95% ethanol and isopropanol; slightly soluble in ethyl ether; and practically insoluble in water, gastric fluid (simulated, TS, pH 1.1), and intestinal fluid (simulated, TS without pancreatin, pH 7.5).

Ditran is a white to off-white round tablet with a single score on one side and a "$\frac{ST}{51T}$" debossed on the other side .

Clinical Pharmacology

[Pharmacodynamics]

Pharmacotherapeutic group: Alpha and beta blocking agents. ATC code: C07AG02.

Carvedilol is a vasodilating non-selective beta-blocking agent with antioxidant properties. Vasodilation is predominantly mediated through $alpha_1$ receptor antagonism.

Carvedilol reduces the peripheral vascular resistance through vasodilation and suppresses the renin-angiotensin-aldosterone system through beta-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. Beta-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. The properties of carvedilol and its metabolites have been demonstrated in *in vitro* and *in vivo* animal studies and *in vitro* in a number of human cell types.

Clinical studies have shown that the balance of vasodilation and beta-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 beta-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 beta-blocking activity, are rarely seen.

– 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.

Serum lipid profile and electrolytes are not affected.

[Pharmacokinetics]

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 shown in animals.

Carvedilol exhibits a considerable first pass effect. The metabolite pattern reveals intensive metabolism with glucuronidation as one of the major steps. 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. 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.

[Indications]

- Hypertension : 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)
- Treatment of angina pectoris.
- Treatment of symptomatic chronic heart failure : Indicated for the treatment of symptomatic chronic heart failure (CHF) to reduce mortality and cardiovascular hospitalisations, improve patient well-being and slow the progression of the disease. May be used as adjunct to standard therapy, but may also be used in those patients unable to tolerate an ACE inhibitor, or those who are not receiving digitalis, hydralazine or nitrate therapy.

[Dosage and Administration]

Oral administration.

The tablets should be taken with fluid. For CHF patients, carvedilol should be given with food.

Symptomatic chronic heart failure

Initiation of therapy with carvedilol should only be under the supervision of a hospital physician, following a thorough assessment of the patient's condition.

Prior to any subsequent titration of the dose, the patient must be clinically evaluated on the day of up-titration by a health-care professional experienced in the management of heart failure to ensure that the clinical status has remained stable. The dose of carvedilol should not be increased in any patient with deteriorating heart failure since last visit or with signs of decompensated or unstable chronic heart failure.

The dosage must be titrated to individual requirements.

For those patients receiving diuretics and/or digoxin and/or ACE inhibitors, dosing of these other drugs should be stabilised prior to initiation of carvedilol treatment.

Adults

The recommended dose for the initiation of therapy is 3.125mg twice a day for two weeks. If this dose is tolerated, the dosage should be increased subsequently, at intervals of not less than two weeks, to 6.25mg twice daily, followed by 12.5mg twice daily and thereafter 25mg twice daily. Dosing should be increased to the highest level tolerated by the patient.

The recommended maximum daily dose is 25mg given twice daily for all patients with severe CHF and for patients with mild to moderate CHF weighing less than 85kg (187lbs). In patients with mild or moderate CHF weighing more than 85kg, the recommended maximum dose is 50mg twice daily.

During up-titration of the dose in patients with systolic blood pressure < 100mmHg, deterioration of renal and/or cardiac functions may occur. Therefore, before each dose increase these patients should be evaluated by the physician for renal function and symptoms of worsening heart failure or vasodilation. Transient worsening of heart failure, vasodilation or fluid retention may be treated by adjusting doses of diuretics or ACE inhibitors or by modifying or temporarily discontinuing carvedilol treatment. Under these circumstances, the dose of carvedilol should not be increased until symptoms of worsening heart failure or vasodilation have been stabilised.

If carvedilol is discontinued for more than two weeks, therapy should be recommenced at 3.125mg twice daily and up-titrated in line with the above dosing recommendation.

Elderly

As for adults.

Children

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

Hypertension

Once daily dosing is recommended.

Adults

The recommended dose for initiation of therapy is 12.5mg once a day for the first two days. Thereafter the recommended dosage is 25mg once a day. Although this is an adequate dose in most patients, if necessary the dose may be titrated up to a recommended daily maximum dose of 50mg given once a day or in divided doses.

Dose titration should occur at intervals of at least two weeks.

Elderly

An initial dose of 12.5mg daily is recommended. This has provided satisfactory control in some cases. If the response is inadequate the dose may be titrated up to the recommended daily maximum dose of 50mg given once a day or in divided doses.

Children

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

Angina

Adults

The recommended dose for initiation of therapy is 12.5mg twice a day for the first two days. Thereafter, the recommended dosage is 25mg twice a day.

Elderly

The recommended maximum daily dose is 50mg given in divided doses.

Children

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

Patients with co-existing hepatic disease

Carvedilol is contraindicated in patients with hepatic dysfunction.

Patients with co-existing renal dysfunction

No dose adjustment is anticipated as long as systolic blood pressure is above 100mmHg.

[Contraindications]

Hypersensitivity to the active substance or to any of the excipients.

Carvedilol is contraindicated in patients with marked fluid retention or overload requiring intravenous inotropic support.

Patients with obstructive airways disease, liver dysfunction.

As with other beta-blocking agents: History of bronchospasm or asthma, 2nd and 3rd degree A-V heart block, (unless a permanent pacemaker is in place), severe bradycardia (< 50 bpm), cardiogenic shock, sick sinus syndrome (including sino-atrial block), severe hypotension (systolic blood pressure < 85mmHg), metabolic acidosis and phaeochromocytoma (unless adequately controlled by alpha blockade).

[Warnings and Precautions]

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.

In chronic heart failure patients, worsening cardiac failure or fluid retention may occur during up-titration of carvedilol. If such symptoms occur, the dose of diuretic should be adjusted and the carvedilol dose should not be advanced until clinical stability resumes.

Occasionally it may be necessary to lower the carvedilol dose or temporarily discontinue it. Such episodes do not preclude subsequent successful titration of carvedilol.

In hypertensive patients who have chronic heart failure controlled with digoxin, diuretics and/or an ACE inhibitor, carvedilol should be used with caution since both digoxin and carvedilol may slow A-V conduction.

As with other drugs with beta-blocking activity, carvedilol may mask the early signs of acute hypoglycaemia in patients with diabetes mellitus. Alternatives to beta-blocking agents are generally preferred in insulin-dependent patients. In patients with diabetes, the use of carvedilol 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.

Reversible deterioration of renal function has been observed with carvedilol therapy in chronic heart failure patients with low blood pressure (systolic BP < 100mmHg), 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.

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

Although angina has not been reported on stopping treatment, discontinuation should be gradual (1 - 2 weeks) particularly in patients with ischaemic heart disease, as carvedilol has beta-blocking activity.

Carvedilol may be used in patients with peripheral vascular disease. Pure beta-blockers can precipitate or aggravate symptoms of arterial insufficiency. However as carvedilol also has alpha-blocking properties this effect is largely counterbalanced.

Carvedilol, as with other agents with beta-blocking activity, may mask the symptoms of thyrotoxicosis.

If carvedilol induces bradycardia, with a decrease in pulse rate to less than 55 beats per minute, the dosage of carvedilol should be reduced.

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

In patients suffering from the peripheral circulatory disorder Raynaud's phenomenon, there may be exacerbation of symptoms.

Patients with a history of psoriasis associated with beta-blocker therapy should be given carvedilol only after consideration of the risk-benefit ratio.

In patients with phaeochromocytoma, an alpha-blocking agent should be initiated prior to the use of any beta-blocking agent. There is no experience of the use of carvedilol in this condition. Therefore, caution should be taken in the administration of carvedilol to patients suspected of having phaeochromocytoma.

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

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:

Do not take this medicine if you have a history of wheezing due to asthma or other lung diseases. Consult your doctor or pharmacist first.

[Interaction with other medicinal products]
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.

Patients taking an agent with β-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.

Isolated cases of conduction disturbance (rarely with haemodynamic disruption) have been observed when carvedilol and diltiazem were given concomitantly. Therefore, as with other drugs with beta-blocking activity, careful monitoring of ECG and blood pressure should be undertaken when co-administering calcium channel blockers of the verapamil or diltiazem type, or class I antiarrhythmic drugs. These types of drugs should not be co-administered intravenously in patients receiving carvedilol.

The effects of insulin or oral hypoglycaemics may be intensified. Regular monitoring of blood glucose is therefore recommended.

Trough plasma digoxin levels may be increased by approximately 16% in hypertensive patients co-administered carvedilol and digoxin. Increased monitoring of digoxin levels is recommended when initiating, adjusting or discontinuing carvedilol. Concomitant administration of carvedilol and cardiac glycosides may prolong AV conduction time.

When treatment with carvedilol and clonidine together is to be terminated, carvedilol should be withdrawn first, several days before gradually decreasing the dosage of clonidine.

Care may be required in those receiving inducers of mixed function oxidases e.g. rifampicin, as serum levels of carvedilol may be reduced or inhibitors of mixed function oxidases e.g. cimetidine, as serum levels may be increased.

During general anaesthesia, attention should be paid to the potential synergistic negative inotropic effects of carvedilol and anaesthetic drugs.

[Pregnancy and Lactation]

Pregnancy
There are no adequate data from the use of 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 clearly necessary (i.e. unless the anticipated benefits outweigh the potential risks).

Lactation
It is unknown whether carvedilol is excreted in human breast milk. Animal studies have shown excretion of carvedilol or its metabolites in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with carvedilol should be made taking into account the benefit of breast-feeding to the child and the benefit of carvedilol therapy to the woman.

[Side Effects]

Clinical Trials
Adverse events are listed separately for CHF because of differences in the background diseases.

In chronic heart failure:

Haematological

Rare: thrombocytopenia.
Leucopenia has been reported in isolated cases.

Metabolic
Common: weight increase and hypercholesterolaemia. Hyperglycaemia, hypoglycaemia and worsening control of blood glucose are also common in patients with pre-existing diabetes mellitus.

Central nervous system
Very common: dizziness, headache are usually mild and occur particularly at the start of treatment. Asthenia (including fatigue).

Cardiovascular system
Common: bradycardia, postural hypotension, hypotension, oedema (including generalised, peripheral, dependent and genital oedema, oedema of the legs, hypervolaemia and fluid overload).

Uncommon: syncope (including presyncope), AV-block and cardiac failure during up-titration.

Gastro-intestinal system
Common: nausea, diarrhoea, and vomiting.

Skin and appendages
Dermatitis, and increased sweating.

Others
Common: vision abnormalities.

Rare: acute renal failure and renal function abnormalities in patients with diffuse vascular disease and/or impaired renal function.

The frequency of adverse experiences is not dose dependent, with the exception of dizziness, abnormal vision and bradycardia.

In hypertension and angina:

The profile is similar to that observed in chronic heart failure although the incidence of events is generally lower in patients with hypertension or angina treated with carvedilol.

Blood chemistry and haematological
Isolated cases of changes in serum transaminases, thrombocytopenia and leucopenia have been reported.

Central nervous system
Common: dizziness, headaches and fatigue, which are usually mild and occur particularly at the beginning of treatment.

Uncommon: depressed mood, sleep disturbance, paraesthesia, asthenia.

Metabolic
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.

Cardiovascular system
Common: bradycardia, postural hypotension, especially at the beginning of treatment.

Uncommon: syncope, hypotension, disturbances of peripheral circulation (cold extremities, PVD, exacerbation of intermittent claudication and Raynauds phenomenon). AV-block, angina pectoris (including chest pain), symptoms of heart failure and peripheral oedema.

Respiratory system
Common: asthma and dyspnoea in predisposed patients.

Rare: stuffy nose. Wheezing and flu-like symptoms.

Gastro-intestinal system
Common: gastro-intestinal upset (with symptoms such as nausea, abdominal pain, diarrhoea).

Uncommon: constipation and vomiting.

Skin and appendages
Uncommon: skin reactions (e.g. allergic exanthema, dermatitis, urticaria, pruritus, lichen planus-like reactions, and increased sweating). Psoriatic skin lesions may occur or existing lesions exacerbated.

Others
Common: pain in the extremities, reduced lacrimation.

Uncommon: cases of sexual impotence and disturbed vision.

Rare: dryness of the mouth and disturbances of micturition and eye irritation.

Isolated cases of allergic reactions have been reported.

[Toxicity and treatment of overdose]

Symptoms and signs
Profound cardiovascular effects such as hypotension and bradycardia would be expected after massive overdose. Heart failure, cardiogenic shock and cardiac arrest may follow. There may also be respiratory problems, bronchospasm, vomiting, disturbed consciousness and generalised seizures.

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

In addition to general procedures, vital signs must be monitored and corrected, if necessary under intensive care conditions.

Patients should be placed in the supine position. Atropine, 0.5mg to 2mg i.v. and/or glucagon 1 to 10mg i.v. (followed by a slow i.v. infusion of 2 to 5mg/hour if necessary) may be given when bradycardia is present. Pacemaker therapy may be necessary. For excessive hypotension, intravenous fluids may be administered. In addition, norepinephrine may be given, either 5 to 10 micrograms i.v., repeated according to blood pressure response, or 5 micrograms per minute by infusion titrated to blood pressure. Bronchospasm may be treated using salbutamol or other beta$_2$-agonists given as aerosol or, if necessary, by the intravenous route. In the event of seizures, slow i.v. injection of diazepam or clonazepam is recommended. In cases of severe overdose with symptoms of shock, supportive treatment as described should be continued for a sufficiently long period of time, i.e. until the patient stabilises, since prolonged elimination half life and redistribution of carvedilol from deeper compartments can be expected.

[Package]
A box of 10 tablets x 10 strips; a box of 7 tablets x 20 strips.

[Storage]
Store below 30°C and away from excess heat and moisture.

[Shelf-life]
Three years

Registration NO.：Taiwan: PM- 047460

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