SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Sotalol 160mg Tablets

2. Qualitative and Quantitative Composition

Each tablet contains 160mg Sotalol hydrochloride

For Excipients see 6.1.

3. Pharmaceutical Form

Tablet

Round, blue coloured, flat bevelled edged tablets with a break line on one side.

4.1 Therapeutic indications

Sotalol 160mg Tablets are indicated for:

Ventricular arrhythmias:

- Treatment of life-threatening ventricular tachyarrhythmias;
- Treatment of 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

Posology

Paediatric population
There is no relevant use of Sotalol in the paediatric population.
The initiation of treatment or changes in dosage with Sotalol should follow an appropriate medical evaluation including ECG control with measurement of the corrected QT interval, and assessment of renal function, electrolyte balance, and concomitant medications (see section 4.4).

As with other antiarrhythmic agents, it is recommended that Sotalol 40mg Tablets be initiated and doses increased in a facility capable of monitoring and assessing cardiac rhythm. The dosage must be individualized and based on the patient's response. Proarrhythmic events can occur not only at initiation of therapy, but also with each upward dosage adjustment.

In view of its β-adrenergic blocking properties, treatment with Sotalol 40mg Tablets 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 4.4).

Method of administration

The following dosing schedule can be recommended:

The initial dose is 80 mg, administered either singly or as two divided doses.

Oral dosage of sotalol 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 a daily dose of 160 to 320 mg administered in two divided doses at approximately 12 hour intervals. Some patients with life-threatening refractory ventricular arrhythmias may require doses as high as 480 - 640 mg/day. These doses should be used under specialist supervision and should only be prescribed when the potential benefit outweighs the increased risk of adverse events, particularly proarrhythmias (see section 4.4).

Dosage in renally impaired patients

Because sotalol is excreted mainly in urine, the dosage should be reduced when the creatinine clearance is less than 60 ml/min according to the following table:

Creatinine clearance (ml/min)	**Adjusted doses**
> 60	Recommended Dose
30-60	½ recommended Dose
10-30	¼ recommended Dose
< 10	Avoid Sotalol

The creatinine clearance can be estimated from serum creatinine by the Cockroft and Gault formula:

Men: (140 - age) x weight (kg) / 72 x serum creatinine (mg/dl)

Women: idem x 0.85

When serum creatinine is given in μmol/l, divide the value by 88.4 (1mg/dl = 88.4 μmol/l).

Dosage in hepatically impaired patients

Since Sotalol is not subject to first-pass metabolism, patients with hepatic impairment show no alteration in clearance of Sotalol. No dosage adjustment is required in hepatically impaired patients.

4.3. Contraindications

Sotalol should not be used where there is evidence of:

- sick sinus syndrome
- second and third degree AV heart block unless a functioning pacemaker is present
- congenital or acquired 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
- history of chronic obstructive airway disease or bronchial asthma
- hypersensitivity to sotalol, other betablockers or any of the excipients in the formulation.
- metabolic acidosis
- renal failure (creatinine clearance < 10 ml/min).

4.4. Special warnings and precautions for use

Abrupt Withdrawal
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. 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 one to two weeks. Because coronary artery disease is common and may be unrecognised in patients receiving Sotalol, abrupt discontinuation in patients with arrhythmias may unmask latent coronary insufficiency. In addition, hypertension may develop.

Proarrhythmias
The most dangerous adverse effect of Class I and Class III antiarrhythmic drugs (such as sotalol) is the aggravation of pre-existing arrhythmias or the provocation of new

arrhythmias. Drugs that prolong the QT-interval may cause torsades de pointes, a polymorphic ventricular tachycardia associated with prolongation of the QT-interval. Experience to date indicates that the risk of torsades de pointes is associated with the prolongation of the QT-interval, slow heart rate, reduction in serum potassium and magnesium, high plasma sotalol concentrations and with the concomitant use of sotalol and other medications which have been associated with torsades de pointes (see section 4.5: Interactions). Females may be at increased risk of developing torsades de pointes.

Other risk factors for torsades de pointes were excessive prolongation of the QTc and history of cardiomegaly or congestive heart failure.

The incidence of torsades de pointes is dose dependent. Torsades de pointes usually occurs within 7 days of initiating therapy or escalation of the dose and can progress to ventricular fibrillation.

In clinical trials of patients with sustained VT/VF the incidence of severe proarrhythmia (torsades de pointes or new sustained VT/VF) was <2% at doses up to 320 mg. The incidence more than doubled at higher doses.

Patients with sustained ventricular tachycardia and a history of congestive heart failure have the highest risk of serious proarrhythmia (7%).

Proarrhythmic events must be anticipated not only on initiating therapy but with every upward dose adjustment. Initiating therapy at 80 mg with gradual upward dose titration thereafter reduces the risk of proarrhythmia. In patients already receiving sotalol caution should be used if the QTc exceeds 500msec whilst on therapy, and serious consideration should be given to reducing the dose or discontinuing therapy when the QTc-interval exceeds 550 msec. Due to the multiple risk factors associated with torsades de pointes, however, caution should be exercised regardless of the QTc-interval.

Electrolyte Disturbances
Sotalol should not be used in patients with hypokalaemia or hypomagnesaemia prior to correction of imbalance; these conditions can exaggerate the degree of QT prolongation, and increase the potential for torsades de pointes. Special attention should be given to electrolyte and acid-base balance in patients experiencing severe or prolonged diarrhoea or patients receiving concomitant magnesium- and/or potassium-depleting drugs.

Congestive Heart Failure
Beta-blockade may further depress myocardial contractility and precipitate more severe heart failure. Caution is advised when initiating therapy in patients with left ventricular dysfunction controlled by therapy (i.e. ACE Inhibitors, diuretics, digitalis, etc); a low initial dose and careful dose titration is appropriate.

Recent MI
In post-infarction patients with impaired left ventricular function, the risk versus benefit of sotalol administration must be considered. Careful monitoring and dose titration are critical during initiation and follow-up of therapy. The adverse results of clinical trials involving antiarrhythmic drugs (i.e. apparent increase in mortality) suggest that Sotalol should be avoided in patients with left ventricular ejection fractions ≤ 40% without serious ventricular arrhythmias.

Electrocardiographic Changes

Excessive prolongation of the QT-interval, >500 msec, can be a sign of toxicity and should be avoided (see Proarrhythmias above). Sinus bradycardia has been observed very commonly in arrhythmia patients receiving sotalol in clinical trials. Bradycardia increases the risk of torsades de pointes. Sinus pause, sinus arrest and sinus node dysfunction occur in less than 1% of patients. The incidence of 2nd- or 3rd-degree AV block is approximately 1%.

Anaphylaxis
Patients with a history of anaphylactic reaction to a variety of allergens may have a more severe reaction on repeated challenge while taking beta-blockers. Such patients may be unresponsive to the usual doses of adrenaline used to treat the allergic reaction.

Anaesthesia
As with other beta-blocking agents, Sotalol 40mg Tablets should be used with caution in patients undergoing surgery and in association with anaesthetics that cause myocardial depression, such as cyclopropane or trichloroethylene.

Diabetes Mellitus
Sotalol should be used with caution in patients with diabetes (especially labile diabetes) or with a history of episodes of spontaneous hypoglycaemia, since beta-blockade may mask some important signs of the onset of acute hypoglycaemia, e.g. tachycardia.

Thyrotoxicosis
Beta-blockade may mask certain clinical signs of hyperthyroidism (e.g., tachycardia). Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockade which might be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm.

Renal Impairment
As sotalol is mainly eliminated via the kidneys the dose should be adjusted in patients with renal impairment (see dosage-section 4.2).

Psoriasis
Beta-blocking drugs have been reported rarely to exacerbate the symptoms of psoriasis vulgaris.

This medicine contains less than 1mmol sodium (23mg) per tablet, which is to say essentially ‘sodium free’.

4.5. Interaction with other medicinal products and other forms of interaction

Antiarrhythmics
Class 1a antiarrhythmic drugs, such as disopyramide, quinidine and procainamide and other Class III antiarrhythmic drugs such as amiodarone and bepridil are not recommended as concomitant therapy with sotalol, because of their potential to prolong refractoriness (see 4.4 Special Warnings and Precautions). The concomitant use of other beta-blocking agents with sotalol may result in additive Class II effects.

Other drugs prolonging the QT-interval

Sotalol 160mg Tablets should be given with extreme caution in conjunction with other drugs known to prolong the QT-interval such as phenothiazines, tricyclic

antidepressants, terfenadine and astemizole. Other drugs that have been associated with an increased risk for torsades de pointes include erythromycin IV, halofantrine, pentamidine, and quinolone antibiotics**.**

Floctafenine

beta-adrenergic blocking agents may impede the compensatory cardiovascular reactions associated with hypotension or shock that may be induced by Floctafenine.

Calcium channel blocking drugs

Concurrent administration of beta-blocking agents and calcium channel blockers has resulted in hypotension, bradycardia, conduction defects, and cardiac failure. Beta-blockers should be avoided in combination with cardiodepressant calcium-channel blockers such as verapamil and diltiazem because of the additive effects on atrioventricular conduction, and ventricular function.

Potassium-Depleting Diuretics

Hypokalaemia or hypomagnesaemia may occur, increasing the potential for torsade de pointes (see Special Warnings and Precautions for Use).

Other potassium-depleting drugs

Amphotericin B (IV route), corticosteroids (systemic administration), and some laxatives may also be associated with hypokalaemia; potassium levels should be monitored and corrected appropriately during concomitant administration with sotalol.

Clonidine

Beta-blocking drugs may potentiate the rebound hypertension sometimes observed after discontinuation of clonidine; therefore, the beta-blocker should be discontinued slowly several days before the gradual withdrawal of clonidine.

Digitalis glycosides

Single and multiple doses of sotalol do not significantly affect serum digoxin levels. Proarrhythmic events were more common in sotalol treated patients also receiving digitalis glycosides; however, this may be related to the presence of CHF, a known risk factor for proarrhythmia, in patients receiving digitalis glycosides. Association of digitalis glycosides with beta-blockers may increase auriculo-ventricular conduction time.

Catecholamine-depleting agents

Concomitant use of catecholamine-depleting drugs, such as reserpine, guanethidine, or alpha methyldopa, with a beta-blocker may produce an excessive reduction of resting sympathetic nervous tone. Patients should be closely monitored for evidence of hypotension and/or marked bradycardia which may produce syncope.

Insulin and oral hypoglycaemics

Hyperglycaemia may occur, and the dosage of antidiabetic drugs may require adjustment. Symptoms of hypoglycaemia (tachycardia) may be masked by beta-blocking agents

Neuromuscular blocking agents like Tubocurarin

The neuromuscular blockade is prolonged by beta-blocking agents

Beta-2-receptor stimulants

Patients in need of beta-agonists should not normally receive sotalol. However, if concomitant therapy is necessary beta-agonists may have to be administered in increased dosages.

Drug/Laboratory interaction

The presence of sotalol in the urine may result in falsely elevated levels of urinary metanephrine when measured by photometric methods. Patients suspected of having phaeochromocytoma and who are treated with sotalol should have their urine screened utilising the HPLC assay with solid phase extraction.

4.6 Fertility, pregnancy and lactation

Pregnancy

Animal studies with sotalol hydrochloride have shown no evidence of teratogenicity or other harmful effects on the foetus. Although there are no adequate and well-controlled studies in pregnant women, sotalol hydrochloride has been shown to cross the placenta and is found in amniotic fluid. 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 foetus and neonate. There is an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period. Therefore, sotalol should be used in pregnancy only if the potential benefits outweigh the possible risk to the foetus. The neonate should be monitored very carefully for 48 - 72 hours after delivery if it was not possible to interrupt maternal therapy with sotalol 2-3 days before the birthdate.

Breast-feeding
Most beta-blockers, particularly lipophilic compounds, will pass into breast milk although to a variable extent. Breast feeding is therefore not recommended during administration of these compounds.

4.7. Effects on Ability to Drive and Use Machines

There are no data available, but the occasional occurrence of side-effects such as dizziness and fatigue should be taken into account (see 4.8 Undesirable effects).

4.8 Undesirable effects

Sotalol is well tolerated in the majority of patients, with the most frequent adverse effects arising from its beta-blockade properties. Adverse effects are usually transient in nature and rarely necessitate interruption of, or withdrawal from treatment. These include dyspnoea, fatigue, dizziness, headache, fever, excessive bradycardia and/or hypotension. If they do occur, they usually disappear when the dosage is reduced. The most significant adverse effects, however, are those due to proarrhythmia, including torsades de pointes (see section 4.4).

Frequency is defined using the following convention: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000) including isolated reports, not known (cannot be estimated from the available data)

The following are adverse events considered related to therapy:

Cardiac disorders
Common: Bradycardia, dyspnoea, chest pain, palpitations, oedema, ECG abnormalities, hypotension, arrhythmia, syncope, cardiacfailure, presyncope

Skin and subcutaneous tissue disorders
Common: Rash
Unknown: Alopecia, Hyperhidrosis

Blood and lymphatic system disorders
Unknown: Thrombocytopenia

Gastro-intestinal disorders
Common: Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence

Musculoskeletal, connective tissue and bone disorders
Common: Muscle spasms

Nervous system disorders
Common: Fatigue, dizziness, asthenia, light-headedness, headache, paraesthesia, dysgeusia

Psychiatric disorders
Common: Sleep disorder, mood altered, depression, anxiety

Reproductive system and breast disorders
Common: Sexual dysfunction

Eye disorders
Common: Visual disturbances

Ear and labyrinth disorders
Common: Hearing disturbances

General disorders and administration site conditions
Common: Pyrexia

In clinical trials, 3256 patients with cardiac arrhythmias (1363 with sustained ventricular tachycardia) received oral Sotalol, of whom 2451 received the drug for at least 2 weeks. The most significant adverse events were torsade de pointes and other serious new ventricular arrhythmias (see section 4.4), which occurred at the following rates:

Patient Populations			
	VT/VF (n=1,363)	**NSVT/PVC** (n=946)	**SVA** (n=947)
Torsade de Pointes	4.1%	1.0%	1.4%
Sustained VT/VF	1.2%	0.7%	0.3%

VT = ventricular tachycardia; VF = ventricular fibrillation; NSVT = nonsustained ventricular tachycardia; PVC = premature ventricular contractions; SVA = supraventricular arrhythmia.

Overall, discontinuation because of unacceptable adverse events was necessary in 18% of all patients in cardiac arrhythmia trials. The most common adverse events leading to discontinuation of Sotalol are listed in the table below:

Fatigue	4%
Bradycardia (<50 bpm)	3%
Dyspnoea	3%
Proarrythmia	2%
Asthenia	2%
Dizziness	2%

Cold and cyanotic extremities, Raynaud's phenomenon, increase in existing intermittent claudication and dry eyes have been seen in association with other beta-blockers.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal products 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

Intentional or accidental overdosage with sotalol has rarely resulted in death. Haemodialysis results in a large reduction of plasma levels of sotalol.

Symptoms and treatment of overdosage: The most common signs to be expected are bradycardia, congestive heart failure, hypotension, bronchospasm and hypoglycaemia. In cases of massive intentional overdosage (2-16 g) of sotalol the following clinical findings were seen: hypotension, bradycardia,

prolongation of QT-interval, premature ventricular complexes, ventricular tachycardia, torsades de pointes.

If overdosage occurs, therapy with SOTALOL should be discontinued and the patient observed closely. In addition, if required, the following therapeutic measures are suggested:

Bradycardia

Atropine (0.5 to 2 mg IV), another anticholinergic drug, a beta-adrenergic agonist (isoprenaline, 5 microgram per minute, up to 25 microgram, by slow IV injection) or transvenous cardiac pacing

Heart Block (second and third degree)

Transvenous cardiac pacing

Hypotension

Adrenaline rather than isoprenaline or noradrenaline may be useful, depending on associated factors

Bronchospasm

Aminophylline or aerosol beta-2-receptor stimulant

Torsades de pointes

DC cardioversion, transvenous cardiac pacing, adrenaline, and/or magnesium sulphate.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: beta blocking agents, non-selective, ATC Code - C07AA07

D,l-sotalol is a non-selective hydrophilic β-adrenergic receptor blocking agent, devoid of intrinsic sympathomimetic activity or membrane stabilizing activity.

Sotalol has both beta-adrenoreceptor blocking (Vaughan Williams Class II) and cardiac action potential duration prolongation (Vaughan Williams Class III) antiarrhythmic properties. Sotalol has no known effect on the upstroke velocity and therefore no effect on the depolarisation phase.

Sotalol uniformly prolongs the action potential duration in cardiac tissues by delaying the repolarisation phase. Its major effects are prolongation of the atrial, ventricular and accessory pathway effective refractory periods.

The Class II and III properties may be reflected on the surface electrocardiogram by a lengthening of the PR, QT and QTc (QT corrected for heart rate) intervals with no significant alteration in the QRS duration.

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. Although significant beta-blockade may occur at oral doses as low as 25 mg, Class III effects are usually seen at daily doses of greater than 160 mg.

Its β-adrenergic blocking activity causes a reduction in heart rate (negative chronotropic effect) and a limited reduction in the force of contraction (negative inotropic effect). These cardiac changes reduce myocardial oxygen consumption and cardiac work. Like other β-blockers, sotalol inhibits renin release. The renin-suppressive effect of sotalol is significant both at rest and during exercise. Like other beta adrenergic blocking agents, sotalol produces a gradual but significant reduction in both systolic and diastolic blood pressures in hypertensive patients. Twenty-four-hour control of blood pressure is maintained both in the supine and upright positions with a single daily dose.

5.2. Pharmacokinetic Properties

The bioavailability of oral sotalol is essentially complete (greater than 90%). After oral administration, peak levels are reached in 2.5 to 4 hours, and steady-state plasma levels are attained within 2-3 days. The absorption is reduced by approximately 20% when administered with a standard meal, in comparison to fasting conditions. Over the dosage range 40-640 mg/day sotalol displays dose proportionality with respect to plasma levels. Distribution occurs to a central (plasma) and a peripheral compartment, with an elimination half-life of 10-20 hours. Sotalol does not bind to plasma proteins and is not metabolised. There is very little inter-subject variability in plasma levels. Sotalol crosses the blood brain barrier poorly, with cerebrospinal fluid concentrations only 10% of those in plasma. The primary route of elimination is renal excretion. Approximately 80 to 90% of a dose is excreted unchanged in the urine, while the remainder is excreted in the faeces. Lower doses are necessary in conditions of renal impairment (see Dosage and Administration in patients with renal dysfunction). Age does not significantly alter the pharmacokinetics, although impaired renal function in geriatric patients can decrease the excretion rate, resulting in increased drug accumulation.

5.3. Preclinical Safety Data

No further particulars.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate dihydrate
Maize Starch
Povidone K30
Sodium starch glycollate (Type A)
Talc
Magnesium stearate
Indigocarmine Aluminium Salt E132

6.2. Incompatibilities

None

6.3. Shelf Life

36 months

6.4. Special Precautions for Storage

Do not store above 25°C. Store in original package.

6.5. Nature and Contents of Container

The tablets are packed in 14's blisters constituted from a PVC/ PVdC and aluminium foil. Two such blisters are packed in a carton for a pack of 28 tablets.

6.6. Instruction for Use/Handling

None

7 MARKETING AUTHORISATION HOLDER

Milpharm Limited,
Ares,
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West End Road,
South Ruislip HA4 6QD,
United Kingdom

8. Marketing Authorisation Number

PL 16363/0129

9. Date of First Authorisation/Renewal of Authorisation

21 July 2003

10 DATE OF REVISION OF THE TEXT

21/09/2022