

## **SUMMARY OF PRODUCT CHARACTERISTICS**

### **1 NAME OF THE MEDICINAL PRODUCT**

Sotalol Hydrochloride 160mg Tablets.

### **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each tablet contains sotalol hydrochloride 160mg.

Excipient with known effect:

Each tablet contains 53.50mg of lactose (as lactose monohydrate).

For the full list of excipients, see section 6.1.

### **3 PHARMACEUTICAL FORM**

Tablets for oral administration.

White, round, biconvex tablets of diameter 8.9mm–9.1mm and height of 3.8mm–4.2mm, marked “SOT” on one side and scored on the other.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

### **4 CLINICAL PARTICULARS**

#### **4.1 Therapeutic indications**

Sotalol hydrochloride 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 hydrochloride 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 4.4 Warnings and precautions).

As with other antiarrhythmic agents, it is recommended that Sotalol hydrochloride 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  $\beta$ -adrenergic blocking properties, treatment with Sotalol 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 80mg, administered in either one or two divided doses. Oral dosage of Sotalol Hydrochloride 40mg Tablets 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 will respond to a daily dose of 160 – 320mg 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 4.4 Warnings).

### Dosage in renally impaired patients

Because sotalol hydrochloride 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:

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

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

Men: 
$$\frac{(140 - \text{age}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dl)}}$$

Women: idem x 0.85

When serum creatinine is given in  $\mu\text{ mol/l}$ , divide the value by 88.4 ( $1\text{mg/dl} = 88.4 \mu\text{ mol/l}$ ).

#### 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**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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 any of the components of 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 beta-blocker 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 hydrochloride) 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, reduction of the heart rate, reduction in serum potassium and magnesium, high plasma sotalol concentrations and with the concomitant use of sotalol hydrochloride and other medications which have been associated with torsades de pointes (see 'Interaction with other medicinal products and other forms of interaction' section 4.5.) Females may be at increased risk of developing torsades de pointes.

The incidence of torsades de pointes is dose dependent. Torsades de pointes, usually occurs early after 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 320mg. The incidence more than doubled at higher doses.

Other risk factors for torsades de pointes were excessive prolongation of the QTc and history of cardiomegaly or congestive heart failure. Patients with substandard 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 80mg with gradual upward dose titration thereafter reduces the risk of proarrhythmia. In patients already receiving sotalol hydrochloride caution should be used if the QTc exceeds 500msec whilst on therapy, and serious consideration should be given to dose reduction or discontinuation of therapy when the QTc –interval exceeds 550 msec. Due to multiple risk factors associated with torsades de pointes, however, caution should be exercised regardless of the QTc-interval.

### Electrolyte Disturbances

Sotalol hydrochloride should not be used in patients with hypokalaemia or hypomagnesaemia before correction of the imbalance, since conditions of this nature 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 myocardial infarction

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. Sotalol hydrochloride should be avoided in patients with left ventricular ejection fractions  $\leq 40\%$  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' section above). Sinus bradycardia has been observed very commonly in arrhythmia patients receiving sotalol hydrochloride 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, and may be unresponsive to the usual doses of adrenaline used to treat allergic reaction.

### Anaesthesia

As with other beta-blocking agents sotalol hydrochloride 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

Caution should be exercised 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 carefully managed to avoid abrupt withdrawal of beta-blockade which might be followed by the 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 'Posology and method of administration' section 4.2.).

#### Psoriasis

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

#### This medicine contains Lactose:

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucosegalactose malabsorption should not take this medicine.

#### This medicine contains Sodium:

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

## **4.5 Interaction with other medicinal products and other forms of interaction**

#### Antiarrhythmics

Class Ia 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 section 4.4). The concomitant use of other beta-blocking agents with Sotalol may result in additive Class II effects.

#### Other drugs prolonging the QT-interval

Sotalol 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 produced by floctafenine.

#### Calcium channel blocking drugs:

Concurrent administration of betablocking agents and calcium channel blockers has resulted in hypotension, bradycardia, conduction defects, and cardiac failure. Betablockers 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 section 4.4).

#### Other Potassium-depleting diuretics

Amphotericin B (IV), corticosteroids (systemic administration) and some laxatives (also potassium-depleting) may be associated with the hypokalemia. 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 the 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 hydrochloride do not significantly affect serum digoxin levels. Proarrhythmic events were more common in sotalol hydrochloride 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 methyl dopa, 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

Neuromuscular blockade is prolonged by beta-blocking agents.

#### Beta-2-receptor stimulants:

Patients in need of beta-agonists should not normally receive sotalol hydrochloride. 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, if measured photometrically. Patients being treated with sotalol hydrochloride and suspected of having pheochromocytoma should have their urine screened by HPLC analysis 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 the foetus and neonate. Therefore sotalol hydrochloride 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 hydrochloride 2-3 days before the birthdate. There is an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period

#### 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 section 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 dyspnea, 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 ( $\geq 1/10$ ); common ( $\geq 1/100$ ,  $< 1/10$ ); uncommon ( $\geq 1/1,000$ ,  $< 1/100$ ); rare ( $\geq 1/10,000$ ,  $< 1/1,000$ ); very rare ( $< 1/10,000$ ) including isolated reports.

The following are adverse events considered related to therapy with Sotalol:

System Organ Class	Common
Cardiac disorders	Bradycardia Dyspnoea Chest pain Palpitations Oedema Electrocardiogram abnormal Hypotension Arrhythmia Syncope Presyncope Cardiac failure
Skin and subcutaneous tissue disorder	Rash
Gastrointestinal disorder	Nausea Vomiting Diarrhoea Dyspepsia Abdominal pain Flatulence
Musculoskeletal, connective tissue and bone disorders	Muscle spasms
Nervous system disorders	Headache Dizziness Fatigue Asthenia Lightheadedness Paraesthesia Dysgeusia
Psychiatric disorders	Sleep disorder Mood altered Depression Anxiety
Reproductive system and breast disorders	Sexual dysfunction

Eye disorders	Visual disturbance
Ear and labyrinth disorders	Hearing disturbances
General disorders and administration site	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 two 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:

<b>Patient Populations</b>			
	<b>VT/VF</b> (n=1,363)	<b>NSVT/PVC</b> (n=946)	<b>SVA</b> (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 = non sustained ventricular tachycardia; PVC = premature ventricular contraction; 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%
- proarrhythmia	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 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](http://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 overdose with sotalol hydrochloride has rarely resulted in death.

Symptoms and treatment of overdose:

The most common signs of sotalol overdose are bradycardia, congestive heart failure, hypotension, bronchospasm and hypoglycaemia.

In patients who have taken large intentional overdoses (2-16g) hypotension, bradycardia, prolongation of QT-interval, premature ventricular complexes, ventricular tachycardia and torsades de pointes have been found.

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

Bradycardia: Can be treated by atropine (0.5 to 2mg IV) administered intravenously, and if need be isoprenaline (approximately 5 micrograms per minute, up to 25 microgram) by slow intravenous injection or transvenous cardiac pacing.

Heart block of second or third degree: Can be treated by 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 beta-adrenergic receptor blocking agent, devoid of intrinsic sympathomimetic activity or membrane stabilizing activity.

Sotalol hydrochloride has both beta-adrenoreceptor blocking (Vaughan Williams Class II) and cardiac action potential duration prolongation (Vaughan Williams Class

III) antiarrhythmic properties. Sotalol hydrochloride has no known effect on upstroke velocity and therefore no effect on the depolarisation phase.

Sotalol hydrochloride 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 hydrochloride 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  $\beta$ -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  $\beta$ -blockers, sotalol inhibits renin release. The reninsuppressive 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-fourhour 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 hydrochloride is essentially complete (greater than 90%).

### Absorption

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.

### Distribution

Over the dosage range 40-640mg/day sotalol hydrochloride displays dose proportionality with respects to plasma levels. Distribution occurs to a central (plasma) and a peripheral compartment, with an elimination half-life of 10-20 hours.

Sotalol hydrochloride does not bind to plasma proteins and is not metabolised. There is very little inter-subject variability in plasma levels. Sotalol hydrochloride crosses the blood brain barrier poorly, with cerebrospinal fluid concentrations only 10% of those in plasma.

### Elimination

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 the geriatric patients can decrease the excretion rate, resulting in increased drug accumulation.

## 5.3 Preclinical safety data

No further information is presented.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Maize starch

Lactose monohydrate

Hydroxypropylcellulose

Sodium starch glycollate

Colloidal silicon dioxide

Magnesium stearate

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

Five years.

### **6.4 Special precautions for storage**

Store below 25°C. Store in the original package in order to protect from light.

### **6.5 Nature and contents of container**

Polypropylene/Aluminium or PVDC/ PVC/Aluminium blister packs in a cardboard box.

28, 56 tablets.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**7 MARKETING AUTHORISATION HOLDER**

Crescent Pharma Ltd  
Key House, Sarum Hill,  
Basingstoke,  
RG21 8SR, United Kingdom

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 20416/0582

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 03/03/1998  
Date of latest renewal: 27/03/2009

**10 DATE OF REVISION OF THE TEXT**

29/08/2023