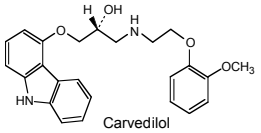
Xicard™

(CARVEDILOL TABLETS)

Tablets 6.25mg,12.5mg, 25mg

DESCRIPTION

Carvedilol is a nonselective β-adrenergic blocking agent with α_1-blocking activity. Chemically it is (2RS)-1-(9H-Carbazol-4-yloxy)-3-[[-2-(2-methoxyphenoxy)ethyl]amino]propan-2-ol. Its molecular formula is $C_{24}H_{26}N_2O_4$. It is a racemic mixture with the following structure:



Carvedilol

QUALITATIVE & QUANTITATIVE COMPOSITION

XICARD (Carvedilol) is available for oral administration as:

1. Xicard Tablets 6.25mg
   Each tablet contains:
   Carvedilol BP…6.25mg
2. Xicard Tablets 12.5mg
   Each tablet contains:
   Carvedilol BP…12.5mg
3. Xicard Tablets 25mg
   Each tablet contains:
   Carvedilol BP…25mg

CLINICAL PHARMACOLOGY

Mechanism of Action

Carvedilol is a vasodilating non-selective beta-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 beta-blockade. 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.

Pharmacokinetics

Absorption

Carvedilol is rapidly and extensively absorbed following oral administration, with absolute bioavailability of approximately 25% to 35% due to a significant degree of first pass metabolism. The rate of absorption is delayed by taking carvedilol with food with no significant difference in extent of bioavailability.

Distribution

Carvedilol is more than 98% bound to plasma proteins, primarily with albumin. The steady-state volume of distribution is approximately 115L, indicating substantial distribution into extravascular tissues.

Metabolism

Carvedilol is extensively metabolised. It is metabolized primarily by aromatic ring oxidation and glucuronidation. The oxidative metabolites are further metabolized by conjugation via glucuronidation and sulfation. Demethylation and hydroxylation at the phenol ring produce three active metabolites with β-receptor blocking activity.

Excretion

The average elimination half-life of carvedilol is approximately 7 to 10 hours. Plasma clearance is approximately 500-700mL/min. The primary route of excretion is via the feces. Elimination is mainly biliary. Less than 2% of the dose is excreted unchanged in the urine.

Special Populations

Hepatic Insufficiency

Compared to healthy subjects, hepatic insufficient patients exhibit significantly higher concentrations of carvedilol (approximately 4 to 7 fold) following single dose therapy.

Renal Insufficiency

Although carvedilol is metabolized primarily by the liver, plasma concentrations of carvedilol have been reported to be increased in patients with renal impairment. However, no dose adjustment is required for patients with moderate to severe renal insufficiency.

Geriatric

Plasma levels of carvedilol average about 50% higher in the elderly compared to young subjects.

Pediatric

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

THERAPEUTIC INDICATIONS

Essential Hypertension: XICARD (Carvedilol) is indicated 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 Pectoris: XICARD (Carvedilol) is indicated for the treatment of chronic stable angina and unstable angina.

Chronic Heart Failure: XICARD (Carvedilol) is indicated for the treatment of symptomatic patients with stable, mild, moderate and severe chronic heart failure of ischemic or cardiomyopathic origin as an adjunct to standard therapy (diuretics, ACE inhibitors and digitalis) to increase the survival and to reduce the risk of hospitalization. It may be used in patients who are not receiving digitalis, hydralazine or nitrate therapy.

DOSAGE AND ADMINISTRATION

Treatment with XICARD (Carvedilol) 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.

Dosage must be individualized in the following diseases:

Essential Hypertension:

The recommended starting dose of XICARD (Carvedilol) is 12.5mg once daily or 6.25mg twice daily increased after two days to 25mg once daily or 12.5mg twice daily.

Alternatively, an initial dose of 6.25mg is given twice daily, increased after one or two weeks to 25mg once daily or 12.5mg twice daily. The dose may be increased further, if necessary, at intervals of at least 2 weeks to 50mg once daily or 25mg twice daily.

XICARD (Carvedilol) should be taken with food to slow the rate of absorption and reduce the incidence of orthostatic effects. Addition of diuretic can be expected to produce additive effects and exaggerate the orthostatic component of XICARD (Carvedilol).

Elderly patients:

A dose of 12.5mg once daily or 6.25mg twice daily may be adequate.

Angina Pectoris:

The recommended dose for initiation of therapy is 12.5mg twice daily for the first two days. Thereafter the recommended dose is 25mg twice daily. If necessary, the dose may subsequently be increased at intervals of at least two weeks up to the recommended maximum daily dose of 50mg twice daily.

Alternatively, an initial dose of 6.25mg twice daily and increased after 3 to 10 days, based on tolerability to 12.5mg twice daily, then again to the target dose of 25mg twice daily.

Chronic Heart Failure:

Dosage must be closely monitored by a physician during up titration. The recommended dose for initiation of therapy is 3.125mg twice daily for two weeks. If tolerated the dose should be increased, at intervals of not less than 2 weeks, to 6.25mg, 12.5mg and 25mg twice daily. The dose should not exceed 25mg twice daily in patients weighing less than 85kg or 50mg twice daily in patients weighing more than 85kg.

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

XICARD (Carvedilol) should be taken with food to slow the rate of absorption.

ADVERSE REACTIONS:

Carvedilol is generally well tolerated. Dizziness, headache, fatigue are the most frequently reported adverse effects. These symptoms are usually mild and occur particularly at the beginning of the treatment.

Adverse effects in chronic heart failure:

Common: Postural hypotension, hypotension, bradycardia, oedema, nausea, diarrhea, vomiting, weight increase, hypercholesterolemia, hyperglycemia, hypoglycemia, worsening control of blood glucose in patients with pre-existing diabetes mellitus, vision abnormalities.

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

Rare: Thrombocytopenia, acute renal failure and renal function abnormalities with diffuse vascular diseases and/or impaired renal function. Isolated cases of leucopoenia have been reported.

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

Adverse effects in Hypertension and Angina Pectoris:
The incidence of adverse effects in these patient populations is lower, however, the following adverse reactions have been reported:
Common: Bradycardia, postural hypotension (especially at the beginning of treatment), asthma, dyspnea in predisposed patients, gastrointestinal upset (nausea, abdominal pain, diarrhea), pain in extremities, reduced lacrimation.
Uncommon: Depressed mood, sleep disturbances, paresthesia, asthenia, syncope, hypotension, disturbances of peripheral circulation, AV block, angina pectoris, symptoms of heart failure, peripheral oedema, constipation, vomiting, cases of sexual impotence, disturbed vision, skin reactions. Psoriatic skin lesions may occur or existing lesions exacerbated.
Rare: Stuffy nose, wheezing and flu-like symptoms, dryness of mouth and disturbances of micturition and eye irritation.
Isolated cases of increase in serum transaminases, thrombocytopenia, leucopoenia and allergic reaction have been reported.
Due to the β-blocking properties it is also possible for latent diabetic mellitus to become manifest, manifest diabetes to be aggravated, and blood glucose counter-regulation to be inhibited.

CONTRAINDICATIONS:
Carvedilol is contraindicated in patients having:
- Hypersensitivity to carvedilol or any component of the product.
- Stable/decompensated heart failure, severe bradycardia, severe hypotension cardiogenic shock.
- 2nd & 3rd degree AV block.
- Sick sinus syndrome
- History of Chronic Obstructive Pulmonary Disease (COPD) that constrict the respiratory tract (such as bronchial asthma, chronic bronchitis, pulmonary emphysema), allergic rhinitis, swelling of laryngeal mucosa.
- Clinically manifest liver dysfunction.

WARNINGS/PRECAUTIONS
- Patients with coronary artery disease, who are being treated with carvedilol, should be advised against abrupt discontinuation of therapy. As with other β-blockers, when discontinuation of carvedilol is planned, the patients should be carefully observed and advised to limit physical activity to a minimum. If the angina worsens or acute coronary insufficiency develops, it is recommended that carvedilol be promptly reinstituted, at least temporarily. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue carvedilol therapy abruptly even in patients treated only for hypertension or heart failure.
- β-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease. Caution should be exercised in such individuals.
- Rarely, use of carvedilol in patients with congestive heart failure has resulted in deterioration of renal function. In patients with low blood pressure (systolic blood pressure <100mmHg), ischemic heart disease and diffuse vascular disease, and/or underlying renal insufficiency, it is recommended that renal function be monitored during up-titration of carvedilol and the drug discontinued or dosage reduced if worsening of renal function occurs.
- Vasodilatory symptoms often do not require treatment, but it may be useful to separate the time of dosing of carvedilol from that of the ACE inhibitor or to reduce temporarily the dose of the ACE inhibitor. The dose of carvedilol should not be increased until symptoms of worsening heart failure or vasodilation have been stabilized. Fluid retention (with or without transient worsening heart failure symptoms) should be treated by an increase dose of diuretics. The dose of carvedilol should be reduced if patients experience bradycardia (heart rate < 55beats/minute).
- Worsening heart failure or fluid retention may occur during up-titration of carvedilol. If such symptoms occur, diuretics should be increased and the carvedilol dose should not be advanced until clinical stability resumes. Occasionally it is necessary to lower the carvedilol dose or temporarily discontinue it.
- Caution should be taken in the administration of carvedilol to patients suspected of having pheochromocytoma.
- Caution should be taken in the administration of carvedilol to patients suspected of having Prinzmetal's variant angina.
- Patients with bronchospastic disease should, in general, not receive β-blockers. Carvedilol may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents.
- During treatment with carvedilol the eyes must be examined regularly at 6-month intervals.
- 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.
- Patients with a history of psoriasis associated with beta-blocker therapy should be given carvedilol only after consideration of the risk-benefit ratio.

Pregnancy
There are no adequate or well-controlled studies in pregnant women. Carvedilol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether carvedilol is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from carvedilol, a decision should be made whether, to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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

Drug Interactions
Catecholamine-depleting agents: Patients taking both agents 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.
Clonidine: When concomitant treatment with agents having β-blocking properties and clonidine is to be terminated, the β-blocking agent should be discontinued first. Clonidine therapy can then be discontinued several days later by gradually decreasing the dosage.
Cyclosporine: Due to wide inter-individual variability in the dose adjustment required, it is recommended that cyclosporine concentrations be monitored closely after initiation of carvedilol therapy and that the dose of cyclosporine be adjusted as appropriate.
Digoxin: Increased monitoring of digoxin is recommended when initiating, adjusting, or discontinuing carvedilol.
Calcium channel blockers: As with other agents with β-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.
Insulin or oral hypoglycemics: Agents with β-blocking properties may enhance the blood-sugar-reducing effect of insulin and oral hypoglycemics. In congestive heart failure patients, there is a risk of worsening hyperglycemia. Therefore, in patients taking insulin or oral hypoglycemics, regular monitoring of blood glucose is recommended.
Inducers and inhibitors of hepatic metabolism: 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.
Anesthetic agents: If treatment with carvedilol is to be continued preoperatively, particular care should be taken when anesthetic agents which depress myocardial function, such as ether, cyclopropane, and trichloroethylene, are used.
Inhibitors of CYP2D6: Interactions of carvedilol with strong inhibitors of CYP2D6 (such as quinidine, fluoxetine, paroxetine, and propafenone) have not been studied, but these drugs would be expected to increase blood levels of the R (+) enantiomer of carvedilol.
α1-receptor antagonists: 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., α1-receptor antagonists) or have hypotension as part of their adverse effect profile.

STORAGE
Store below 30°C.
Protect from sunlight & moisture.
The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
XICARD (Carvedilol) Tablets 6.25mg are available in blister pack of 10's.
XICARD (Carvedilol) Tablets 12.5mg are available in blister pack of 10's.
XICARD (Carvedilol) Tablets 25mg are available in blister pack of 10's.

Keep out of reach of children.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

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