CARDILOL®

Carvedilol

ACTION

Cardiac agent, non-selective beta- and alpha1-receptor blocker.

INDICATIONS

Essential hypertension:

Cardilol 25 mg is indicated for the treatment of essential (non-organically determined) hypertension.

Chronic stable angina pectoris:

Cardilol 25 mg is indicated for the treatment of chronic stable angina pectoris.

Chronic heart failure:

Cardilol 6.25 mg and 25 mg are indicated for the treatment of stable chronic heart failure of all degrees of severity, whether ischemic or non-ischemic in origin - in addition to treatment with diuretics, ACE inhibitors and optionally digitalis.

Notice to patients with heart failure:

Patients to be treated with the drug should have a reduced left-ventricular ejection fraction and should have been clinically stable (no change in NYHA class or basic therapy and no admission to hospital because of heart failure) for approximately 4 weeks before the start of treatment with Cardilol.

DOSAGE AND ADMINISTRATION

The daily dose will be determined by your physician. Please observe the instructions for use, as otherwise Cardilol may not work as it should.

What dose of Cardilol should be used, and how often?

Hypertension

Treatment should be started with ½ tablet of Cardilol 25 mg (12.5 mg carvedilol) per day for the first two days. Treatment can then be continued with 1 tablet of Cardilol 25 mg (25 mg carvedilol) per day. A daily dose of 1 tablet of Cardilol 25 mg is generally sufficient.

Only the physician can decide whether the dose should be increased. Where the effect is inadequate, the dose can be increased after a minimum of 14 days to 1 tablet of Cardilol 25 mg (25 mg carvedilol) twice daily. An individual dose of 25 mg or a daily dose of 50 mg carvedilol should not be exceeded.

Dosage in elderly patients: A daily dose of ½ tablet of Cardilol 25 mg (12.5 mg carvedilol) is also recommended for elderly patients at the start of treatment. In some patients this dose has been found to bring about satisfactory fall in blood pressure even during long-term treatment. Where the effect is inadequate, the dose can be increased at intervals of at least 14 days up to maximum levels (individual dose of 25 mg or daily dose of 50 mg carvedilol).

Chronic stable angina pectoris

Treatment should be started with ½ tablet of Cardilol 25 mg (12.5 mg carvedilol) twice daily on each of the first two days and then continued with 1 tablet of Cardilol 25 mg (25 mg carvedilol) twice daily. A dose of 1 tablet of Cardilol 25 mg (25 mg carvedilol) twice daily is generally sufficient.

Where the effect is inadequate, the dose can be increased after a minimum of 14 days to 2 tablets of Cardilol 25 mg (50 mg carvedilol) twice daily.

Dosage in elderly patients: In elderly patients on long-term therapy a dose of 1 tablet of Cardilol 25 mg (25 mg carvedilol) twice daily should not be exceeded.

Chronic heart failure

Cardilol should always be used in combination with the standard treatment of heart failure, which consists of diuretics, digitalis, ACE inhibitors, and/or other vasodilators.

Treatment with Cardilol must not be started until the patient has been stabilized on the conventional basic therapy for heart failure, i.e. the dosage of this standard therapy must have been stable for at least 4 weeks prior to the start of treatment with Cardilol.

Only physicians with specialist qualifications in internal medicine and/or cardiology may use Cardilol in patients with chronic heart failure.

The recommended dose at the beginning of treatment is 3.125 mg carvedilol twice daily for 2 weeks. If this dose is tolerated it should be increased at intervals of at least 2 weeks to 6.25 mg carvedilol twice daily,12.5 mg carvedilol twice daily, and 25 mg carvedilol twice daily. The dosage can be titrated in this way up to the highest dose tolerated by the patient. Dividable tablets with different content of active ingredient (Cardilol 6.25 mg and Cardilol 25 mg) are available for the adjustment of therapy.

The maintenance dose must be established for each patient individually with strict medical monitoring. Long-term treatment should then proceed with the highest individual dose. The minimal effective dose is 6.25 mg carvedilol twice daily. The maximum dose is generally 25 mg carvedilol twice daily. Only in patients weighing over 85 kg with mild to moderate chronic heart failure, a cautious attempt may be made to increase the dose up to a maximum of 50 mg carvedilol twice daily, provided that the patient is closely monitored.

In patients weighing less than 85 kg the maximum dose should not exceed 25 mg carvedilol twice daily. In patients weighing over 85 kg a cautious attempt may be made to increase the dose up to a maximum of 50 mg carvedilol twice daily, provided that the patient is closely monitored.

The dose of Cardilol may be increased only if the patient's clinical condition is satisfactory and stable, i.e. if there are no sign of worsening of the heart failure and no clinically relevant side effects, especially ones caused by vasodilatation (e.g. a decrease in blood pressure or dizziness). Patients must therefore be checked for such symptoms, in particular, before each dose increment. Frequent and regular medical checks (e.g. of renal function, body weight, blood pressure, heart rate, and heart rhythm) must also be carried out, particularly during the dose titration period (increase of the dose to the maintenance level). A deterioration in the symptoms of heart failure and side effects due to the vasodilating action of Cardilol often occur for a short time only and should be treated by temporarily reducing the dose of the product or if nessesary by suspending treatment. However, if the symptoms are caused primarily by fluid retention, the dose of diuretic can be increased temporarily. An exaggerated fall in blood pressure may occur after the first dose of Cardilol or after dose increment, particularly in patients with severe heart failure (NYHA≥III) and /or on high dose diuretic therapy. Therefore, in order to prevent an uncontrolled fall in blood pressure, such patients should remain under medical supervision for about 2 hours after the first dose of Cardilol and after any dose increment. Where treatment with Cardilol has been interrupted for more than two weeks it should be resumed with 3.125 mg carvedilol twice daily for two weeks followed by gradual dose titration as described above.

Dosage in patients with impaired renal function

The appropriate dose must be established for each patient individually. On the basis of the pharmacokinetic parameters of carvedilol in heart failure alone, no dosage adjustment of Cardilol is required.

Note on tablet division:

Place the tablet on a hard surface and press down with one thumb on the left of the dividing groove and the other thumb on the right. The tablet can thus be readily split into halves.

How and when should Cardilol be used?

Cardilol should be swallowed whole with sufficient liquid. Unless otherwise prescribed the drug should generally be taken in the morning or one tablet in the morning and one in the evening. It is recommended that Cardilol be taken with meals in order to retard the absorption of the active ingredient and thus possibly to reduce circulatory regulation disturbances on change of position (orthostatic effects).

For how long should Cardilol be used?

The duration of treatment will be determined by your physician. Treatment with Cardilol is generally long-term therapy and if possible should not be stopped abruptly, but rather tapered off over 1-2 weeks. In order to prevent any exacerbation of angina pectoris, antianginal therapy can if necessary be given during this tapering-off period.

CONTRAINDICATIONS

When should you not use Cardilol?

Cardilol should not be used in any of the following cases:

- In patients hypersensitive to the active ingredient carvedilol or to other ingredients of the product,
- in cardiogenic shock,
- in pronounced myocardial insufficiency (decompensated heart failure),
- in acute pulmonary embolism,
- in Prinzmetal's angina,
- in the presence of pronounced low blood pressure (systolic pressure < 90 mmHg),
- in bradycardia (patients who are receiving Cardilol for heart failure should have a resting heart rate of at least 65 beats/min),
- in certain disturbances of stimulus formation/conduction in the heart (2nd and 3rd-degree atrioventricular block),
- in cases of sick sinus syndrome or sinoatrial block (exception: pacemaker therapy),
- in cor pulmonale (heart failure due to respiratory disease),
- in bronchial asthma or other respiratory diseases with a bronchospastic component (e.g. chronic obstructive lung disease),
- in the presence of an untreated pheochromocytoma (tumour of adrenal medulla),
- in the presence of severely impaired liver functions in metabolic acidosis,
- in patients currently receiving MAO inhibitors (exception: MAO-B inhibitors),
- in patients receiving simultaneous intravenous treatment with verapamil, diltiazem, or other antiarrhythmic drugs.

SPECIAL WARNINGS

Cardilol should not be used in the following situations, as insufficient clinical data are available: labile or organically determined (secondary) hypertension, stimulus conduction disturbances in the heart (complete bundle-branch block),tendency to a fall in blood pressure on changing position (orthostatic hypotension), acute inflammatory heart disease,hemodynamically relevant alterations in the heart valves or cardiac outflow tracts, end stages of peripheral arterial occlusive disease, and simultaneous treatment with certain antihypertensives (alpha$_1$-receptor antagonists or alpha$_1$ receptor agonists).

When does the use of Cardilol call for particular care?

Under any of the circumstances described below, you may take Cardilol only under certain conditions and only with particular care. Please refer to your physician for further information. These restrictions also apply if any of the circumstances described below applied to you previously. As only limited clinical experience is available on use of Cardilol in patients with unstable angina pectoris, its use in this condition calls for particular care. Caution is required when Cardilol is used in patients with peripheral vascular disease, as beta-blocker can trigger or exacerbate the signs and symptoms of arterial blood flow disturbances. Patients with angiospasm in fingers or toes (Raynaud's disease) may experience a worsening of symptoms. In patients with history of severe hypersensitivity reactions and in those receiving desensitisation therapy, the use of beta-blockers calls for particular care because of the possibility that such hypersensitivity reactions may be intensified.

In patients with a personal or family history of psoriasis, drugs with beta-blocking properties (such as Cardilol) should be used only after a careful consideration of risks and benefits.

What must you be aware of in the event of pregnancy and breastfeeding?

As insufficient data are available on use in pregnancy, Cardilol should be used in pregnancy only after a careful consideration of risks and benefits.

Carvedilol and/or its metabolites pass into breast milk. Women therefore refrain from breastfeeding during treatment with Cardilol.

What needs to be noted in the case of children, adolescents, and the elderly?

Cardilol should not be used in children or juveniles under 18 years of age, as insufficient clinical data are available on its use in this age group. In the elderly (persons over 70 years old) an exaggerated fall in blood pressure may occur after the first dose of Cardilol or after dose increments. Elderly patients therefore remain under medical supervision for about 2 hours after the first dose of Cardilol and after any dose increments.

WARNINGS AND PRECAUTIONS FOR USE

What precautionary measures must be taken?

Patients with a tumour of the adrenal medulla (pheochromocytoma) may be treated with beta-blockers only after effective alpha-receptor blockade. As no data are available on treatment with Cardilol in such situations, the drug should not be used if the presence of a pheochromocytoma is suspected.

In the event - in justified exceptional cases - of Cardilol and clonidine being used simultaneously, the clonidine must not be withdrawn until a few days after the end of the treatment with Cardilol, and then must be withdrawn gradually.

As the possibility of more frequent and/or more severe attacks of angina pectoris, and in rare instances of heart attacks, and also of abrupt transient peaks of blood pressure, cannot be ruled out in the event of a sudden withdrawal of Cardilol, particularly in patients with chronic stable angina pectoris and patients with myocardial blood flow disturbances (ischemically determined heart failure), treatment with Cardilol should not be broken off abruptly. It is recommended that the dose be reduced gradually over 1-2 weeks. If necessary, simultaneous antianginal therapy may be given to prevent any deterioration of angina pectoris.

An exaggerated fall in blood pressure may occur after the first dose of Cardilol or after dose increments, particularly in patients with severe heart failure (NYHA ≥III) and/ and salt and/or fluid deficiency (e.g. patients on high-dose diuretic therapy), but also in the elderly (≥70 years) and in persons whose blood pressure is already low (e.g. systolic pressure <100 mmHg). Therefore, in order to prevent an uncontrolled fall in blood pressure, such patients should remain under medical supervision for about 2 hours after the first dose of Cardilol and after any dose increments. Frequent and regular medical checks must be carried out, e.g. on renal functions, body weight, blood pressure, heart rate and cardiac rhythm, particularly during the dose titration period(dose increase to the maintenance level). Only physicians with specialist qualifications in internal medicine and/or cardiology may use Cardilol in patients with chronic heart failure.

Especially at the beginning of treatment, patients with heart failure may experience a deterioration in their symptoms, in particular increased fluid retention. In order to combat this, an increase in the dose of diuretic may be tried initially. Occasionally, however, it may be necessary to reduce the dose of Cardilol or to suspend treatment temporarily.

In patients with heart failure and low blood pressure (systolic pressure < 100 mmHg) who also suffer from myocardial blood flow disturbances (ischemic heart disease), generalised vascular diseases, or impaired renal function, a deterioration of renal function may occur during treatment with Cardilol, though this is usually reversible. The renal function of patients with these risk factors must therefore be checked at frequent intervals during the dose titration phase of Cardilol therapy. Should renal function deteriorate, the dose of Cardilol should be reduced or treatment stopped altogether. Cardilol can cause an appreciable decrease in heart rate. As a rule the dose of Cardilol should be reduced if the heart rate falls below 55 beats/min. Cardilol should be used with caution in patients with first-degree atrioventricular block because of the adverse effect on stimulus conduction from the atrium to the ventricle (AV conduction).

Administration of Cardilol simultaneously with calcium antagonists or antiarrhythmics calls for careful monitoring of blood pressure, heart rate, and cardiac rhythm (ECG required, especially in the case of verapamil or diltiazem), as it can lead to a greater decrease in blood pressure, a slow heart rate, and/or heart rhythm disturbances.

In connection with anesthesia it should be noted that the effects on heart function (negative inotropism) and the blood pressure-lowering action of Cardilol and of some anesthetics and narcotics may undergo mutual potentiation.

Particularly careful medical monitoring is required in diabetics with large fluctuations in blood glucose level, as the early warning signs and symptoms of an acute fall in blood glucose level (hypoglycemia) may be masked or delayed. In patients who have both heart failure and diabetes mellitus the use of Cardilol may impair control of blood glucose. The blood glucose level of such patients must therefore be checked regularly at the beginning of treatment and after any change in the dose of Cardilol, and the hypoglycemic therapy should be adjusted as required. Careful monitoring of blood glucose by a physician is also necessary during strict diets. Cardilol can mask the signs and symptoms of an overactive thyroid gland (hyperthyroidism). The possibility of reduced tear flow must be taken into account in patients who wear contact lenses.

What must you be aware of when driving vehicles, operating machinery, or working without firm support?

No studies have been performed on effects of Cardilol on patients' fitness to drive or to operate machinery. Patients treated with this drug should have regular medical checkups. Because of individually variable reactions (e.g. dizziness, tiredness), the ability to drive, operate machinery, or work without firm support may be impaired. This applies particularly at the start of treatment, after dose increments, on changing products, and in combination with alcohol.

SIDE EFFECTS

What are the possible side effects of Cardilol?

Central nervous system: Dizziness, headache, and tiredness occur occasionally. These effects are usually mild and occur particularly at the start of treatment. Hallucinations, confusion, depression, sleep disturbances, and nightmares occur rarely. Psychosis occurs in isolated cases.

Cardiovascular system: Particularly after the first dose of Cardilol and after dose increments, though also on standing up after lying down (orthostasis), patients occasionally develop an excessive drop in blood pressure (hypotension) accompanied by symptoms such as dizziness, visual blackout, and in rare instances transient loss of consciousness (syncope).

There have been occasional reports of slowing down of the pulse and rare reports of a sensation of coldness in the limbs, exacerbation of symptoms in patients with intermittent claudication due to impaired blood flow in the legs and in patients with angiospasm of the fingers and toes (Raynaud's disease), angina pectoris, and fluid accumulation in the tissues (edema). Disturbances of atrioventricular stimulus conduction (AV block) can be exacerbated by Cardilol. Total AV block has been reported in isolated cases. Patients with Prinzmetal's angina may experience an exacerbation of symptoms.

The following have been observed in patients with heart failure, especially after dose increments: frequently, dizziness; occasionally, edema at various sites and of various degree of severity; and rarely, complete AV block or exacerbation of heart failure.

Kidneys: In patients with heart failure and in patients with generalised vascular disease and/or impaired renal function, a deterioration in renal function, and in rare instances renal failure, may occur.

Respiratory tract: Due to a possible increase in airway resistance, patients with a tendency to bronchospastic reactions may develop asthma attacks. There have been occasional reports of shortness of breath and rare reports of blocked nose.

Gastrointestinal tract: Nausea, vomiting, abdominal pain, and diarrhea occur occasionally. Constipation occurs rarely.

Skin: Skin reactions (e.g. isolated cases of hives (urticaria), itching, lichen planus-like reactions, and rare cases of allergic eruptions) have been reported during treatment with Cardilol.

Special warning:

In isolated cases drugs with beta-blocking properties (e.g. Cardilol) can cause psoriasis, aggravate the signs and symptoms of psoriasis, or lead to psoriasis-like (psoriasiform) skin eruptions.

Blood: In rare instances there have been changes in certain liver function values in the blood (serum transaminases) and decreases in platelet and white blood cell counts (thrombocytopenia and leucopenia).

Metabolism: In view of the beta-blocking properties of the substance, it is impossible to rule the possibility of latent diabetes becoming manifest, of existing diabetes becoming worse, of blood-glucose counterregulation being inhibited.

Signs of a low blood glucose level or of an overactive thyroid gland (such as a rapid heart rate) may be masked. Abnormally high blood glucose levels (hyperglycemia), weight gain, and elevated cholesterol levels can occasionally occur in patients with heart failure (with regard to diabetic patients).

Other side effects

There have been occasional reports of limb pains and rare reports of sensory disturbances (paresthesias), disturbed vision, eye irritation, dryness of the mouth, disturbances of urination and erectile dysfunction. Contact lens wearers in particular should note that tear flow may be reduced during treatment with Cardilol.

The following side effects have been found to be dose-dependent: dizziness, visual disturbances, excessively slow heart rate, and exacerbation of heart failure.

Should you experience any side effects not mentioned in this package leaflet, please inform your physician or pharmacist.

What countermeasures should be taken against side effects?

Should you experience any of the side effects referred to above, please inform your physician. Depending on the severity of the side effect, the physician will decide what action needs to be taken.

Drug Interactions

What other medications influence the action of Cardilol, and what must you be aware of when using other medications at the same time as Cardilol?

Please note that the information given below, can apply also to recently used medications.

In patients treated simultaneously with Cardilol and other medicinal products the following points in particular should be noted:

- Simultaneous treatment with Cardilol and cardiac glycosides can lead to a greater decrease in heart rate and to delayed stimulus conduction (AV conduction) in the heart.
- On simultaneous administration of Cardilol and digoxin, the serum digoxin level was found to be increased by 16%, and on simultaneous administration of digitoxin the serum digitoxin level was found to be increased by about 13%. Intensified monitoring of serum glycoside levels is therefore recommended at the beginning and end of simultaneous treatment with Cardilol and on changes in the dose of this treatment.
- There may be an increase in the effect of other antihypertensive agents or of drugs that can cause a fall in blood pressure as a side effect such as certain sedatives (barbiturates, phenothiazines), drugs for the treatment of depression (tricyclic antidepressants), vasodilators, and alcohol.
- Simultaneous administration of Cardilol and reserpine, guanethidine, methyldopa, clonidine, or guanfacine can cause additional slowing of the heart rate.
- When Cardilol is administered simultaneously with oral calcium antagonists, particularly those of the verapamil and diltiazem type, or other antiarrhythmic drugs, the cardiodepressive action may be increased. Careful monitoring of the blood pressure, heart rate, and heart rhythm (ECG) is therefore required under these conditions.
- On simultaneous administration of Cardilol and certain narcotics and anesthetics the effects on heart function (negative inotropism) and the blood-pressure lowering action of the two drugs may potentiate each other. Therefore, before undergoing anesthesia, please inform the physician that you are taking Cardilol.
- Cyclooxygenase inhibitors (e.g. acetylsalicylic acid, corticosteroids) can weaken the antihypertensive effect of Cardilol.
- The action of insulin or of oral antihyperglycemic drugs may be potentiated. Signs of low blood glucose (hypoglycemia) may be masked or weakened (particularly the increased heart rate). Regular checks of blood glucose are therefore necessary in diabetics.
- Cimetidine, hydralazine, and alcohol can increase the systemic availability of Cardilol, as via enzyme inhibition they inhibit the breakdown of the active ingredient in the liver. Careful monitoring is therefore recommended in patients who are also taking these drugs.
- Rifampicin increases the metabolic degradation of carvedilol via enzyme induction and thus reduces the action of Cardilol.

OVERDOSAGE

What should be done if too much Cardilol has been taken?

Overdosage can lead to a pronounced fall in blood pressure, slowing down of heart rate, heart failure, cardiogenic shock,and even cardiac arrest. Respiratory problems, bronchospasm and generalized convulsions can also occur.

If overdosage of Cardilol is suspected you should contact your physician, who will decide on the appropriate action depending on the severity of the intoxication.

What must you do if you have taken too little Cardilol or omitted a dose?

If, exceptionally, you forget to take a dose of Cardilol, do not increase the number of tablets you take on the next occasion. Continue taking the drug as before, as prescribed by your physician.

What must you do if you interrupt or prematurely end treatment?

The dosage of Cardilol should be changed only on the physician's instructions. This applies also to discontinuation of treatment. Cardilol must never be broken off abruptly but should be withdrawn gradually.

STORAGE

Store in a dry place below 25°C, away from light.

PRESENTATIONS

Tablets	
CARDILOL 3.125 mg:	Carvedilol 3.125 mg
CARDILOL 6.25 mg:	Carvedilol 6.25 mg
CARDILOL 12.5 mg:	Carvedilol 12.5 mg
CARDILOL 25 mg:	Carvedilol 25 mg

Excipients:

Sucrose, Lactose monohydrate, Crospovidone, Povidone, Magnesium stearate, Colloidal silicon dioxide, Opadry white.

THIS IS A MEDICAMENT

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous.
- Follow the doctor's prescription strictly, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Manufactured by:
HIKMA Pharmaceuticals, Amman-Jordan

Keep medicament out of the reach of children

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