

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Beta-Cardone Tablets 40mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Sotalol Hydrochloride 40mg

For excipients see 6.1

3 PHARMACEUTICAL FORM

Tablet

Green, circular, flat-faced tablets with bevelled edges, with "Evans/BC4" on one face.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ventricular arrhythmias: Treatment of life-threatening ventricular tachyarrhythmias and symptomatic non- sustained ventricular tachyarrhythmias.

Supraventricular arrhythmias: Prophylaxis of paroxysmal atrial tachycardia, paroxysmal atrial fibrillation, paroxysmal A-V nodal re-entrant tachycardia, paroxysmal A-V re-entrant tachycardia using accessory pathways, and paroxysmal supraventricular tachycardia after cardiac surgery. Maintenance of normal sinus rhythm following conversion of atrial fibrillation or atrial flutter.

4.2 Posology and method of administration

Oral administration in adults:

When administering Beta-Cardone to a patient for the first time, it is desirable to start with a low dose and gradually increase the dose until the desired response is obtained; this is especially important in the elderly, as a general rule the heart rate should not be reduced to less than 55 beats per minute.

Before starting treatment or increasing the dose the corrected QT interval should be measured and renal function, electrolyte balance, and concomitant medications assessed. Treatment with sotalol should be initiated and doses increased in a facility capable of monitoring and assessing cardiac rhythm. The dosage must be individualised and based on the patient's response. Proarrhythmic events can occur not only at initiation of therapy, but also with each upward dosage adjustment.

Treatment with Beta-Cardone should not be discontinued suddenly, especially in patients with ischaemic heart disease (angina pectoris, prior acute myocardial infarction) or hypertension, to prevent exacerbation of the disease (see section "abrupt withdrawal" under Special Warnings).

The following are guidelines for oral administration.

The initial dose is 80mg, as one or two divided doses. Oral dosage should be adjusted gradually allowing 2-3 days between dosing increments in order to attain steady-state, and to allow monitoring of QT intervals. Most patients respond to 160 to 320mg per day, in two divided doses.

The dosage should be reduced in renal impairment. Creatinine clearance: 60-30ml/min.: ½ recommended dose. Creatinine clearance 30-10ml/min.: ¼ recommended dose.

Administration in children:

Beta-Cardone is not intended for administration to children.

4.3 Contraindications

Sick sinus syndrome; long QT syndromes, Torsades de Pointes; symptomatic sinus bradycardia; uncontrolled congestive heart failure; cardiogenic shock; anaesthesia that produces myocardial depression; untreated phaeochromocytoma; hypotension (except due to arrhythmia); Raynaud's phenomenon and severe peripheral circulatory

disturbances; chronic obstructive airway disease or bronchial asthma; renal failure (creatinine clearance <10 ml/min.).

Beta-Cardone should not be given to patients suffering from heart block or patients with Prinzmetal's angina and those have a history of bronchospasm.

In patients with poor cardiac reserve β -blockade can precipitate heart failure; in such cases, sotalol hydrochloride therapy should not be commenced until the patient has been controlled by therapy (ACE inhibitors, cardiac glycosides or, if necessary, diuretic therapy - see Interactions).

Diabetic ketoacidosis and metabolic acidosis: Sotalol hydrochloride should not be given to patients suffering from diabetic ketoacidosis or metabolic acidosis; therapy with sotalol hydrochloride can be commenced or resumed when the metabolic condition has been corrected.

Beta-Cardone should not be given to patients hypersensitive to Sotalol

4.4 Special warnings and precautions for use

Beta-Cardone should not be given to patients who have a history of asthma or bronchospasm.

Beta-blockers may increase the sensitivity towards allergens and the seriousness of anaphylactic reactions.

Patients with a history of psoriasis should take beta-blockers only after careful consideration.

Abrupt withdrawal: Patients should be carefully monitored when discontinuing chronically administered sotalol, particularly those with ischaemic heart disease. If possible the dosage should be gradually reduced over a period of 1 to 2 weeks, if necessary at the same time initiating replacement therapy. Hypersensitivity to catecholamines is observed in patients withdrawn from beta-blocker therapy. Occasional cases of exacerbation of angina pectoris, arrhythmias and in some cases myocardial infarction have been reported after abrupt discontinuation of therapy. Abrupt discontinuation may unmask latent coronary insufficiency. In addition, hypertension may develop.

Proarrhythmias: Rarely, Beta-Cardone causes aggravation of pre-existing arrhythmias or the provocation of new arrhythmias.

Risk factors for Torsades de Pointes include prolongation of the QT interval, bradycardia, reduction in serum potassium and magnesium, and history of cardiomegaly or congestive heart failure, sustained ventricular tachycardia.

Proarrhythmic events can occur on initiating therapy and with every upward dose adjustment. The incidence of Torsades de Pointes is dose dependent.

Caution should be used if the QTc exceeds 500 msec whilst on therapy. It is advisable to reduce dose or discontinue therapy when the QTc interval exceeds 550 msec.

Electrolyte disturbances: Sotalol should not be used in patients with hypokalaemia or hypomagnesaemia. Potassium levels should be monitored. In conditions likely to provoke hypokalaemia/hypomagnesaemia, such as persistent diarrhoea, appropriate corrective clinical measures should be taken.

Heart failure: Beta-blockade may precipitate heart failure.

Following myocardial infarction careful monitoring and dose titration are critical during initiation and follow-up of therapy. Sotalol should be avoided in patients with left ventricular ejection fractions $\leq 40\%$ without serious ventricular arrhythmias.

Thyrotoxicosis: Beta-blockade may mask certain clinical signs of hyperthyroidism.

Treated diabetes: Beta-Cardone, like other β -blocking agents, may reduce or mask the usual pre-hypoglycaemic warning signs. It may be necessary to adjust the dose of anti-diabetic therapy.

General anaesthesia: If desired, Beta-Cardone may be stopped four days prior to surgery. However, where sudden withdrawal might expose the patient to severe angina or arrhythmias, anaesthesia can proceed provided that the following precautions are taken.

1. Vagal dominance is counteracted by premedication with atropine sulphate (0.25 to 2.0mg) administered intravenously.
2. Anaesthetic agents such as ether, chloroform, cyclopropane, trichlorethylene, methoxyflurane and enflurane are not used.

Alcoholism: β -adrenoceptor blocking drugs may precipitate cardiac failure in alcoholic patients.

Upper respiratory infections: In these conditions patients without a history of airways obstruction may suffer bronchospasm from β -blockade.

The product labelling will bear a statement warning against use in patients with a history of wheezing or asthma.

Patients with rare hereditary problems of galactose intolerance, the Lapp-lactose deficiency, or glucose-galactose malabsorption should not take this medicine

4.5 Interaction with other medicinal products and other forms of interaction

In combined therapy, clonidine should not be discontinued until several days after withdrawal of Beta-Cardone.

Use with great caution with drugs that also prolong QT interval, e.g. disopyramide, amiodarone, class I antiarrhythmic agents, calcium antagonists of the verapamil type or tricyclic antidepressants.

Concomitant potassium-depleting diuretics may increase the potential for Torsade de Pointes.

Proarrhythmic events are more common in patients also receiving digitalis glycosides.

Phenothiazines, terfenadine, astemizole, diltiazem and halofantrine.

Concomitant use of reserpine, guanethidine, or alpha methyl dopa: Closely monitor for evidence of hypotension and/or marked bradycardia, syncope.

Tubocurarine: Neuromuscular blockade is prolonged by beta-blocking agents.

Calcium antagonists: Dihydropyridine derivatives such as nifedipine. The risk of hypotension may be increased. In patients with latent cardiac insufficiency, concomitant treatment with beta-blockers may lead to cardiac failure.

Prostaglandin synthetase inhibiting drugs may decrease the hypotensive effects of beta-blockers

Sympathomimetic agents: may counteract the effect of beta-adrenergic agents.

Concomitant administration of tricyclic antidepressants, barbiturates and phenothiazines as well as other antihypertensive agents may increase the blood pressure lowering effect.

Precautions for use:

Insulin and oral antidiabetic drugs, may intensify the blood sugar lowering effect (especially non-selective beta-blockers)

Beta-adrenergic blockade may prevent the appearance of signs of hypoglycaemia (tachycardia).

Cimetidine, hydralazine and alcohol induce increased levels of hepatically metabolised beta-blockers.

4.6 Fertility, Pregnancy and lactation

Use in pregnancy should be avoided.

Pregnancy: Animal studies with sotalol hydrochloride have shown no evidence of teratogenicity or other harmful effects on the foetus. Nevertheless its use throughout pregnancy should be avoided unless it is absolutely necessary as it crosses the placenta and may cause foetal bradycardia.

Beta-blockers reduce placental perfusion which may result in intrauterine foetal death, immature and premature deliveries. In addition, adverse effects (especially hypoglycaemia and bradycardia) may occur in the foetus and neonate. There is an increased risk of cardiac and pulmonary complications in neonate in the postnatal period. Most beta-blockers, particularly lipophilic compounds, will pass into breast milk although to a variable extent.

Lactation: Infants should not be fed with breast milk from mothers being treated with Beta-Cardone.

Newborns exposed near delivery should be closely observed for the first 24-48 hours for signs and symptoms of beta-blockade.

4.7 Effects on ability to drive and use machines

Side-effects such as dizziness and fatigue should be taken into account.

4.8 Undesirable effects

The most significant adverse effects are those due to proarrhythmia, including Torsades de Pointes. There is an increased risk of Torsades de Pointes in women.

Also bradycardia, dyspnoea, chest pain, palpitations, oedema, ECG abnormalities, hypotension, proarrhythmia, syncope, heart failure, presyncope. Nausea/vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, cramps, fatigue, dizziness, asthenia, light-headedness, headache, sleep disturbances, depression, paraesthesia, mood changes, anxiety, sexual dysfunction, visual disturbances, taste abnormalities, hearing disturbances, fever, slowed AV-conduction or increase of an existing AV-block, cold and cyanotic extremities, Raynaud's phenomenon, increase of intermittent claudication.

Beta-blockers, even those with apparent cardioselectivity should not be used in patients with asthma or a history of obstructive airways disease unless no alternative treatment is available. In such cases, the risk of inducing bronchospasm should be appreciated and appropriate precautions taken. If bronchospasm should occur after the use of Beta-Cardone it can be treated with a beta₂-agonist by inhalation e.g. salbutamol (the dose of which may need to be greater than the usual dose in asthma) and, if necessary, intravenous atropine 1mg.

There have been reports of skin rashes especially exacerbation of psoriasis and disorders of lacrimation including dry eyes and conjunctivitis. In most cases the symptoms have cleared when the treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Cessation of therapy with a β -blocker should be gradual.

An increase in anti-nuclear Antibodies has been seen; its clinical relevance is not clear.

Blood and lymphatic system disorders

- Thrombocytopenia - frequency not known (cannot be estimated from the available data)

Skin and subcutaneous tissue disorders

- Alopecia - frequency not known (cannot be estimated from the available data)
- Hyperhidrosis - frequency not known (cannot be estimated from the available data)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms of overdose are: bradycardia, hypotension, bronchospasm and acute cardiac insufficiency.

After ingestion of an overdose or in the case of hypersensitivity, the patient should be kept under close supervision and treated in an intensive care ward. Absorption of any drug material still present in the gastro-intestinal tract can be prevented by gastric lavage, administration of activated charcoal and a laxative. Artificial respiration may be required. Bradycardia or extensive vagal reactions should be treated by administering atropine or methylatropine. Hypotension and shock should be treated with plasma/plasma substitutes and if necessary, catecholamines. The beta-blocking effect can be counteracted by slow intravenous administration of isoprenaline hydrochloride, starting with a dose of approximately 5 micrograms/minute, or dobutamine, starting with a dose of 2.5 micrograms/minute, until the required effect has been obtained.

In refractory cases isoprenaline can be combined with dopamine. If this does not produce the desired effect either, intravenous administration of 8-10 mg of glucagon may be considered. If required the injection should be repeated within one hour, to be followed - if required - by an i.v. infusion of glucagon at an administration rate of 1-3 mg/hour. Administration of calcium ions, or the use of a cardiac pacemaker may also be considered. In patients intoxicated with hydrophilic beta-blocking agents haemodialysis or haemoperfusion may be considered.

Prolongation of the QTc interval has been reported. Transvenous pacing may be required.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: C 07AA 07 Beta blocking agents, non selective.

Sotalol has both beta-adrenoreceptor blocking (Vaughan Williams Class II) and cardiac action potential duration prolongation (Vaughan Williams Class III) antiarrhythmic properties. The d- and l-isomers of sotalol have similar Class III antiarrhythmic effects while the l-isomer is responsible for virtually all of the beta-blocking activity.

5.2 Pharmacokinetic properties

Sotalol is completely absorbed from the gastrointestinal tract and peak plasma concentrations are obtained about 2 or 3 hours after a dose. It is excreted unchanged in the urine. After oral administration the plasma half-life has been shown to be 17 hours. It is not bound to plasma proteins. The lipid solubility is very low.

5.3 Preclinical safety data

None stated

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Maize Starch
Pregelatinised Starch
Talc
Magnesium Stearate
Dispersed Blue 11076
Quinoline Yellow Lake 19248

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Beta-Cardone Tablets should be protected from light.

6.5 Nature and contents of container

Polypropylene securitainers containing 100 or 500 tablets.
PVC/PVdC and foil blister strips containing 28 or 56 tablets.

6.6 Special precautions for disposal

None

7 MARKETING AUTHORISATION HOLDER

BEXIMCO PHARMA UK LTD
284 Station Road
Harrow
Middlesex HA1 2EA
Untied Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 36760/0005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 January 1993 / 11 May 2000

10 DATE OF REVISION OF THE TEXT

01/09/2020